Determinants of, and outcomes associated with antihypertensive-associated incident diabetes and metabolic syndrome in hypertensive patients in the ASCOT-trial

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Abstract

Controversy exists whether the adverse effects on glucose metabolism and the increased incidence of new-onset diabetes (NOD) associated with beta-blockers and/or diuretics translate into adverse cardiovascular (CV) events, and thereby seriously detract from the beneficial effects of the these agents. Furthermore, little is known about the determinants of NOD among hypertensive patients. Controversy also surrounds the clinical utility of the metabolic syndrome (MetS) and its role in predicting NOD and CV outcomes. In this thesis I present an evaluation of these issues using the database of the Anglo-Scandinavian Cardiac Outcomes Trial.

Increase in the baseline fasting plasma glucose (FPG), body mass index, serum triglyceride and systolic blood pressure significantly increased the risk for NOD. In contrast, randomisation to amlodipine ± perindopril treatment (in comparison with atenolol ± thiazide), high HDL -cholesterol, alcohol use and age over 55 years were significant protective factors. On further analysis, cumulative-mean glucose (CMG) and FPG were found to be independent and significant risk factors for CV outcomes and death. Allocation to atenolol-based treatment (vs. amlodipine-based treatment) was associated with a significantly greater increase in CMG levels, and a progressive worsening of glycaemic status (normoglycaemia, impaired glycaemia and NOD) after 1 year of follow-up. Worsening glycaemic status was found to have a significant and linear relationship with increased risk of CV outcomes and death.

The MetS, after adjustment for its constituent components, was found to be an independent predictor for stroke and death, but not for coronary outcomes. Furthermore, the MetS was associated with a 22% increased risk of NOD, after adjusting for its individual components, and was found to be a significantly better predictor of NOD than impaired fasting glucose.

In summary, these data suggest that among hypertensive patients, antihypertensive agents are important determinants for the development of NOD, and the antihypertensive-associated in-trial glycaemic worsening is associated with increased risk of CV outcomes and death. I have also shown that, in routine clinical practice, the MetS has an important role as an easy-to-use predictor for the risk of NOD, CV outcomes and death; and that the increased risk of CV outcomes and death associated with the MetS is independent of the influence of its constituent components.

Statement of Originality

I hereby declare that all work presented in this thesis is my own.

Dr Ajay K Gupta

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Dedicated to the everlasting memories of my father, late Mr Yash Pal Gupta, who always encouraged me to strive for excellence, and taught that patience, hard work and perseverance is the path to success and glory.

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Glossary

a ROC	Area under the receiver-operating characteristics
AACE	American Association of Clinical Endocrinologist
AASK	African American Study of Kidney Disease and Hypertension
ACCOMPLISH	Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension
ACE	Angiotensin converting enzyme
ACE	Angiotensin-converting enzyme
ALLHAT	Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial
ALT	Alanine transaminase
ARB	Angiotensin-receptor blocker
ARIC	Atherosclerosis Risk in Communities
ASCOT	Anglo Scandinavian cardiovascular outcome trial
BIC	Bayesian information criterion
BMI	Body mass index
BP	Blood pressure
BPLA	Blood pressure lowering arm
BPLTTC	Blood pressure Lowering Treatment Trialists' Collaboration
CAPPP	Captopril Prevention Project
CCB	Calcium channel blockers
CHARM	Candesartan in Heart Failure --Assessment of Reduction in Mortality and Morbidity program
CHD	Coronary heart disease
CI	Confidence interval
CMG	Cumulative mean glucose
CV	Cardiovascular
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DREAM	Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication
DREAM	Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication s
EDIC	Epidemiology of Diabetes Interventions and Complications
EGIR	European Group for Study of Insulin Resistance
FOS	Framingham Offspring Study
FPG	Fasting plasma glucose
HDL	High density lipoprotein
HOPE	Heart Outcomes Prevention Evaluation
HR	Hazard ratio
IDF	International Diabetes Federation

IDI	Integrated discrimination improvement
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
INSIGHT	Intervention as a Goal in Hypertension Treatment trial
INVEST	International Verapamil SR-Trandolapril Study
LIFE	Losartan Intervention for Endpoint reduction
LLA	Lipid lowering arm
MI	Myocardial infarction
NCEP-ATP	The National Cholesterol Education Panel (NCEP)-Adult Treatment Panel (ATP),
NHANES	National Health and Nutrition Survey
NNT	Number needed to treat
NOD	New-onset diabetes
NRI	Net reclassification improvement
ONTARGET	Ongoing Telmisartan Alone and In Combination with Ramipril Global End Point Trial
OR	Odds ratio
RAAS	Renin-angiotensin aldosterone system
RAS	Renin-angiotensin system
RR	Risk ratio
SAHS	San Antonio Heart Study
SCOPE	Study on Cognition and Prognosis in Elderly
SHEP	Systolic Hypertension in the Elderly Program
STAR	Study of Trandolapril/Verapamil SR and insulin Resistance
T2DM	Type2 diabetes mellitus
VALUE	Valsartan Antihypertensive Long-term Use Evaluation
VLDL	Very low density lipoproteins

List of publications

Peer reviewed publications arising from the studies in this dissertation:

1. Gupta AK; Prieto-Merino D; Dahlöf B; Sever PS; Poulter NR; ASCOT Investigators. (Aug 2011). **Metabolic syndrome, impaired fasting glucose and obesity, as predictors of incident diabetes in 14 120 hypertensive patients of ASCOT-BPLA: comparison of their relative predictability using a novel approach.** Diabet Med. 28:941-947.
2. Gupta AK; Dahlof B; Sever PS; Poulter NR; Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm Investigators. (Jul 2010). **Metabolic syndrome, independent of its components, is a risk factor for stroke and death but not for coronary heart disease among hypertensive patients in the ASCOT-BPLA.** Diabetes Care. 33:1647-1651.
3. Gupta AK; Dahlof B; Dobson J; Sever PS; Wedel H; Poulter NR; Anglo-Scandinavian Cardiac Outcomes Trial Investigators. (May 2008). **Determinants of new-onset diabetes among 19,257 hypertensive patients randomized in the Anglo-Scandinavian Cardiac Outcomes Trial--Blood Pressure Lowering Arm and the relative influence of antihypertensive medication.** Diabetes Care. 31:982-988.

Peer reviewed publications that are related to this dissertation, but not the studies

1. Gupta AK; Poulter NR. (12 Oct 2010). **The concept of the metabolic syndrome is it dead yet?.** J Am Coll Cardiol. 56:1355-1356.
2. Gupta AK; Poulter NR. (9 Jul 2007). **Antihypertensive-associated incident diabetes: controversy persists.** Arch Intern Med. 167:1433.

Presentations of the study findings in a few selective conferences (with published abstracts)

- Gupta AK; Dahlof B; Sever PS; Wedel H; Poulter NR; A; Anglo-Scandinavian Cardiac Outcome trial investigators. Relationship Of Baseline-And Cumulative Mean Fasting Plasma Glucose, Incident Diabetes At One Year, And Blood Pressure Treatment Allocation With Cardiovascular Events And Deaths Among Hypertensive Patients In ASCOT-BPLA: **2nd CODHY** October 2008, Barcelona,
- Gupta AK; Dahlof B; Sever PS; Wedel H; Poulter NR; A; Anglo-Scandinavian Cardiac Outcome trial investigators. Relationship of baseline-and cumulative mean fasting plasma glucose with cardiovascular events and deaths among hypertensive patients in ASCOT-BPLA: **European Society of Cardiology conference** , Aug 30-Sept 3, 2008, Munich
- Gupta AK; Dahlof B; Dobson J; Sever PS; Wedel H; Poulter NR; Anglo-Scandinavian Cardiac Outcome. Determinants of new-onset diabetes among 19,257 hypertensive patients randomized in the Anglo-Scandinavian Cardiac Outcomes Trial-blood pressure lowering arm and the relative influence of antihypertensive medication. **21st Scientific Meeting of the International-Society-of-Hypertension/5th Asian-Pacific Congress of Hypertension**/29th Annual Scientific Meeting of the Japanese-Society-of-Hypertension. 31:982-988. (2008).

- Gupta AK; Poulter NR; Dahlot B; Sever PS; Wedel H; ASCOT Investigators. Role of metabolic syndrome, independent of its components, in prediction of cardiovascular outcomes in hypertensive patients of ASCOT- BPLA. **56th Annual Scientific Session of the American-College-of-Cardiology.** 49:417A-417A. (2007).
- Gupta AK, Dahlof B, Sever PS, Poulter NR , ASCOT investigators: Role of metabolic syndrome, independent of its components, in prediction of cardiovascular outcomes in hypertensive patients of ASCOT-BPLA, **British Hypertension Society Conference**, September 2007. Cambridge, UK
- Gupta AK, Dahlof B, Sever PS, Poulter NR , ASCOT investigators The metabolic syndrome, independent of its components and other variables, is a predictor of new onset diabetes. **American Society of Hypertension Conference** 2007, May 19-22, Chicago, USA

Chapter 1

INTRODUCTION

Determinants of, and Outcomes Associated with Antihypertensive-associated Incident Diabetes and the Metabolic Syndrome in Hypertensive Patients in the ASCOT-Trial

1 Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide and accounted for 30% of all deaths in 2004 (1). According to a World Health Organisation (WHO) report, there were a total of 17.4 million CVD deaths in 2004 of which 7.2 million were coronary heart disease (CHD) deaths and 5.7 million were stroke deaths (2). Unfortunately, the numbers of CVD-related deaths are likely to rise substantially over the next few decades. It has been estimated that there will be 24 million CVD-related deaths in 2015 and this is likely to escalate rapidly until CVD accounts for nearly three-quarters of all deaths in 2030 (2-4). These worrisome projections are primarily driven by the ageing population, and the rapidly accelerating prevalence of cardiovascular risk factors including obesity, diabetes, hypertension and dyslipidaemia. It is therefore imperative that suitable preventative strategies are adopted in a systematic way to reduce the increasing burden of CVD-related morbidity and mortality. Whilst the primordial prevention strategies need to target lifestyle modifications, physical inactivity and dietary factors on a population level, there is a clear role for individual-based treatment strategies to reduce the risk of CVD among those at a higher risk. For the latter strategy to be successful, it is important that research is done to identify effective treatment strategies, and to develop easy-to-use tools to identify those at highest risk of CVD.

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1.1 Hypertension and Diabetes:

Among all cardiovascular risk factors, raised blood pressure (BP) is the leading cause of death, and was estimated to be responsible for 13.5% of all deaths globally in 2004 (1, 5). In 2000, it was estimated that there were 1 billion patients with hypertension worldwide, and this was projected to rise to 1.5 billion by 2030 (6). Among hypertensive patients in the community, it has been estimated (using data from national and regional surveys) that only half of all hypertensive patients are receiving treatment (7, 8). In the 2006 Health Survey for

England, it was found that nearly 70% of all hypertensive patients had uncontrolled BP, defined as systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg (9). Similar proportions of hypertensive patients with uncontrolled BPs (defined as ≥140/90 mm Hg) were reported using the 1999 to 2004 National Health and Nutrition Examination Survey (NHANES) data from the USA (10). Reports from other regions suggest even poorer rates of BP control than those seen in developed economies such as the USA and England (11-13). This situation is particularly unfortunate, since BP reduction with the use of antihypertensive medications is one of the most readily available and effective ways to reduce the cardiovascular burden worldwide. A meta-analysis reported that for each 10 mmHg reduction in systolic BP, the risk of stroke decreases by a third, and coronary heart disease (CHD) by a quarter (14, 15). The reported benefits of BP reduction on cardiovascular outcomes have been shown to occur regardless of the choice of antihypertensive drug treatment regimen (15). However, in contrast to this finding when the observed reductions in CHD risk associated with the use of antihypertensive agents were compared with the expected reductions from observational studies it was found that for the same degree of BP-lowering, there was a discernible gap between observed and expected CHD events (16, 17). This apparent gap between observed and expected CHD event rates has been attributed, by some, to the adverse metabolic effects—including those on glucose and lipid metabolism —induced by the diuretic and beta-blockers used in the trials of antihypertensive agents (18). Indeed, it is now well established that these two antihypertensive drug classes are associated with an increased risk of new-onset diabetes. However, globally, these drugs continue to be the most commonly-used antihypertensive agents (8, 19-21), and diuretics continue to be recommended as first line agents in several hypertension guidelines (22-24). This is, in part, because although several studies have shown adverse metabolic effects (including increased rates of new-onset diabetes) associated with these drugs, they have failed to demonstrate any associated increase

in adverse cardiovascular outcomes (25-27). These findings have added some credence to the claim that antihypertensive-induced new-onset diabetes is 'innocent'(27). However this message is counter-intuitive, since it has been well established that diabetes is a major independent risk factor for CVD.

These controversies notwithstanding, little is known about the determinants of new-onset diabetes in patients with hypertension. A small number of early trials (28, 29), albeit with methodological limitations (30), have described the importance of baseline body mass index (BMI) and fasting plasma glucose (FPG) in predicting the risk of incident diabetes. However, none of the previous studies in hypertensive patients have described a risk score that easily identifies patients at high risk of developing diabetes. It is important that preventive strategies are devised to target modifiable risk factors for new-onset diabetes, particularly among high risk hypertensive patients identified by these risk scores, to reduce the development of incident diabetes. This is particularly important given that the co-existence of hypertension and diabetes substantially increases the risk of CVD.

1.2 The metabolic syndrome and cardiovascular outcomes and diabetes

The metabolic syndrome, defined as a clustering of cardio-metabolic risk factors such as dyslipidaemia, dysglycaemia, hypertension and obesity (31-33), is associated with an increased risk of incident diabetes, cardiovascular morbidity and mortality, and all-cause mortality (34). Recently, the clinical usefulness of the metabolic syndrome diagnosis in routine clinical practice has been intensely debated (35-38). One of the pivotal issues in this debate is whether the cardiovascular risk associated with the metabolic syndrome is greater than the cumulative risk of its individual components (35, 39). Unfortunately, studies evaluating this issue have provided equivocal results (40-45), primarily because of

differences in the study design, outcomes, adjustments for confounders, and definitions used for the metabolic syndrome (31-33). The additional benefits of using the metabolic syndrome over other tools for predicting the risk of incident diabetes has also been questioned. For example, recent studies have shown that the risk of new-onset diabetes associated with the metabolic syndrome is no greater than that associated with the use of fasting plasma glucose alone (46). On the other hand, if the metabolic syndrome, independent of the influence of its constituent components, is proven to be a significant predictor of new-onset diabetes, cardiovascular outcomes and death, then it could be an extremely useful tool in routine clinical practice. Hence, these issues need further evaluation, considering their potentially important clinical implications.

1.3 Overview and structure of the thesis

In the context of CVD prevention, it is important that the controversies and issues raised in sections 1.1 and 1.2 are resolved. In the following dissertation, using the database of the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) (47, 48), I have evaluated these issues in 4 separate analytical studies. In these 4 studies, I have focussed separately on:

a) The predictors of new-onset diabetes among hypertensive patients, and the development of a risk score to identify those at highest risk (study1: chapter 6)
b) The impact of antihypertensive-associated glucose changes and new-onset diabetes on cardiovascular outcomes and death among hypertensive patients (study 2: chapter 7).
c) The clinical usefulness of the metabolic syndrome, independent of the influence of its constituent components, in predicting the risk of coronary and stroke events, and all-cause mortality (study3: chapter 8).

d) The relative performance of the metabolic syndrome as a predictor of new-onset diabetes among hypertensive patients compared with obesity and impaired fasting glucose (study 4: chapter 9).

1.3.1 Structure of the thesis:

This thesis is structured around the 4 studies (Chapter 6 to 9). Each of these studies is described separately, in a standalone chapter, with relevant background information in details, description of the study findings and in-depth discussion. Other chapters provide supportive and contextual information (in brief), considered relevant to all 4 studies. Below is brief description of the content of all following chapters:

- Chapter 2 includes a discussion of the epidemiology of hypertension, diabetes and the metabolic syndrome, and briefly outlines a few other issues that may be relevant to all 4 analytical studies.
- Chapter 3 describes the aims and objectives of the 4 studies.
- In Chapter 4, I have described the study design and main results from the ASCOT-BPLA.
- In Chapter 5, I have briefly outlined the statistical methods used in one or more of these 4 analyses.
- In Chapters 6 to 9, I have reviewed the relevant literature, and described and discussed the findings from each of the 4 studies separately.
- Chapter 10 summarises the conclusions from the findings of the 4 studies, and discusses their implications for future research.

Chapter 2

BACKGROUND

Hypertension, Antihypertensive Medications, Diabetes and Metabolic Syndrome: Their Relationships with the Cardiovascular Outcomes—A Brief Overview

2.1 Summary

Hypertension, diabetes, dyslipidaemia and obesity are modifiable cardiovascular risk factors, which frequently co-exist (more than that by chance), and have complex inter-relationships. Clustering of these risk factors is commonly known as metabolic syndrome. Insulin resistance is believed to be one of the important underlying pathogenetic links, responsible for their co-existence, and the association with the cardiovascular outcomes. The importance of these risk factors (and also the metabolic syndrome) is that each is an independent risk factor for cardiovascular disease (CVD), and all respond similarly to primary preventative strategies (such as lifestyle modifications and dietary changes) and are amenable to pharmacological treatment. Moreover, when one or more of these risk factors/conditions are present, it is possible to reduce the likelihood of development of the others, and also CVD, by initiating lifestyle and dietary changes and/or pharmacological interventions.

To provide general context to the 4 studies mentioned in chapter 1, in this chapter, I will briefly describe a few aspects that are common to each study. As previously mentioned, further details specific to each study are discussed in their corresponding chapters (Chapters 6 to 9). In this chapter, I will discuss the following:

a. Prevalence of hypertension, its association with CVD, and the role of different antihypertensive drug classes in reducing cardiovascular outcomes.
b. Prevalence of diabetes and the risk of CVD associated with diabetes.
c. Hypertension, diabetes, and antihypertensive medications: mechanisms explaining the diabetogenic potential of antihypertensive agents.
d. Prevalence and definitions of the metabolic syndrome, its underlying patho-physiological mechanisms, and controversies surrounding its clinical utility.

2.2 Hypertension

According to the World Health Organisation (WHO), high blood pressure (BP) (hypertension) is the single most preventable cause of premature death (1). It is estimated that raised BP accounts for about 47% of all ischaemic heart disease burden, 54% of all strokes, and is responsible for nearly 8 million deaths annually, worldwide (1, 2). It is, therefore, unsurprising that BP control is considered the most important preventive strategy, to combat the rapidly surging global burden of CVD (3, 5, 6).

2.2.1 Prevalence of hypertension: trends and challenges

Hypertension is one of the most prevalent cardiovascular risk factor in the community (1, 3, 6). In 2000, it was estimated that 26.4% of the world's adult population (>20 years of age) had hypertension, and the prevalence was predicted to rise to 29.5% in 2030 (6). It was further projected that the increase in the worldwide prevalence of hypertension would primarily be fuelled by increasing numbers of patients with hypertension in developing countries, and not in developed countries. Indeed, in 2010, it already seems that these projections are likely to be true, with a rapidly increasing prevalence of hypertension in developing countries, across all gender and age-groups (6, 49-53). In contrast, recent data arising from developed countries suggests that previously apparent increases in the prevalence of hypertension may be levelling off. For example, in an evaluation of trends in the prevalence of hypertension in the USA from 1999 to 2008 (54), the prevalence of hypertension among adults (> 20 years) remained static (at approximately 30%); similar trends were noted in men and women, and across all ethnic- and age-groups (54).

The divergent trends in the prevalence of hypertension in developed and developing countries are consistent with the findings of Danaei et al who systematically evaluated reports from health examination surveys conducted worldwide between 1980 and 2008 (55) . According to their findings, since the 1980's, worldwide mean systolic BP decreased by 0.8 mm Hg per decade in men and 1 mm Hg per decade in women (55). Systolic BP fell most in developed countries (predominantly, over the last two decades), whereas mean systolic BP levels increased significantly in developing countries in Asia and Africa. These recent data provide mixed messages. First, that the rapidly escalating prevalence of hypertension in developing countries will pose substantial challenges in future, particularly as the majority of the world's population lives in such countries. Second, hypertension continues to be a substantial problem in developed countries, and recent reductions in hypertension prevalence and mean systolic BP are likely to be offset by the increasing prevalence of obesity, given the strong association between obesity and hypertension (56, 57). Third, (a more positive message arising from the reduction in systolic BP in developed countries) that BP reduction on a population scale is possible.

This decrease in mean systolic BP in the developed countries correlates well with two other observations in these countries. First, recent surveys in the USA and UK have shown trends towards improved awareness and treatment of hypertension. Second, trends evaluating cardiovascular outcomes over the last two decades suggest that there have been significant reductions in CVD rates in developed countries. For example in the USA, from 1997 to 2008, the death rate from CVD declined by 27.8% (58). Advances in the treatment of coronary events and risk factors, including BP control, are important contributors to this recent decline. A study reported that about half of the CVD mortality reduction could be attributed directly to the ready availability of effective treatment options (59). Among strategies for CVD prevention, antihypertensive medications play a crucial role (60-62). These observations taken together

illustrate the pivotal importance of antihypertensive treatment in reducing the worldwide burden of cardiovascular morbidity and mortality.

In summary, careful evaluation of recent data suggests that the worldwide prevalence of hypertension will continue to increase over next few decades (6) and may indeed be greater than previously estimated if current trends in developing countries continue and the obesity epidemic remains unchecked in developed countries. This increase in hypertension prevalence will pose substantial challenges for global public health, particularly CVD-related morbidity and mortality. On the other hand, these data also suggest that there is a huge (as yet untapped) potential for reduction in cardiovascular morbidity and mortality, by increasing awareness, treatment and control of hypertension. This assertion is based on the fact that, in 2008, an estimated 978 million patients with hypertension worldwide had uncontrolled BPs (55).

2.2.2 Antihypertensive medications and cardiovascular morbidity and mortality

Since, the findings of the first landmark trial in 1967 (63), antihypertensive agents are routinely used to reduce cardiovascular risk among hypertensive individuals. Currently, several different antihypertensive drug classes are available. These differ in their mechanism, and site of action, which theoretically offers potential advantages and also disadvantages in specific situations. However, in routine clinical practice, these off-target effects are small in magnitude, and are often ignored in favour of the primary effect on the BP lowering (except when there are specific compelling indications for, or contra-indications to, the use of particular drugs). This approach in routine practice is justified in that; firstly, BP lowering is the most important factor reducing cardiovascular risk; secondly, that small off-target actions are not usually thought to have any clinically significant effect. Whilst this approach is likely to be correct, it does need further examination, particularly given the fact that similar BP lowering can usually be achieved by

other agents. Therefore, it is important to re-evaluate whether the small off-target effects associated with some of these antihypertensive agents (such as increases in glucose and lipid levels with thiazide diuretics, or reduction in glucose levels with angiotensin converting enzyme [ACE] inhibitors) would impact the cardiovascular benefits associated with the BP lowering effect of these agents, for same level of BP control.

Epidemiological studies have shown that a decrease in systolic BP of 10 mm Hg reduces the risks of stroke and coronary heart disease (CHD) by 36% and 25%, respectively (14, 64-66). An earlier meta-analysis (reporting on the cardiovascular benefits of 'older' antihypertensive treatment agents) has shown a relatively lesser CHD benefit (18) than that expected from epidemiological studies (14, 64-66) . This apparent shortfall in CHD avoidance was blamed on adverse effects, particularly on glucose and lipid metabolism associated with use of diuretics and beta-blockers in the trials included in the meta-analysis (18, 67). However, if this conjecture was true, then antihypertensive drug classes, such as ACE inhibitors and angiotensin receptor blocker (ARB's), which have beneficial impacts on glucose and lipid metabolism should have significantly greater cardiovascular benefits than those due to BP reduction alone. The data on this to date are inconsistent, and controversy persists whether any drug class has an added advantage over others (17, 68, 69), either because of site or mechanism of action, or because of other pleiotropic effects. Similarly, evidence is lacking whether small adverse effects associated with antihypertensive agents translate into increased cardiovascular events, thereby blunting the beneficial effect of BP lowering.

Over the last 5 years, the findings of two large-scale clinical trials provide indications that cardiovascular benefits are greater, for same level of BP control, with the use of metabolically neutral or protective agents compared with the use beta-blockers and diuretics,

alone or in combination (47, 70, 71). For example in the BP lowering arm of the Anglo-Scandinavian Cardiac Outcome trial (ASCOT-BPLA), those allocated to an amlodipine-based treatment regimen (amlodipine with the addition of perindopril as required) had significantly lower risks of death, stroke and cardiovascular events, compared with those allocated an atenolol-based treatment regimen (atenolol with a thiazide diuretic added as required) (47) (see chapter 4). It can be argued that the observed differences in mortality between the two treatment regimen, could be due to differences in mean systolic BP between the two treatment groups (-2.8 mm Hg); however, in a separate analysis, it was found that these small systolic BP differences contribute only a small proportion of the observed differences in cardiovascular events and deaths in the 2 treatment groups. Consequently, there are likely to be other reasons for differences between the groups. One possible reason is that adverse effects on glucose metabolism associated with atenolol-based treatment may have blunted the gains associated with BP-lowering, leading to lesser cardiovascular benefit than among those allocated to amlodipine-based treatment.

Likewise, the findings of the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial could be interpreted in a similar way (71, 72). In this trial, the combination of an ACE inhibitor and calcium-channel blocker (CCB) was associated with lower cardiovascular morbidity and mortality, compared with the combination of an ACE inhibitor and diuretic. Given that the BP difference between treatment arms was negligible, it can be postulated that the adverse metabolic potential of diuretics in the ACE inhibitor/ diuretic combination, compared with the metabolically neutral (or protective) combination of ACE inhibitor/ CCB may have had a role in the differential rates of cardiovascular outcomes. This hypothesis is further supported by the Study of Trandolapril/Verapamil SR and insulin Resistance (STAR) trial (73) in which the

combination of diuretic and ARB was associated with worsening insulin resistance, increased glucose levels and increased risk of new-onset diabetes, compared with the combination of CCB and ACE inhibitor. This was interpreted as implying that the metabolically protective effects of ARBs are unable to completely offset the adverse diabetogenic effects of diuretics.

However, this hypothesis is not supported by the findings of a recent meta-analysis evaluating the cardiovascular impact of antihypertensive agents stratified by drug class (15). In a meta-analysis of 147 clinical trials, Law et al reported that, for the same magnitude of the BP lowering, there were no apparent differences in the cardiovascular benefits associated with any antihypertensive drug classes. Similarly, another meta-analysis by the BP Lowering Treatment Trialists' Collaboration (BPLTTC) did not report any significant differences in cardiovascular outcomes between different antihypertensive drug classes (17, 69). Of note, the Law meta-analysis (74) included only study-level data, which may have diminished its ability to detect heterogeneity, if any, at the individual level. Likewise, in the BPLTTC analysis, the lack of adjustments for add-on antihypertensive agents (and other non-study antihypertensive agents) may have obscured heterogeneity (if present) between individual drugs. It is therefore more likely that a well-planned randomised clinical trial would provide a specific answer to this question The closest trials in that regard are ASCOT-BPLA and ACCOMPLISH; the findings of both suggest that, for the same level of BP control, antihypertensive agents with associated beneficial and neutral metabolic potential (such as ACE inhibitors and CCB) are superior at preventing cardiovascular events than agents with adverse metabolic potential (such as beta-blockers and diuretics), alone or in combination. Indeed, these conjectures are now supported by recommendations in the recently released BHS-NICE guidelines(75, 76); however, these are not yet accepted widely, and much more research needs to be done to reach a worldwide consensus.

2.3 Diabetes

The rapidly increasing prevalence of diabetes (fuelled by an obesity epidemic) is becoming worrisome, particularly because it will lead to increases in cardiovascular morbidity and mortality. Therefore, it is imperative that strategies are identified and adopted that will help in the primary prevention of diabetes. However, it is equally important that research is undertaken to reduce the CVD burden associated with diabetes (secondary prevention). In the sections below, I will briefly outline recent trends in the prevalence of diabetes, and the challenges posed by them. I will also discuss a few issues relevant for prevention of CVD among those with diabetes.

2.3.1 Prevalence of diabetes:

In 2009, it was estimated that there were 285 million people with diabetes worldwide, and it was projected that their numbers would increase substantially by 50% in next two decades, to an estimate of about 440 million people by 2030 (77, 78). Most of this increase is likely to be due to rapidly increasing numbers of patients from developing countries; however, even in developed countries, the prevalence of diabetes is expected to grow (because of the epidemic of obesity). Indeed, the trend of increasing prevalence of diabetes in developed countries has been apparent for last decade or so. For example, in the UK, in 2004 it was estimated that there were 1.8 million people with diabetes (79); in 2010, the number of patients with diabetes has risen 2.3 million(80). Similarly, in the USA, in 2002, there were 18 million adults (aged > 20 years) with diabetes, representing 8.7% of all adults (81); in 2010 there were an additional 7.6 million people with diabetes, and the proportion of adults with diabetes had increased further by 2.6% (82). Given the rapidly increasing prevalence of diabetes in both the developed and developing world, it is likely that current projections of an

estimated 440 million people with diabetes in the world by 2030 may turn out to be a gross underestimate, if the recent trends continue unabated.

2.3.2 Diabetes: the challenges

According to a WHO estimate in 2004, raised blood glucose was responsible for 6% of all deaths worldwide (1, 3). Since then the attributable mortality related to diabetes has increased, such that in 2010 an IDF estimate suggested that diabetes is responsible for 4 million (7.3%) of all deaths worldwide (83). Of these diabetes-related deaths, it is estimated that between 50% and 80% are due to cardiovascular causes (79, 84). This is consistent with the findings of several other studies that have shown that presence of diabetes, compared with its absence, is associated with a 2 to 4-fold increased risk of CVD (85-88). Indeed, it has been shown that the risk of a CHD event is similar among those patients with a history of previous myocardial infarction (but without diabetes) and those with diabetes (but no previous coronary event) (89). These findings form the basis of the National Cholesterol Education Panel (NCEP)-Adult Treatment Panel (ATP)-III (NCEP-ATP) panel recommendation (90, 91), that patients with diabetes should have a similar lipid-lowering (and other) targets as those patients with a previous history of a coronary event. However, a few other studies have questioned this recommendation (92, 93). A common refrain amongst these studies is that, in the absence of other risk factors, hyperglycaemia is not associated with an excessive cardiovascular risk; therefore, not all patients with diabetes have risk equivalency with those with a pre-existing coronary disease (37, 92, 93). Notwithstanding these controversies, studies have consistently reported increased risks of stroke, death and CHD among those with diabetes, compared with those without (86, 94). Overall, it is estimated that the presence of diabetes is associated with shortening of total life-span by 7.5 years for men, and 8.2 years for women (95).

In addition to the increased risk of macrovascular complications (CHD, stroke and peripheral vascular disease), people with diabetes have substantially increased risks of microvascular complications (nephropathy, retinopathy and neuropathy)(78). Because of this, diabetes is one of the leading causes of end stage renal disease (ESRD), blindness and non-traumatic amputation - all of which are associated with a considerable disability and morbidity (78, 96). In addition to causing substantial disability, the vascular complications (both micro- and macrovascular) are also associated with considerable treatment and management related costs. In 2006, the direct costs related to diabetes were estimated to be about $232 billion per annum worldwide, which increased by 62% to $ 376 billion in 2010 (77, 97). Considering the substantial socio-economic burden associated with the complications of diabetes, it is unsurprising that interventional studies have particularly focused on the secondary prevention of these complications (78, 98, 99).

Several trials conducted among patients with diabetes have shown the importance of glycaemic control on reducing micro-vascular complications; however, the results have been inconsistent in demonstrating the benefits of glycaemic control on macrovascular outcomes (100-107). Whilst it is beyond the scope of this thesis to discuss in detail the various trials which have failed to show benefits of glycaemic control on cardiovascular outcomes (98, 108), it is important to draw attention to two important findings. First, the long-term follow-up of both the UK Prospective Diabetes Study(UKPDS)(109, 110) and the Diabetes Control and Complications Trial (DCCT) (111) have shown a beneficial legacy effect of intensive glycaemic control (compared with routine treatment) on macrovascular outcomes. Second, a recent meta-analysis summarising results of intensive glycaemic control intervention trials have shown that intensive in-trial glycaemic control may also have an important role in reducing the macrovascular complications during the course of the trial, even if individual

trials have failed to demonstrate this effect in their respective reports (104). Besides glycaemic control, there are other important factors that may influence cardiovascular risk in patients with diabetes. Observational studies have clearly shown that co-existing cardiovascular risk factors (blood pressure, dyslipidaemia, smoking, obesity etc) exert a multiplicative effect on diabetes-associated cardiovascular risks (85, 112). Indeed, this hypothesis was investigated in the STENO-2 study, which evaluated benefits of targeted multi-risk interventions over the long-term (mean follow-up, 7.8 years), in a small group of patients with type 2 diabetes (n, 160) (113, 114). The findings suggest that, among patients with diabetes, multi-factorial risk interventions are able to reduce cardiovascular risk significantly (53% reduction in CVD among those allocated to intensive therapy, compared with conventional therapy). Another observational study looked for any additive effect of simultaneous BP and blood sugar control in a group of newly-diagnosed patients with diabetes (115), and found important benefits with the use of both strategies together (additive reductions in diabetes-related endpoints by 21% per 1% decrease in glycosylated haemoglobin levels, and by 11% per 10 mm Hg decrease in systolic BP). Indeed, recent results from the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial (116) showed that BP lowering, regardless of initial BP levels, is associated with reduced cardiovascular risk in patients with diabetes. This effect was independent of that exerted by intensive glycaemic control. Similar benefits of BP lowering were apparent in other previous trials (117).

In summary, the rapidly escalating prevalence of diabetes is likely to offset the recent decline in CVD rates, because of the increased cardiovascular risk associated with diabetes. It is also increasingly apparent that diabetes-related complications can be reduced by using a multi-factorial approach, including intensive glycaemic control and BP-lowering. However,

considering the challenges posed by the increasing number of patients with diabetes, it is clear that primary prevention strategies focussing on prevention of diabetes are likely to be more cost-effective. It is important that lifestyle modifications or pharmacotherapy-based strategies are initiated early amongst high risk populations (such as those with hypertension or metabolic syndrome) to decrease the burden of this disease.

2.4 Hypertension, Diabetes and antihypertensive medications

Hypertension and diabetes frequently co-exist, and are independent risk factors for each other. Insulin resistance is a common underlying link between the two conditions, and is present in the majority of patients with type 2 diabetes and > 50% of those with hypertension (118, 119). It is therefore unsurprising that patients with hypertension have an increased risk of new-onset diabetes (> 2 fold) compared with those without hypertension (120, 121). Similarly, it is estimated that > 80% of patients with diabetes will develop hypertension during their life-time (119, 122). Since, both hypertension and diabetes are independent predictors of CVD, it is not surprising that their co-existence nearly doubles the risk of CVD compared with either alone (123-126). Among those with diabetes in the Multiple Risk Factor Intervention Trial, the presence of hypertension (compared with its absence) was associated with a nearly 2-fold increased risk of CHD mortality (127). Similarly, in the UKPDS, intensive BP lowering was the most effective strategy to reduce risk of cardiovascular events and all-cause mortality (128). These findings clearly suggest that, among the patients with either diabetes or hypertension, development of the other condition should be avoided by initiating lifestyle modifications and other strategies, including drug-based. In this context, the choice of antihypertensive medications among hypertensive patients should be considered carefully, as some may increase the risk of new-onset diabetes (129, 130).

In Chapter 6 I discuss in detail the evidence related to the diabetogenic potential of antihypertensive agents. Briefly, both beta-blockers and diuretics adversely affect glucose metabolism, whereas ACE inhibitors and ARB's have a beneficial effect. A detailed discussion on the mechanisms behind the diabetogenic and/or protective effects of different antihypertensive agents is beyond the scope of this thesis; however, in the following sections I will briefly outline a few pathophysiological mechanisms related to commonly used antihypertensive drug classes.

2.4.1. Pathophysiological basis of the influence of antihypertensive agents on glucose metabolism:

For each antihypertensive drug class, carbohydrate metabolism may be potentially influenced by several pathophysiological mechanisms. Some of these mechanisms are common to all (or most) antihypertensive drug classes. For example, the haemodynamic effect induced by antihypertensive agents is used to explain their respective impact on the glucose metabolism (131, 132). According to this theory, increases or decreases in peripheral blood flow (vasodilatation or vasoconstriction, respectively) associated with antihypertensive agents will similarly influence glucose uptake by skeletal muscle, which in turn determines peripheral insulin sensitivity. For example, if an antihypertensive agent causes peripheral vasodilatation, it will result in greater glucose uptake and improved insulin sensitivity (i.e. decreased insulin resistance). Conversely, if an antihypertensive agent causes peripheral vasoconstriction, it will decrease the peripheral glucose-uptake and thereby worsen insulin sensitivity.

2.4.1. a. Diuretics: In early 1960's, it was known that diuretics adverse affected glucose metabolism (133-135). In 1963, Wolf et al reported worsening of glucose tolerance with the use of benzodiazine (a diuretic) (136). The causality of this effect was subsequently

confirmed, in other studies which clearly demonstrated the reversal of glucose changes after diuretic withdrawal (133-135, 137-140). On the contrary, several other studies reported no appreciable increase in glucose levels with short-term (1 to 6 years) use of diuretics (141, 142). Lewis et al, in 1976, suggested that altered glucose metabolism associated with diuretics occurs only after continuous and long-term (> 6 years) use (141). Similar findings were reported in the European Working party on Hypertension in the Elderly study, where glucose levels were unchanged (compared with placebo) after 1 year of diuretic use (142). Of note, those allocated to the diuretic arm in this study received a combination of a thiazide and a potassium-sparing diuretic. It is therefore likely that there was delay in diuretic-related alteration in glucose metabolism, because of the associated (protective) effect of the potassium-sparing diuretic. Similarly, the findings of Lewis et al could be refuted on the basis of the observational nature of the study, the small sample size (n, 51), lack of a proper comparator, and inadequate adjustments for confounding variables (141).

During the period between the 1960's and the early 1990's, the use of diuretics as an agent of choice continued unquestioned, mainly because of their excellent tolerability and substantial cardiovascular benefits related to BP lowering, and in spite of their adverse effects on carbohydrate metabolism. However, over the last two decades, given the ready availability of other equally efficacious (and probably safer) antihypertensive agents, there is a resurgence of interest in the cardiovascular impact of the adverse effects on glucose metabolism associated with diuretics. Recent data related to diuretic use and the development of new-onset diabetes is discussed in Chapter 6, and clinical trial evidence related to adverse cardiovascular outcomes (if any) associated with diuretic use is discussed in Chapter 7. Below is a brief outline of the pathophysiological basis of the increase in glucose levels associated with use of thiazide or thiazide-like diuretics.

Table 2.1 lists several probable pathways that may explain the adverse impact of diuretics on glucose metabolism. Among them, the impact on glucose metabolism of diuretic-induced hypokalemia is the most attractive, and perhaps the most investigated, mechanism (143). Studies have shown that experimentally generated states of hypokalemia result in the alteration of glucose metabolism (144, 145). From several animal studies, we know that increased potassium levels increase insulin secretion through ATP-sensitive potassium channels on the surface of beta-islet cells (146). These observations have been postulated to explain the observation that, conversely, insulin secretion (in response to glucose stimuli) is relatively less than expected in thiazide-induced hypokalemia leading to a rise in blood glucose levels (see Figure 2.1)(146). While no direct experimental support exists in support of this hypothesis, it is well supported by observational data from epidemiological studies and clinical trials. For example, in a recent post-hoc analysis of the Systolic Hypertension in the Elderly Program (SHEP), the authors found that thiazide-induced diabetes in SHEP was probably mediated through potassium changes in the diuretic-arm of the trial (147).

A haemodynamic basis of action is another mechanism to explain the alteration in glucose uptake induced by diuretics (132). According to this hypothesis, the diuretic induced decrease in the blood volume, results in reduced skeletal muscle blood flow and adversely affects peripheral glucose uptake (131). This hypothesis is supported by observations in animal studies in which, when diuretics, adipose tissue and skeletal muscle were incubated together, the diuretics were found to decrease glucose uptake by adipose tissue and skeletal muscle (139). Other potential mechanisms that can contribute to the relationship between diuretics and hyperglycaemia include hypomagnesaemia, activation of the renin-angiotensin system(RAS) (146), a direct action of thiazide diuretics on insulin secretion (147) and a diuretic-

induced increase in hepatic glucose production (148) (Table 2.1 and Figure 2.2).

2.4.1. b. Beta-blockers: Several studies have clearly established the adverse impact of beta-blockers on carbohydrate metabolism (149). In Chapters 6 and 7, I will discuss the findings of these studies. In this section, a few mechanisms that may explain the basis of the increase in glucose levels associated with use of beta-blockers are briefly discussed:

Table 2.2 enumerates some of the possible explanations for the diabetogenic effect of beta-blockers. Probably the main mechanism is by worsening of insulin sensitivity (150). Several possible explanations exist for this. Foremost is the decrease in peripheral blood flow associated with beta-blocker, ensuing decreased peripheral glucose uptake, and worsening of insulin sensitivity (131, 151). Other likely mechanisms include a direct inhibitory action of beta-blockers on insulin secretion, and insulin metabolic signalling. Increased weight, physical inactivity, and reduction in the activity of certain enzymes (such as skeletal muscle lipoprotein lipase) and insulin clearance may also contribute (150). Aside from the haemodynamic effects of beta-blockers, increased glycogenolysis and direct inhibition of insulin secretion are 2 further important mechanisms (152).

Beta-blockers and diuretics: The diabetogenic effects of beta-blockers are potentiated by the use of diuretics, and the use of both drugs together may affect almost all systems of the human body. Figure 2.3 illustrates several mechanisms by which the two drugs together could adversely impact glucose metabolism, and increase glucose levels (153)

2.4.1. c. ACE inhibitors and ARB's: Several meta-analyses have confirmed that the use of ACE inhibitors or ARBs is associated with decreased risk of developing new-onset diabetes among hypertensive patients as well as among those with the congestive heart failure or coronary artery disease (131, 151, 154-156). In a meta-analysis of 13 trials including 93, 451 patients, Andraws et al reported that the average risk reduction of new-onset diabetes with use of ACE inhibitors and ARBs was comparable, with the odds of developing new-onset diabetes reduced by 28% (odds ratio, 0.72 [95% confidence interval, 0.63 to 0.84]) and 27% (0.73 [0.64 to 0.84]) in trials of ACE inhibitors and ARBs, respectively (155).

Although there are many mechanisms that may explain the protective effects afforded by these drugs (Table 2.3) (131), the haemodynamic effect of ACE inhibitors or ARBs is an important mechanism responsible for improving insulin sensitivity (and reducing the risk of diabetes). According to this hypothesis, RAS system blockers improve insulin sensitivity by increasing perfusion of skeletal muscles and the pancreas, which in turn results in improved peripheral glucose uptake and increased insulin secretion by pancreatic islet cells. However, ACE inhibitors may also reduce insulin resistance by removal of an angiotensin-II (A-II)-related noxious effect on pancreatic cells, increased potassium retention, a beneficial effect on adipocyte differentiation and partial agonist action on peroxisome proliferator–activated receptor –γ (Table 2.3). ARBs may also improve insulin sensitivity by raising adiponectin levels and increasing serine phosphorylation of insulin receptors and insulin receptor substrate. Inhibition of the action of A-II by ARBs or ACE inhibitors may also improve insulin sensitivity by reducing the direct inhibitory effects of A-II on insulin signalling and glucose transport.

2.4.1.d.Calcium channel blockers: Critical analysis of the findings of several observational studies and clinical trials have shown that use of CCBs may only have a neutral metabolic effect (151). This view is consistent with the findings of a network analysis where the effect size associated with CCBs was similar to that associated with placebo use (156). This neutral metabolic profile of CCBs may be the reason why, in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial , those allocated to amlodipine had a significantly higher incidence of diabetes compared with those allocated to valsartan (157). This is because the difference in incidence of new-onset diabetes in the two treatment arms reflects the extent of protection afforded by the use of valsartan (an ARB), rather than any extra harmful effect of amlodipine (a CCB) on glucose metabolism. This finding is supported by an earlier study in which no adverse effect on glucose metabolism was observed with CCB use (158). However, findings of a neutral metabolic effect of CCBs, conflicts with the basic assumptions of the haemodynamic theory as, based on this theory, peripheral vasodilatation associated with CCBs should lead to an improvement in glucose metabolism. This implies that either there may be other mechanisms associated with the use of CCBs that somehow hinders expression of the benefits accrued by their haemodynamic effects, that the haemodynamic theory is not as critically important as previously believed, and that other mechanisms affecting glucose metabolism are equally, if not more, important. It seems that it is likely that the former explanation is true, since a CCB was found to improve insulin mediated glucose uptake by skeletal muscle in an animal study (159), consistent with the basis of haemodynamic theory (131, 160).

2.5 Metabolic syndrome

Metabolic syndrome is a constellation of cardio-metabolic risk factors, including impaired glucose metabolism, obesity, dyslipidaemia and hypertension, which are associated with an

increased risk of CVD and type-2 diabetes.

History: The co-existence of several cardiovascular risk factors has been known since the 1920's, when Kylin documented the clustering of hypertension, hyperglycaemia and gout (161). In 1947, Vague noted the association of upper body adiposity with lipid abnormalities, diabetes and CVD (162). However, it was only in 1980 that significant relationships between obesity and lipid abnormalities (including raised triglyceride levels associated with the abdominal obesity) became clinically more relevant (163). In 1988, Reaven (in his Banting lecture) described the inter-relationships between insulin resistance, hypertension, type 2 diabetes and CVD, and termed this clustering 'syndrome X' (164). However, Reaven did not include abdominal obesity in his list of primary disorders that are characterized by insulin resistance. In 1993, the importance of abdominal obesity as an integral component of the insulin resistance syndrome was clearly established (165) and, in 2000, Lemieux brought together the two concepts of insulin resistance and central adiposity, and coined the term 'hypertiglyceridaemic waist' - a marker of the atherogenic metabolic triad of hyperinsulinaemia, hyper-apolipoproteinaemia B and small dense low density lipoprotein (LDL)-cholesterol (166). During the late 1980's and 1990's, this clustering of metabolic risk factors was variously termed by several authors as syndrome X (164), insulin resistance syndrome (167), and 'the deadly quartet' (168). However, it was not until 1999 that the clustering of metabolic risk factors was properly institutionalised, when the WHO termed it 'metabolic syndrome' (169). The National Cholesterol Education Panel (NCEP)-Adult Treatment Panel (ATP)-III, in 2001, subsequently continued with use of the same term but defined it using slightly different criteria (170).

In the following sections, I will briefly describe various definitions of the metabolic

syndrome, its worldwide prevalence and burden, and the pathophysiological basis of the clustering of cardio-metabolic risk factors. I will also briefly outline a few important issues surrounding the clinical utility of the metabolic syndrome.

2.5.1 Metabolic syndrome: definitions

Table 2.4 describes different criteria (proposed by various organisations) to define the metabolic syndrome. All of these criteria (or definitions) have used the same metabolic risk factors to define the clustering of risk factors, but differ in the cut-off levels of the constituent components. The definitions also differ in their relative emphasis on particular components, or on the underlying pathophysiological basis of the definition (or clustering). For example, the WHO, European Group for Study of Insulin Resistance (EGIR) (171) and International Diabetes Federation (IDF) definitions each use the presence of a constituent component as an essential criterion to emphasise the underlying pathophysiological basis of the clustering of the metabolic factors. Whilst, the WHO identified insulin resistance as the basis of the constellation, the IDF believed that both insulin resistance and central adiposity are the causative mechanisms for metabolic syndrome development; however, they chose central obesity as an essential criterion instead of insulin resistance because they believed that ascertainment of central obesity (rather than demonstration of insulin resistance) is easier, and routinely possible in clinical practice. Also, they believed that use of adiposity as an essential criterion prompts the focus on the obesity epidemic. The EGIR proposed a modification of the WHO definition; first, by excluding all those with diabetes from the scope of the definition and second, by simplifying the essential criteria to include only elevated insulin levels (>75th percentile), instead of other complicated techniques for measurement of insulin resistance (Table 2.4). However, they continued to emphasise insulin resistance as the primary causative mechanism for the clinical clustering of risk factors.

In contrast, the NCEP-ATP III's primary objective in defining the metabolic syndrome was to identify people with a higher risk of CVD and diabetes, rather than concentrating on the mechanisms underlying the syndrome. In choosing their criteria, they focussed on factors (and cut-offs) that can be used (or were being used) routinely in clinical practice. As a result, their definition does not require laborious criteria such as demonstration of insulin resistance, nor does it identify any single criterion to be more important than others. Indeed, the presence of any 3 out of 5 criteria was proposed to make it simpler for clinicians to make a diagnosis of metabolic syndrome in routine practice. Equal weight afforded to each criterion was chosen to specifically provide a clinical message of equal importance of treatment of all cardiovascular risk factors for the prevention of CVD. Retrospectively, it seems that this basic approach worked, as the NCEP-ATP III criteria are the most commonly used to define the metabolic syndrome, both in clinical practice and in research studies. In 2004, a minor change to the cut-off level of fasting plasma glucose was made, to bring that criteria in conformity with the definition proposed by the American Diabetes Association (172).

The American Association of Clinical Endocrinologist (AACE) (173) criteria to define the metabolic syndrome were proposed in 2003. The idea behind these criteria was to mimic the clinical simplicity afforded by the NCEP-ATP criteria, but to maintain equal stress on insulin resistance as the primary cause of clustering of metabolic risk factors. They used the term insulin resistance syndrome, instead of metabolic syndrome, and did not specify a fixed number of co-existent metabolic factors to diagnose the insulin resistance syndrome; instead this decision was left to the clinical judgement of the treating physician. Perhaps this apparent lack of objectivity in these criteria is the reason why this definition of the metabolic syndrome is one of the least used in both research studies and clinical practice.

2.5.2 Prevalence of the metabolic syndrome

Over last few decades, the prevalence of the metabolic syndrome has rapidly increased throughout the world. In 2006, the IDF estimated that nearly a quarter of the world's adult population (>20 years) had metabolic syndrome (83, 174). This statistic is worrisome, particularly since those with metabolic syndrome are at a 2 to 3-fold increased risk of stroke or CHD, and up to a 5-fold increased risk of diabetes (83, 174). Moreover, given worldwide trends of the rising prevalence of hypertension, obesity and diabetes, the proportions of those with the metabolic syndrome may assume frightening proportions over next few decades.

Metabolic syndrome in developed countries: In a recent report, using National Health and Nutrition Survey (NHANES) data gathered between 2003 and 2006, a third (34%) of the adult population (> 20 years) in the USA were estimated to have the metabolic syndrome (defined using the NCEP-ATPIII definition)(175). The prevalence was similar in both men and women, but differed in different age groups. Whilst, the prevalence among men and women at 20 to 39 years of age was 20.3% and 15.6%, respectively, the prevalence was 51.5% and 54.4% among men and women ≥ 60 years of age (175). Ervin et al also reported that the most common metabolic component among adults in the USA was abdominal obesity (53%), followed by raised BP (40%) and hyperglycaemia (39%). Relatively smaller proportions of adults had raised triglycerides (31%) or low HDL cholesterol levels (25%). In another recent report (176), from the Canadian Health Measures Survey (between 2007 to 2009), the prevalence of the metabolic syndrome among adults (≥ 18 years age) was 17.7% and 19.1% using the original and updated NCEP-ATP III criteria, respectively. The reported prevalence of the metabolic syndrome in this study is significantly lesser than that reported from the USA. This could be partly due to the inclusion of younger subjects (18 and 19 year-olds) in the Canadian surveys (instead of > 20 year age in NHANES), which would reduce

the overall prevalence, as younger adults have significantly lower prevalence of each metabolic component. In addition, it could also be due to differences in the health metrics of the two populations, as reflected in lower prevalence of abdominal obesity (35%), hypertension (24%) and hyperglycaemia (16%) among Canadian adults, compared with those in the USA. Of note, the reported prevalence of the metabolic syndrome in the Canadian survey was significantly higher than that reported previously (in 1992), and it is projected that the trends of increasing prevalence of will continue in this region for a foreseeable future. Similar trends have been reported in the UK (177, 178).

Metabolic syndrome in developing countries The prevalence of the metabolic syndrome is rapidly rising in developing countries, and poses a substantial problem. In a recent report from a southern city in India, its prevalence was reported to be 18.3% using NCEP-ATPIII criteria (179). These findings are consistent with the findings of other studies from India (180-182) and Pakistan (183). In a report from Iran, the prevalence of the metabolic syndrome among men and women (age > 20years) was 24.0% and 40.5%, respectively (184). The wide difference in prevalence of the metabolic syndrome among men and women in this report is in keeping with the findings from countries in this region (185). Another important observation from these reports is that in the Middle East, particularly in urban regions, the prevalence of the metabolic syndrome is rapidly assuming epidemic proportions (186), with as many as 65% of all patients attending a community clinic in Jordan reported to have metabolic syndrome (187). In contrast, the prevalence rates of the metabolic syndrome reported from Eastern Asian countries are relatively modest (188); however, when using ethnic-specific waist circumference cut-offs, the prevalence in this region also becomes substantial. For example, in a study of 269 men and 505 women in urban Korea (189), the prevalence using the original NCEP-ATP III criteria was 16.0% and 10.7%, respectively;

however, when ethnic-specific waist circumference criteria were used, the prevalence increased to 29.0% and 16.8% among men and women, respectively.

These reports suggest that prevalence rates of the metabolic syndrome in urban populations in developing countries are no different than the rates seen in Western Europe and America. The data consistently and clearly show that the prevalence increases with age and that there may be gender differences, mainly driven by ethnic and cultural factors. Notwithstanding these issues, the main conclusion from these data is that the metabolic syndrome is a common problem, which will attain epidemic proportions if current trends continue. It is therefore critical that preventive strategies are initiated to reduce this increasing burden of cardiovascular risk factors, and consequent CVD.

2.5.3 Pathophysiological basis of the metabolic syndrome

The primary purpose of the concept of the metabolic syndrome was not to describe/or identify the primary causative basis of the clustering, but to identify those with high cardiovascular risk (172, 190). Indeed, the name 'syndrome' was used to illustrate the fact that there are several probable pathophysiological mechanisms to explain the constellation of risk factors (191). Insulin resistance and central obesity stand out as the most significant causative factors. Other factors that may also play a role in the pathophysiology of this risk concept are genetics, physical activity, ageing, pro-inflammatory state, hormonal changes and alternate concepts such as leptin resistance(192). However, a review of the mechanisms of actions of all these factors is beyond the scope of this dissertation. In the sections below, I will briefly discuss the pathophysiological relationship of the constituent metabolic components with insulin resistance and central obesity only.

2.5.3.a. Role of Insulin resistance

Insulin resistance is the most accepted unifying hypothesis to describe the clustering of risk factors (i.e. metabolic syndrome) (34, 192). Figure 2.4 lists some of the physiological actions of insulin which help to regulate lipid and glucose metabolism. When insulin resistance develops, the physiological regulatory mechanisms get deranged, manifesting clinically as evidence of altered glucose and lipid metabolism (e.g. increased glucose and lipid levels) (Figure 2.5). Prior to the obvious clinical manifestations of insulin resistance –that are predominantly glucocentric – there is an excess of circulating free fatty acids. This happens because the most sensitive pathway of insulin action – the inhibition of lipolysis by insulin – becomes deranged when insulin resistance develops (or is developing). Therefore, lipolysis in adipose tissues is unchecked, leading to increased release of free fatty acids into the circulation (34)(see Figure 2.6). This step is a circular process, because the excess free fatty acid decreases glucose uptake in skeletal muscle, thereby reducing insulin sensitivity, which in turn increases the circulation of free fatty acids. In the liver, excess free fatty acids increases hepatic glucose production and reduces the inhibition of gluconeogenesis by insulin. This results in increased circulating glucose and serum triglyceride levels and excessive secretion of very low density lipoproteins (VLDL). Increased systemic circulation of free fatty acids and glucose also induces pancreatic insulin secretion, causing a state of hyperinsulinaemia. In the setting of hyperinsulinaemia, the vasodilatory effect of insulin is lost, but its renal effect on sodium re-absorption is maintained. Thus, insulin resistance results in increased sodium reabsorption and heightened sympathetic activity, which together contribute to increase BP (Figure 2.6). Despite these mechanisms, it is unlikely that insulin resistance is the only underlying link (35). This is evident from epidemiological studies, in which a quarter of those with the metabolic syndrome did not have evidence of insulin resistance (193); conversely, studies among patients with insulin resistance found that fewer

than 50% of those with insulin resistance have evidence of the metabolic syndrome (193, 194).

2.5.3.b. Role of central obesity

Visceral obesity has been shown to be associated with insulin resistance, and circulatory levels of free fatty acids (Figure 2.7). Studies have shown that elevated levels of free fatty acids reduce peripheral uptake of glucose in skeletal muscle, and decrease insulin sensitivity. Furthermore, in the presence of insulin resistance, free fatty acids stimulate hepatic glucose production, and stimulate secretion of VLDL and apolipoprotein B. In addition, there is increased activity of hepatic lipase which catalyses the removal of lipids from LDL- and HDL-cholesterol, making them dense and small. In addition, increased adiposity is intrinsically linked with raised BP through activation of the RAS system in adipose tissue, and an associated increase in sympathetic nervous activity. Whilst these mechanisms can explain clustering of some of the metabolic components, not all patients with the metabolic syndrome have central obesity. This is because of several reasons. Firstly, central obesity and insulin resistance are not integrally related; there are significant numbers of people with normal weight and waist circumference, who are insulin resistant. Secondly, there is a difference between the metabolic effects of visceral and subcutaneous fat; whilst visceral adiposity would potentiate the clustering of metabolic components, subcutaneous adiposity is relatively metabolically inert. However, clinically, the metric of waist circumference does not differentiate between the two. Therefore, not all people with increased waist circumference have the metabolic derangements, consistent with the metabolic syndrome.

2.5.4. The clinical utility of the metabolic syndrome

The concept of the metabolic syndrome was developed to identify those who are at increased risk of developing CVD or type-2 diabetes. This was confirmed by the findings of several studies that have clearly shown metabolic syndrome to be an independent risk factor for CVD and diabetes. However, there are several issues surrounding the predictability of the metabolic syndrome:

Firstly (and perhaps most importantly), whether the metabolic syndrome predicts the risks of CVD and diabetes, independently of the influence of its constituent components. In Chapter 8 and 9, I have discussed several related aspects in details.

Secondly, whether there is a unifying pathophysiological basis of this concept. I have discussed this issue in section 2.5.3, concluding that there is no single concept that can robustly or consistently underpin the constellation of all metabolic risk components.

Thirdly, whether the metabolic syndrome is a clinical condition, and if so, is there any specific treatment. Metabolic syndrome is definitely not a clinical condition, as there is no definitive cause, nor a specific treatment. It also does not clearly trigger any therapeutic decision, which would be directly beneficial to the patient. Indeed, irresponsible labelling of metabolic syndrome as a clinical condition is a likely reason, why several bodies are against the use of this risk construct.

Finally, whether the diagnosis (label) of metabolic syndrome is useful in clinical practice. The answer to this question is likely to be yes, but only when it is used as a risk construct rather than a medical condition. There is reasonable body of evidence that the use of the

metabolic syndrome as a risk construct is able to identify patients at high risk of diabetes or CVD who would not be identified by other methods (see Chapters 8 and 9). As a risk construct, it is easier to use in routine clinical practice, and the label of the metabolic syndrome encourages initiation of proactive preventive strategies, that may in turn be able to positively affect the outcomes. The use of this label also may be helpful in targeting preventative strategies (e.g. lifestyle and dietary modifications) and, in certain cases, encourage early use of pharmacological interventions. Previous studies among high risk populations have shown that life-style modifications and/or pharmacological interventions can reduce or delay the incidence of diabetes (106, 195-200). Indeed, long term follow-up of some of these studies has shown that these lifestyle and pharmacological strategies are also able to reduce cardiovascular outcomes (111, 201, 202).

In summary, there are several important issues surrounding the clinical utility of the metabolic syndrome; however, pending their resolution either way, it is unwise to completely ignore the utility of the metabolic syndrome as a risk construct.

Chapter 2: Tables

Table 2.1 Potential mechanisms to explain diuretic-induced glucose changes

Mode of action	Mechanism of effect on glucose metabolism
1. Direct	a. Affect glucose-mediated calcium entry into beta-cell, and diminishes the ability to secrete insulin (147) b. In animal models, diuretic use may decrease peripheral utilization of the glucose by adipose tissues and skeletal muscles (139) c. Increases the hepatic glucose production (139, 148) d. Activation of renin-aldosterone , and sympathetic nervous system (146) e. Haemodynamic effect by decreasing the peripheral blood flow to muscle, and increasing the insulin resistance (131)
2. Indirect	a. Hypokalemia: affect the insulin secretion from the beta-cells in response to glucose stimuli (139, 146). b. Hypomagnesaemia (146)

Table 2.2 Probable mechanisms explaining the diabetogenic potential of the beta-blockers.

1. Increased body weight
2. Decreased peripheral blood flow, and uptake of glucose by skeletal muscle
3. Decreased insulin secretion
4. Increased glycogenolysis
5. Increased total peripheral insulin resistance
6. Decreased insulin clearance
7. Decreased adiponectin

Table 2.3 Mechanism explaining the protective effect against new-onset diabetes afforded by ACE inhibitors/ARB

1. Increased skin & muscle blood flow
2. Potassium retention
3. Protection of pancreatic islets from glucotoxicity
4. Removal of angiotensin II-related oxidase stress
5. Agonistic action on peroxisome proliferator-activated receptor gamma
6. Recruitment/differentiation of adipocytes
7. Increased GLUT 4 glucose transportation

GLUT: Glucose transporter

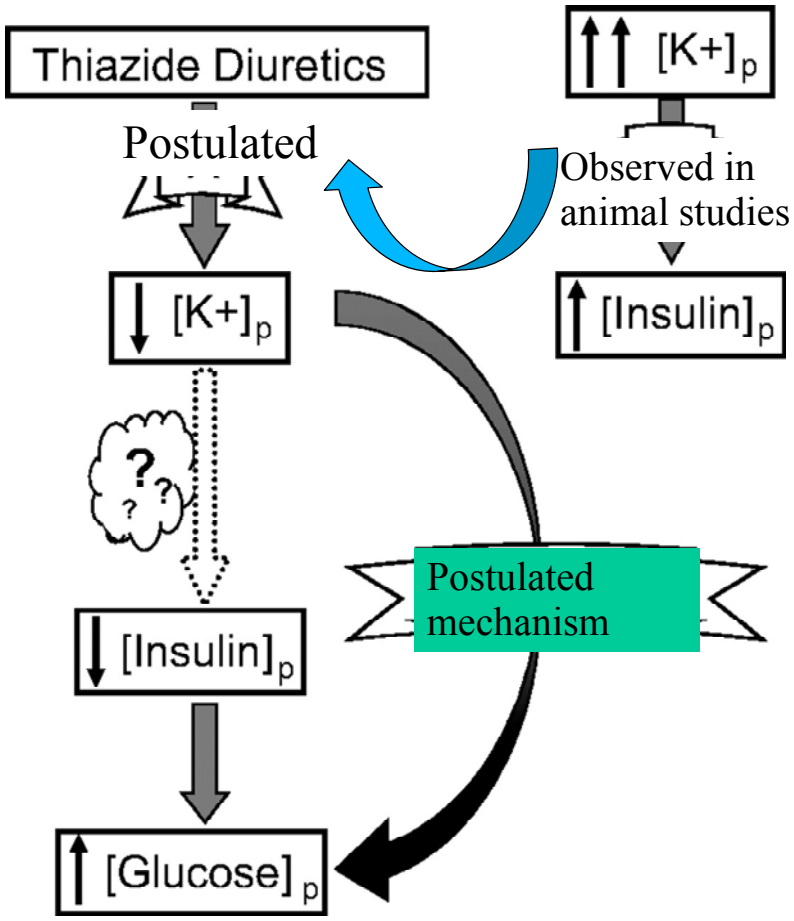
Table 2.4: Criteria proposed for defining the metabolic syndrome by various organizations.

Definition /Clinical measure	**WHO**	**EGIR** (only among non-diabetic population)	**ATPIII & updated ATP III)**(33)	**AACE**	**IDF**
Criteria: overview	1 essential plus any 2 of others	1 essential plus any two of the others	No essential, and any 3 of the others	1 essential plus any number of the others	1 essential plus any 2 of the others
Essential Criteria (if any)	IGT, IFG, T2DM or Insulin resistance plus	Hyperinsulinaemia >75th percentile for population plus	None	IGT or IFG plus	Increased WC (ethnic population specific) plus:
Other clinical measures	any two of the following excluding the essential criteria	any two of the following	Any 3 of the following	any of the following based on clinical judgment	any two of the following
Impaired glucose metabolism	Same as essential criteria (not included in others)	FPG≥6.1 mmol/L	FPG ≥ 6.1 mmol/l or treatment for diabetes (*Updated version 2004: FPG≥ 5.6 mmol/l or treatment of diabetes)*	IFT or IFG but not diabetes	FPG≥ 5.6 mmol/l (or diabetes)
Increased BMI and/or central adiposity	BMI >30 kg/m2 and/or : waist-to-hip ratio >0.90 (men) or >0.85 (women)	WC ≥ 94 cm (men) or ≥ 80 cm(women)	WC >102cm (men) or >88 cm(women)	BMI ≥25 kg/m2	Essential criteria: however, in absence of WC, BMI >30kg/m2 acceptable as essential criteria
Dyslipidaemia	Trig ≥1.7 mmol/l or HDL-cholesterol <0.9 mmol/l(men) or <1.0 mmol/L (women)	Trig ≥2 mmol/l Or HDL-cholesterol <1.0 mmol/L	Trig ≥1.7 mmol/l	Trig ≥1.7 mmol/l Or HDL-cholesterol <1.0 mmol/l (men) or <1.3 mmol/L (women)	Trig ≥1.7 mmol/l or treatment
			HDL-cholesterol <1.0 mmol/l (men) or <1.3 mmol/L (women)		HDL-cholesterol <1.0 mmol/l (men) or <1.3 mmol/L (women) or treatment
Increased blood pressure	>140/90 mm Hg	≥140/90 mm Hg and/or antihypertensive medication	≥135/85mm Hg and/or antihypertensive medication	≥135/85mm Hg	≥135 mm Hg systolic or ≥85mm Hg diastolic and/or antihypertensive medication
Others	Microalbuminuria: albumin excretion >20µg/min	nil	nil	nil	nil

EGIR, European Group for Study of Insulin Resistance; AACE, American Association of Clinical Endocrinologists; IDF, International Diabetes Federation; IGT, Impaired glucose tolerance; IFG, impaired fasting glucose; BMI, body mass index; WC, waist circumference; Trig, triglyceride; FPG, fasting plasma glucose

Chapter 2: Figures

Figure 2.1: Hypothesis for the relationship between thiazide-induced hyperglycaemia and hypokalemia [modified from Carter et al (146)].

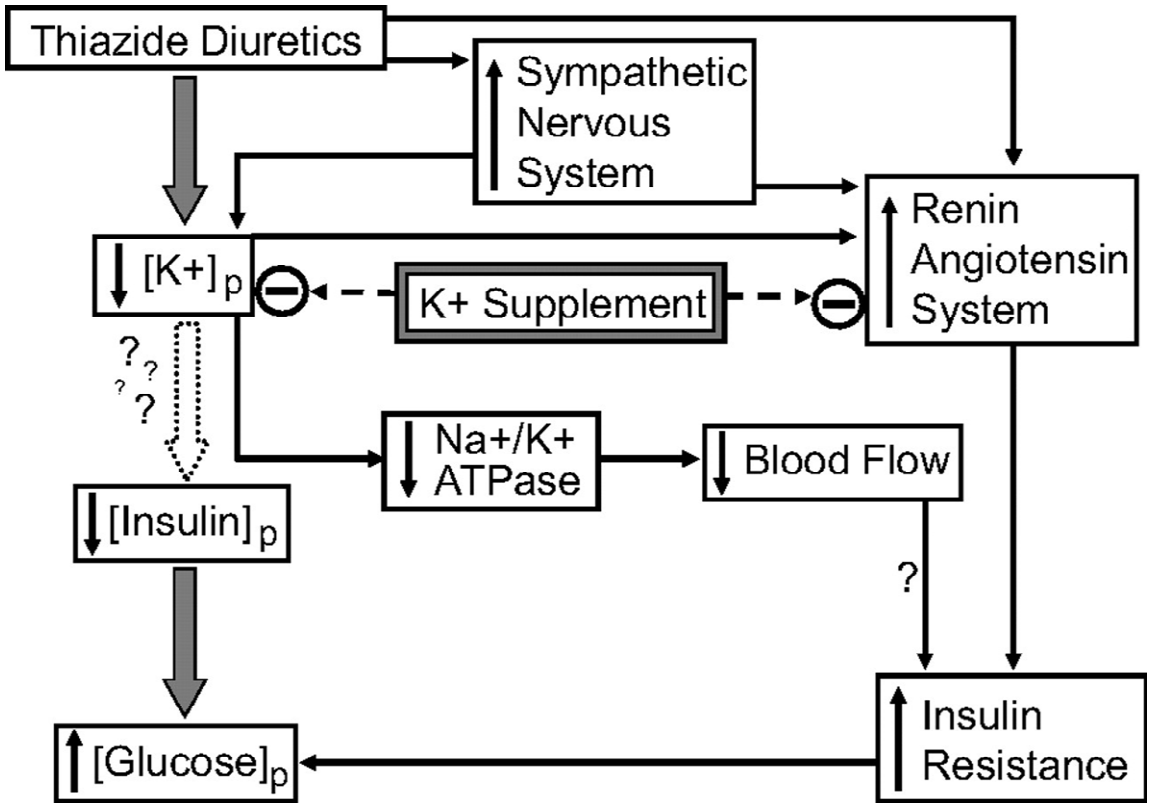


Modified from Carter B L et al. Hypertension 2008;52:30-36

K^+: potassium ; Na^+: sodium

Figure 2.1: Increased levels of serum potassium increases the secretion of insulin through ATP-sensitive potassium channels on the surface of beta-islet cells (146). These observations have been postulated to explain the observation that thiazide-induced hypokalemia may, conversely, diminish insulin secretion (in response to glucose stimuli) leading to a rise in blood glucose levels

Figure 2.2: Alternative pathways by which thiazide diuretics may cause hyperglycaemia [modified from Carter et al (146)].



Carter B L et al. Hypertension 2008;52:30-36

K^+: potassium ; Na^+: sodium

Figure 2.2: Thiazide diuretics may activate renin-angiotensin system either directly or via stimulation of sympathetic nervous system. This in turn worsens insulin resistance, and leads to increase in the blood glucose. These mechanisms are helped by other mechanisms, such as hypokalemia induced by diuretic use, or reduction in blood flow. Both of these directly or indirectly act to worsen insulin resistance.

Figure 2.3: Probable mechanism of adverse effects on glucose metabolism induced by the combination of the beta-blockers and diuretics among obese patients

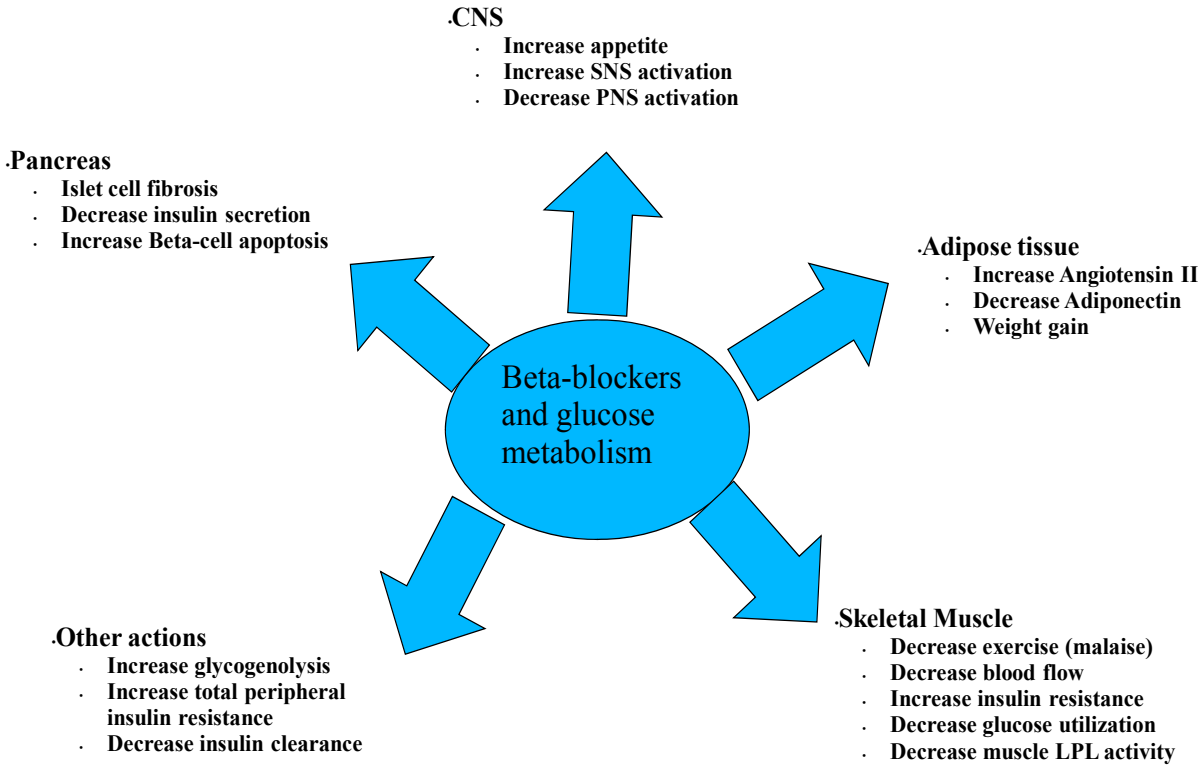


Figure 2.4 Physiological actions of insulin on glucose and lipid metabolisms

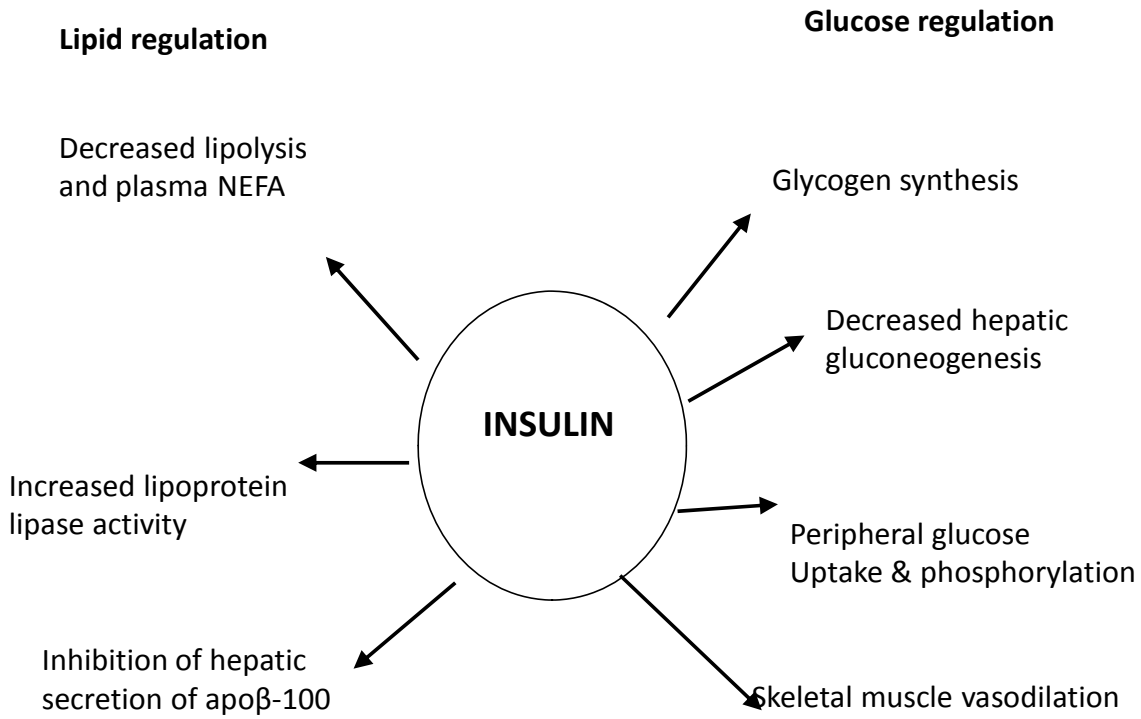
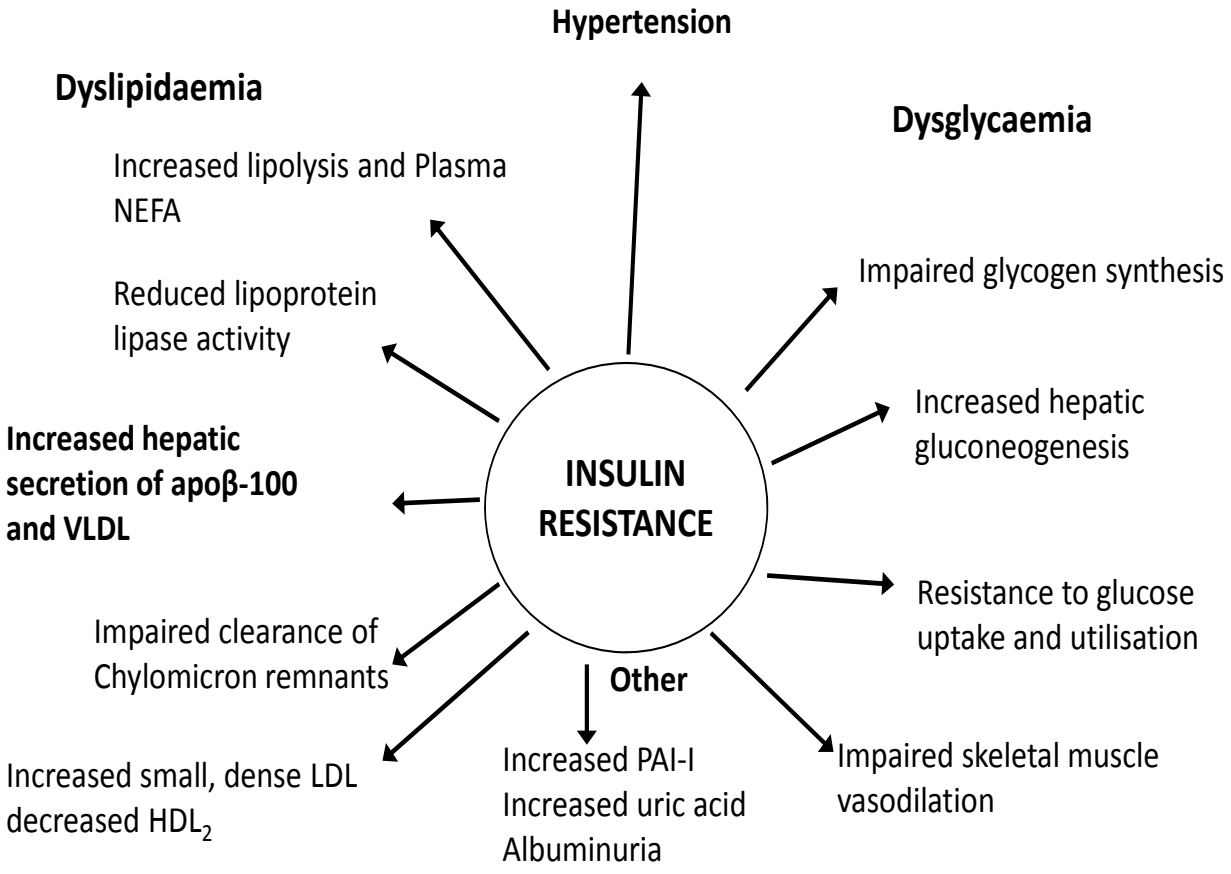
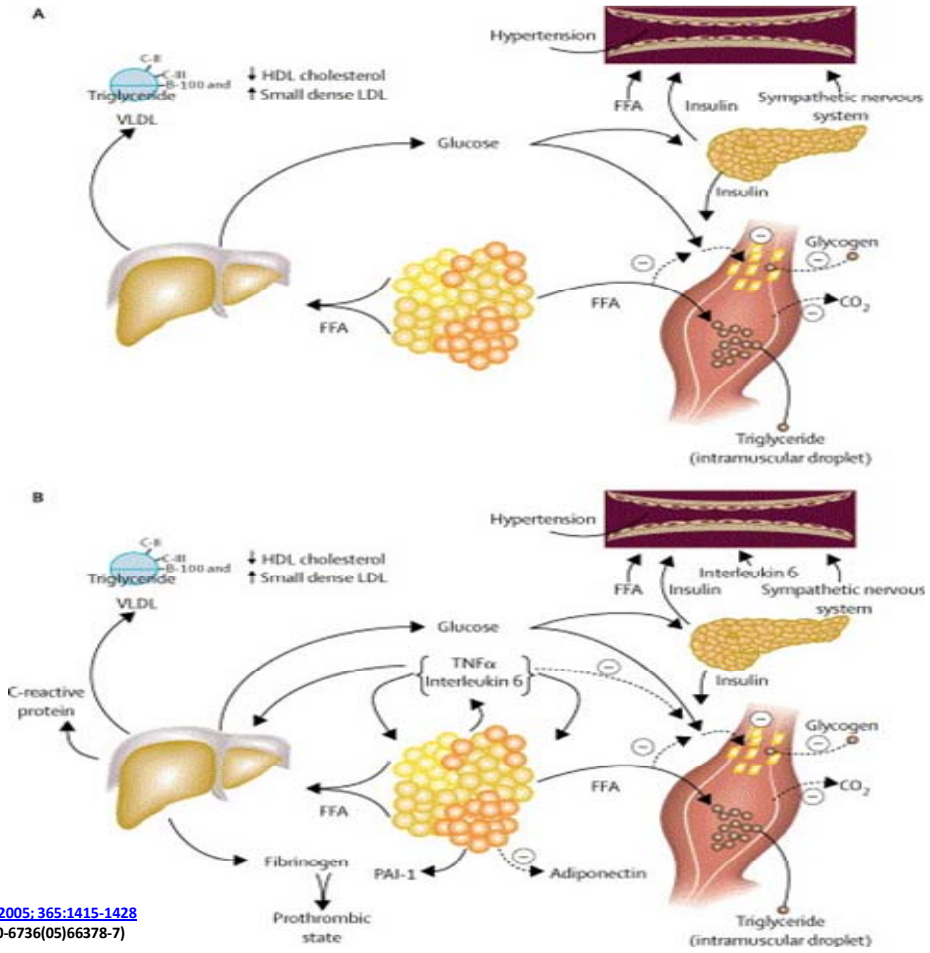


Figure 2.5 Pathophysiological actions associated with the development of insulin resistance.



NEFA = Non-esterified fatty acids; PAI-I = Plasminogen activator inhibitor

Figure 2.6 Pathophysiology of the metabolic syndrome: role of insulin resistance [Modified from Eckel et al (34)].

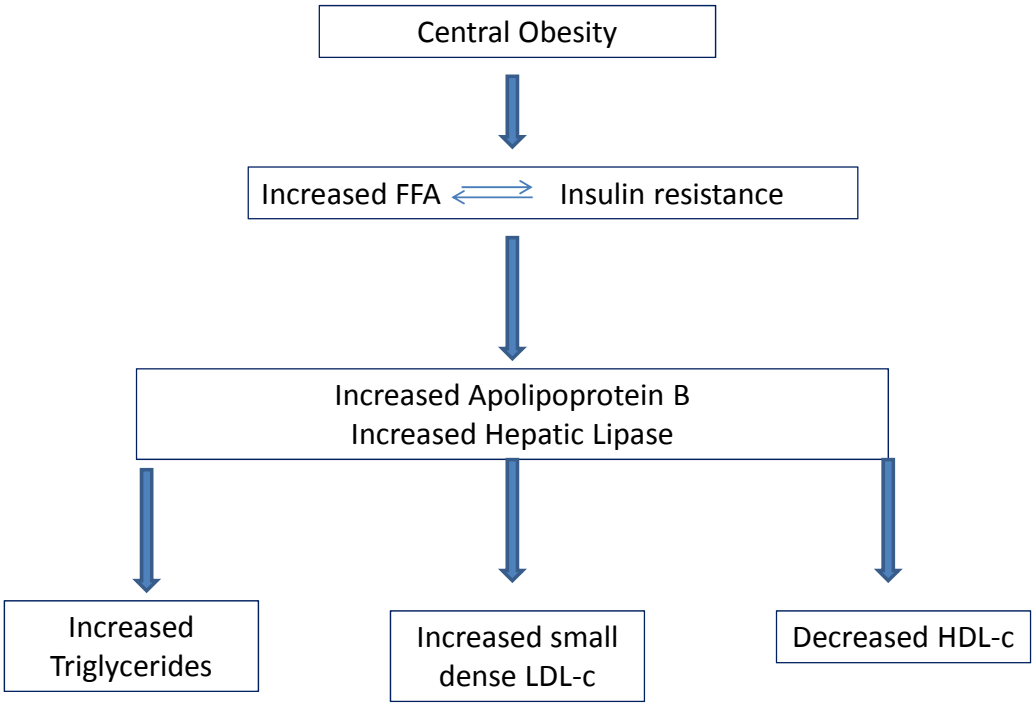


Source: The Lancet 2005; 365:1415-1428
(DOI:10.1016/S0140-6736(05)66378-7)

FFA: Free fatty acids ; VLDL: very low density lipoproteins ; HDL: high density lipoprotein cholesterol ; LDL: low density lipoproteins ; TG: triglyceride; SNS: sympathetic nervous system ; TNF-α: tumor necrosis factor alpha ; PAI1: plasminogen activator inhibitor 1

Figure 2.6: Prior to the obvious clinical manifestations of insulin resistance the inhibition of lipolysis by insulin – becomes deranged, which results in unchecked lipolysis an an excess of circulating free fatty acids into the circulation (34). This step is a circular process, because the excess free fatty acid decreases glucose uptake in skeletal muscle, thereby reducing insulin sensitivity, which in turn increases the circulation of free fatty acids. In the liver, excess free fatty acids increases hepatic glucose production and reduce the inhibition of gluconeogenesis by insulin. This results in increased circulating glucose and serum triglyceride levels and excessive secretion of very low density lipoproteins (VLDL). Increased systemic circulation of free fatty acids and glucose also induces pancreatic insulin secretion, causing a state of hyperinsulinaemia. In the setting of hyperinsulinaemia, the vasodilatory effect of insulin is lost, but its renal effect on sodium re-absorption is maintained. Thus, insulin resistance results in increased sodium reabsorption and heightened sympathetic activity, which together contribute to increase BP.

Figure 2.7 Relationship of central obesity with the components of the metabolic syndrome.



FFA: Free fatty acids ;; HDL: high density lipoprotein cholesterol ; LDL: low density lipoproteins

Figure 2.7: Visceral obesity is associated with insulin resistance, and circulatory levels of free fatty acids, which together may stimulate hepatic glucose production, and secretion of VLDL and apolipoprotein B. In addition, both increase in FFA and insulin resistance, are associated with increased activity of hepatic lipase which catalyses the removal of lipids from LDL- and HDL-cholesterol, making them dense and small. All of these mechanisms together results in increased triglycerides, and small and dense LDL-cholesterol, and decrease in HDL cholesterol.

Chapter 3

AIMS AND OBJECTIVES

Determinants of, and Outcomes Associated with Antihypertensive-associated Incident Diabetes and the Metabolic Syndrome in Hypertensive Patients in the ASCOT-Trial

Chapter 3: Aims and Objectives

3.1 My aims for this PhD are the following:

1. To compare the incidence of new-onset diabetes among those randomised to the two antihypertensive treatment regimens in the ASCOT-BPLA.

2. To determine the baseline predictors of new-onset diabetes among hypertensive patients randomised in the ASCOT-BPLA.

3. To assess the importance of antihypertensive therapy relative to other independent baseline predictors of new-onset diabetes.

4. To develop a risk score to identify those hypertensive patients at baseline, who are at highest risk of developing new-onset diabetes.

5. To evaluate the relationships between baseline FPG, CMG, and antihypertensive treatment allocation among hypertensive patients in the ASCOT-BPLA.

6. To determine the risk of CHD, stroke and death associated with baseline FPG, and CMG levels prior to events.

7. To determine if an increase in CMG from the baseline glucose level is associated with an increase in cardiovascular morbidity and mortality among hypertensive patients.

8. To determine if different antihypertensive treatment regimens differentially influence CMG levels at the end of the study.

9. To compare among those with normoglycaemia, impaired glycaemia and new-onset diabetes after one year of in-trial treatment, and those with pre-existing diabetes at randomisation, the subsequent risk of CHD, stroke and death.

10. To investigate whether there is a linear relationship between worsening levels of glycaemic status (normoglycaemia, impaired glycaemia, new-onset diabetes and pre-existing diabetes) and subsequent cardiovascular risk.

11. To evaluate among hypertensive patients whether the association between the metabolic syndrome and coronary events, stroke events, and all-cause mortality is independent of its constituent components.

12. To compare among hypertensive patients the association between 5 different definitions of the metabolic syndrome and coronary and stroke events and all-cause mortality, after adjusting for the constituent components of each definition.

13. To determine among hypertensive patients, whether the metabolic syndrome is a more accurate predictor of new-onset diabetes compared with IFG alone.

14. To determine whether the risk of new-onset diabetes associated with the metabolic syndrome is greater than the sum of the risk contributed by its constituent components.

15. To determine the role of metabolic syndrome to predict new-onset diabetes, among normoglycaemic hypertensive patients.

Chapter 4

THE ASCOT-BPLA:

STUDY DESIGN & RESULTS

The blood pressure lowering arm of the Anglo-Scandinavian Cardiac Outcomes trial (ASCOT-BPLA): the study design and the main results

Chapter4: The ASCOT-BPLA trial

4.1 Summary:

The blood pressure (BP) lowering arm of the Anglo-Scandinavian Cardiac Outcomes trial (ASCOT-BPLA) was a multi-centre, phase- IV clinical trial, that recruited hypertensive patients from the UK, Ireland and Nordic countries between February, 1998 and May, 2000 (48). All included patients were followed up for a median duration of 5.5 years, until the end of the study (June, 2005) or death (if earlier). The rationale, study design, study methods and main results of ASCOT-BPLA have been previously reported (47, 203), and further details can be found on the trial website (www. ascotstudy.org). In this chapter, a brief outline of salient aspects of the ASCOT-BPLA is presented, to provide supportive context to four studies in this dissertation.

4.2 ASCOT-BPLA: Rationale and Objectives

The rationale of the ASCOT-BPLA was based on several research questions that were in vogue during late 1980's and early 1990's. Primarily, there was insufficient evidence on safety and efficacy of newer antihypertensive agents, such as angiotensin-converting enzyme (ACE) inhibitors and calcium-channel blockers (CCBs). In addition, there was no available clinical trial evidence, comparing the efficacy of different combinations of antihypertensive agents. There was also a controversy over whether the use of 'older' antihypertensive medications, such as beta-blockers and/or diuretics (the standards at that time), is associated with less-than-expected benefits in coronary heart disease (CHD) prevention.

Objectives:

The primary objective of the ASCOT-BPLA was to assess and compare the long-term effects on non-fatal myocardial infarction [MI] (symptomatic and silent MI) and fatal CHD of the

standard antihypertensive regimen (atenolol adding a thiazide diuretic [bendroflumethiazide] if required [atenolol-based regimen]) with a more contemporary regimen (amlodipine adding an ACE inhibitor [perindopril] if required [amlodipine-based regimen]).

There were several other secondary and tertiary objectives, which compared the impact of the two antihypertensive treatment regimens (atenolol-based and amlodipine-based) on respective secondary and tertiary endpoints (see table 4.1 and section 4.3.2).

4.3 Methods:

4.3.1 Study design:

The ASCOT-BPLA trial was a multicentre, phase IV, randomized controlled clinical trial, which used the prospective randomised open blinded endpoints (PROBE) design to randomize 19,342 hypertensive patients to receive one of the two treatment regimens: atenolol-based or amlodipine-based regimen to achieve specified BP targets (defined as < 140/90 mm Hg for patients without diabetes, and < 130/80 mmHg for those with diabetes at baseline). In addition, using a 2X2 factorial design, a sub-sample of all randomized patients (with total cholesterol at baseline of < 6.5 mmol/L) were further randomized to receive either atorvastatin 10 mg or a placebo in the lipid-lowering arm of the ASCOT trial (ASCOT-LLA) (see Figure 4.1)

4.3.2: Outcomes:

The primary outcome of the ASCOT-BPLA was the time to first event of a combination of non-fatal MI and fatal CHD. However, there were several secondary outcomes, including fatal and non-fatal stroke (total stroke), all-cause- and cardiovascular- mortality and total

coronary events. A complete list of all the outcomes evaluated, including those which were termed as tertiary outcomes (such as new-onset diabetes) is provided in table 4.1.

4.3.3 Study participants

The patients were recruited from 686 family practices in the Nordic countries, and 32 regional centres in the UK and Ireland. Table 4.2 provides a complete list of inclusion and exclusion criteria for ASCOT-BPLA.

Briefly, patients with either untreated hypertension (systolic [S] BP ≥160 mmHg or a diastolic [D] BP ≥100 mm Hg) or previously treated hypertension (SBP≥140 mm Hg or DBP ≥90 mm Hg), aged 40-79 years, who had at least three of the following risk factors: male sex, age 55 years or older, microalbuminuria or proteinuria, smoking, ratio of plasma total cholesterol to high-density lipoprotein (HDL)-cholesterol of 6 or higher, or family history of CHD, type 2 diabetes, peripheral arterial disease, previous stroke or transient ischaemic attack were eligible for inclusion.

Exclusion criteria included current or past history of CHD, history of a cerebrovascular event within the previous 3 months, fasting triglycerides greater than 4.5 mmol/L, heart failure, uncontrolled arrhythmias or any clinically important haematological or biochemical abnormality on routine screening (48).

4.3.4 Study procedures

At an initial screening visit, patient eligibility was assessed and informed consent obtained. There was an initial run-in period, before randomization, of 2 to 8 weeks. At the randomisation visit, a detailed baseline clinical assessment, measurements of BP, weight and

height, and laboratory tests, including fasting plasma glucose and lipid profile, were carried out. Patients were then randomised to receive one of the two treatment regimens.

Follow-up: All patients were routinely followed up as per schedule until the end of the study (or death). Follow-up visits were at 6 weeks, 3 months and 6 months after randomization and thereafter, every six monthly. Extra visits were allowed in addition to the scheduled visits, if clinically warranted. At each follow-up visit, anti-hypertensive drug therapy was up-titrated to achieve target BP and information was recorded about adverse events and any new cardiovascular event or procedure, including the cause for any hospital admission.

Fasting blood samples for glucose and lipid profile, and also (but not necessarily) for other routine investigations such as serum electrolytes, serum creatinine and, if allocated to a lipid lowering arm, for liver enzymes, were collected at a screening, randomisation, 6 month and 12 month visits and thereafter, annually.

Study medications and BP-treatment algorithm: Antihypertensive treatment was initiated, by random allocation, with either amlodipine or atenolol, to which either perindopril or bendroflumethiazide +potassium supplement, respectively were added to achieve the target BP. The treatment sequence, doses used and add-on therapy (doxazosin-gastrointestinal transport system [GITS]) of the two antihypertensive regimens are shown in Table 4.3.

4.3.5 Study organisation, structure, and data storage

Two co-ordinating centres, in London and Gothenburg, were responsible for the overall management of the trial in UK/Ireland and the Nordic countries respectively. An independent international steering committee was responsible for the scientific conduct and publication of

results, with a smaller executive committee and working group responsible for day-to-day decisions. The study conformed to good clinical practice guidelines and was done under the guidelines of the Declaration of Helsinki. The protocol and all subsequent amendments to the protocol were reviewed and ratified by central and regional ethics review boards in the UK and by the national ethics and statutory bodies in Ireland and the Nordic countries. The Scandinavian coordinating centre coordinated central data management and analyses, including data cleaning. All submitted information on any potential endpoints was reviewed independently by the members of the endpoint committee, who were unaware of treatment assignment.

4.3.6 Recruitment period and the trial closure.

Patients were recruited between February, 1998, and May, 2000. In October, 2004, the data safety monitoring board recommended that the trial should be stopped on the grounds that there were significant differences in the mortality rates between those allocated to the two treatment groups. This recommendation was accepted by the steering committee, and between December 2004 and June 2005 the trial physicians recalled all patients for a final end-of-study visit. The database was formally closed in the end of June, 2005.

4.4 Main results

Figure 4.2 shows the trial profile of the ASCOT-BPLA. There were 19,257 evaluable patients, who were followed up for a median duration of 5.5 years (a total of 106,153 person years of observation).

Coronary outcomes: Compared with those allocated to atenolol-based therapy, those allocated to amlodipine-based therapy had fewer primary endpoint events (non-fatal MI +

fatal CHD); however, the difference in event rates was not statistically significant (474 vs. 429; unadjusted hazard ratio [HR], 0·90, 95% CI [0.79 to 1.02]), p=0·105) (Figure 4.3). When the time to first event of coronary revascularisation was combined with the other components of the primary outcome (as a post-hoc outcome), the amlodipine-based treatment regimen, compared with the atenolol-based treatment, was associated with a 14% significant reduction in the risk of coronary events or procedures (i.e. combined outcome of non-fatal MI plus fatal CHD plus coronary procedures) (0.86 [0.77 to 0.96]).

Secondary and tertiary outcomes: Comparisons were made of event rates between the two treatment regimens for other pre-specified secondary and tertiary outcomes. Patients allocated to amlodipine-based therapy (compared with those allocated to atenolol-based therapy) had significantly lower rates of fatal and non-fatal stroke (327 vs. 422; 0·77 [0·66 to 0·89]), total cardiovascular events and procedures (1362 vs.1602; 0·84 [0·78 to 0·90]), and all-cause mortality (738 vs. 820; 0·89 [0·81 to 0·99]) (Figure 4.3 and Figure 4.4). In addition, the risk of developing new-onset diabetes was significantly lower among those allocated to amlodipine-based regimen, compared with those allocated to atenolol-based regimen (see chapter 6 for details). Of note, the significant differences in the risk of cardiovascular and coronary events and death, between those allocated to the two treatment regimens were also apparent across all sub-groups of patients, including those groups stratified on the basis of gender, age and presence of co-morbidities, such as diabetes (Figure 4.5).

Limitations: An important criticism of the ASCOT trial is that it randomized a selective population of hypertensive patients (due to inclusion criteria of presence of 3 or more cardiovascular risk factors (48)), and therefore its findings may not be representative of the general hypertensive population. However, the majority of patients in the ASCOT were

recruited from general practices, and are fairly typical of the patients seen routinely. For example, the two most common inclusion (cardiovascular risk factors) criteria in the ASCOT were male gender and age >55 years (see table 4.4). These two characteristics are also the commonest prevailing characteristics amongst the treated hypertensive population in the community. For example, in the Health Survey of England (HSE), 1998, 88% of treated hypertensive subjects had age> 55 years (table 4.4). Therefore, the findings derived from the ASCOT analyses are likely to be applicable to the majority of the patients in the community. However, having said that, there are several obvious differences when characteristics of previously treated hypertensive patients in the ASCOT are compared with those treated in the community using HSE 1998 database (table 4.4 and 4.5). Compared to treated hypertensive patients in the community, those in the ASCOT were more likely to be male, with increased BMI, total cholesterol and serum triglycerides, and with a significantly higher proportions of those with pre-existing diabetes or current smoking; however, the ASCOT population (vs. HSE sample) was younger, with lower systolic and diastolic BPs, and with a lower prevalence of those with history of a previous vascular disease (and none with a history of previous coronary disease) (table 4.4 and table 4.5). Indeed, this variable distribution of the risk factors argues against another criticism of the ASCOT findings: that underlying cardiovascular risk of patients in the ASCOT is much higher compared with those treated in the community. Whilst, in the ASCOT population there was a higher proportions of a few cardiovascular risk factors (current smoking, increased lipids and pre-existing diabetes); the prevalence of a few other (and perhaps more important) risk factors (such as increasing age, presence of previous vascular disease, and increased BP's) was significantly lower. This variable distribution of the risk factors amongst those in the ASCOT, as compared with those in the community in the HSE (1998), may offset some of the excess risk, and may bring the overall cardiovascular risk of the ASCOT population closer to that of the treated hypertensive

patients in the community. Indeed this is clearly evident when the observed mortality rates in the ASCOT are compared with those in the other hypertensive trials, such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (204) and the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial (157); with the mortality rates in the ASCOT trial being much lower than the latter two trials, and more similar to the mortality rates seen amongst hypertensive patients in the community (205).

4.5 Conclusions

The findings of the ASCOT-BPLA trial suggest that the allocation to the amlodipine-based regimen, compared with the allocation to the atenolol-based regimen, is associated with a significant reduction in the risk of coronary and stroke events, and has important survival benefits. The significant differences in the event rates between those allocated to the two treatment groups cannot be explained on the basis of a small mean SBP-difference (2.8 mm Hg) between the two treatment groups (with mean SBP lower among those allocated to amlodipine-based treatment, compared with those allocated to the atenolol-based treatment). Therefore, it is likely that there are other reasons (including differential risks of new-onset diabetes) that may have resulted in the differences in event rates among those allocated to the two BP-treatment regimens, and this needs further evaluation.

Table 4.1 The pre-specified end points of the ASCOT-BPLA

Primary endpoints	
	Non-fatal Ml (including symptomatic and silent) + fatal (CHD)
Secondary endpoints	
	1) Non-fatal Ml (symptomatic only) + fatal CHD 2) All-cause mortality 3) Cardiovascular mortality 4) Fatal and non-fatal stroke 5) Fatal and non-fatal heart failure 6) Total coronary endpoints = fatal CHD + non-fatal Ml (symptomatic and silent) + chronic stable angina + unstable angina + fatal and non-fatal heart failure 7) Total cardiovascular events and procedures (a combination of cardiovascular mortality + non-fatal Ml (symptomatic and silent) + unstable angina + chronic stable angina + life threatening arrhythmias + silent non-fatal heart failure + non-fatal stroke + peripheral arterial disease + revascularization procedures, and retinal vascular thrombosis.
Tertiary endpoints	
	1) Silent Ml 2) Unstable angina 3) Chronic stable angina 4) Peripheral arterial disease 5) Life threatening arrhythmias (ventricular fibrillation or sustained ventricular tachycardia or complete heart block) 6) Development of diabetes mellitus 7) Development of renal impairment

Table 4.2 The inclusion and exclusion criteria for the ASCOT-BPLA

Inclusion criteria (Any 3 of the following)	**Exclusion Criteria (Any one of the following)**
1. Current smoking 2. Diabetes 3. LVH 4. Peripheral vascular disease 5. ECG abnormalities 6. History of early CHD in first degree relative 7. History of cerebrovascular event 8. Age > 55 years 9. Male sex 10. Microalbuminuria or proteinuria 11. Plasma TC/ HDL ratio $\geq$ 6	1) Any contraindications to, or previous history of, major intolerance to dihydropyridine CCBs, ACE inhibitors, alpha-blockers, thiazide diuretics, doxazosin, or statins. 2) Secondary hypertension. 3) Malignant hypertension. 4) Previous clinical MI or currently treated angina pectoris. 5) Stroke, transient ischemic attacks, or cerebrovascular surgery, three months before study onset. 6) Patients requiring CCBs, ACE-inhibitors, alpha-blockers or diuretics for concomitant diseases or conditions. 7) Fasting serum-triglycerides > 4.5 mmol/l. 8) Patients requiring other drugs which are also prescribed for hypertension (e.g. alpha-blockers for prostatism). 9) Second or third-degree A-V block. 10) Clinical congestive heart failure (NYHA II ± IV). 11) Uncontrolled arrhythmias. 12) Concomitant clinically important haematological, gastrointestinal, hepatic (liver function test (ALT)> 3X upper normal level), renal (serum creatinine>200 μmol/l), or other disease which, in the opinion of the investigator, will interfere with the treatment or the patient's ability to complete the study. 13) A history of alcoholism, drug abuse, psychosis, antagonistic personality, poor motivation or other emotional or intellectual problems that are likely to invalidate informed consent, or limit the ability of the subject to comply with the protocol requirements. 14) Participation in any other studies involving investigational or marketed products within 1 month prior to entry into this study or concomitantly with this study. 15) Pregnant or lactating women and those of child-bearing potential (i.e. pre-menopausal without appropriate contraception).

Table 4.3: Blood pressure treatment algorithm of the ASCOT Trial.

ASCOT-Trial	**Antihypertensive Treatment Algorithm**	
Titration Step	***Amlodipine-Based Regimen***	***Atenolol-Based Regimen***
Step 1 (initiate)	Amlodipine 5 mg OD	Atenolol 5 mg OD
Step 2 (up titrate)	Amlodipine 10 mg OD	Atenolol 100 mg OD
Step 3 (add)	Perindopril 4 mg OD	Bendroflumethiazide/K^+ 1.25 mg OD
Step 4 (up titrate)	Perindopril 8 mg OD	Bendroflumethiazide/K^+ 2.5 mg OD
Step 5 (add)	Doxazosin gastrointestinal therapeutic system (GITS) 4 mg	
Step 6 (up titrate)	Doxazosin GITS 8 mg OD	
Step 7 (add)	Another (non-study) antihypertensive agent at investigators discretion (ideally from list of suggested drugs including spironolactone, moxonidine)	

K+: with potassium supplement

Table 4.4: Comparison of the prevalence of cardiovascular risk factors among treated hypertensive patients in the ASCOT trial, and among those in the Health Survey of England, 1998.

Inclusion cardiovascular risk factors in risk profile	ASCOT (n=15,491) (%)	HSE 1998* (n=439) (%)
Male (%)	76.4	41.2
Age ≥ 55 years (%)	64.6	87.7
History or presence of peripheral vascular disease (%)	6.6	Not available
History or presence of diabetes (%)	25.4	12.1
Micro-albuminuria/Proteinuria (%)	61.5	Not available
Current smoker† (%)	28.2	15.0
Ratio of total cholesterol/HDL cholesterol > 6 (%)	24.6	13.7
Previous history of CVD (%)	12.1	28.2‡
Family history of CHD (%)	26.0	20.3**
Presence of left ventricular hypertrophy (%)	12.9	Not available
Presence of other ECG abnormalities (%)	14.9	Not available

* Health Survey of England,1998 was chosen as a community compactor for the ASCOT patients characteristics, as in the ASCOT patient recruitment commenced during same time.
† Current smoking in the ASCOT was defined as any evidence of smoking in recent months, whereas current smoking in the HSE was defined as do you smoke?
** In HSE, family history also included history of stroke in addition to CHD.

Table 4.5: Comparison of baseline characteristics among previously treated hypertensive patients in the ASCOT and in a sample of Health Survey of England,1998,

Baseline characteristics	ASCOT (n=15,491) Mean (SEM)/ %	HSE 1998* (n=439) Mean (SEM)/ %
Age (years)	63.3 (0.07)	66.3
Weight (Kg)	84.7 (0.12)	73.3 (1.18)
BMI (Kg/m2)	28.9 (0.04)	26.4 (0.49)
Total cholesterol (mmol/L)	5.9 (0.01)	4.3 (0.16)
HDL-cholesterol (mmol/L)	1.3 (0.00)	0.8 (0.05)
Alcohol (units/week)	8.2 (0.10)	9.0 (0.63)
Systolic BP (mm Hg)	162.0 (0.14)	173.3 (0.74)
Diastolic BP (mm Hg)	93.4 (0.08)	90.6 (0.60)

* Health Survey of England,1998 was chosen as a community compactor for the ASCOT patients characteristics, as in the ASCOT patient recruitment commenced during same time.

Figures: Chapter 4

Figure 4.1 The ASCOT-BPLA trial design

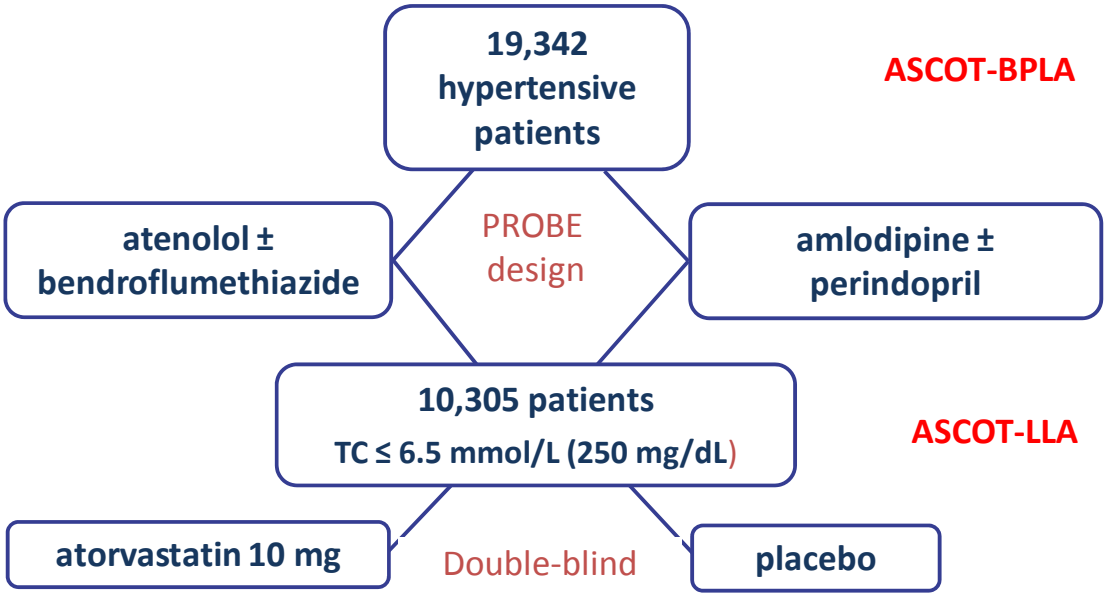


Figure 4.2 The ASCOT-BPLA trial profile

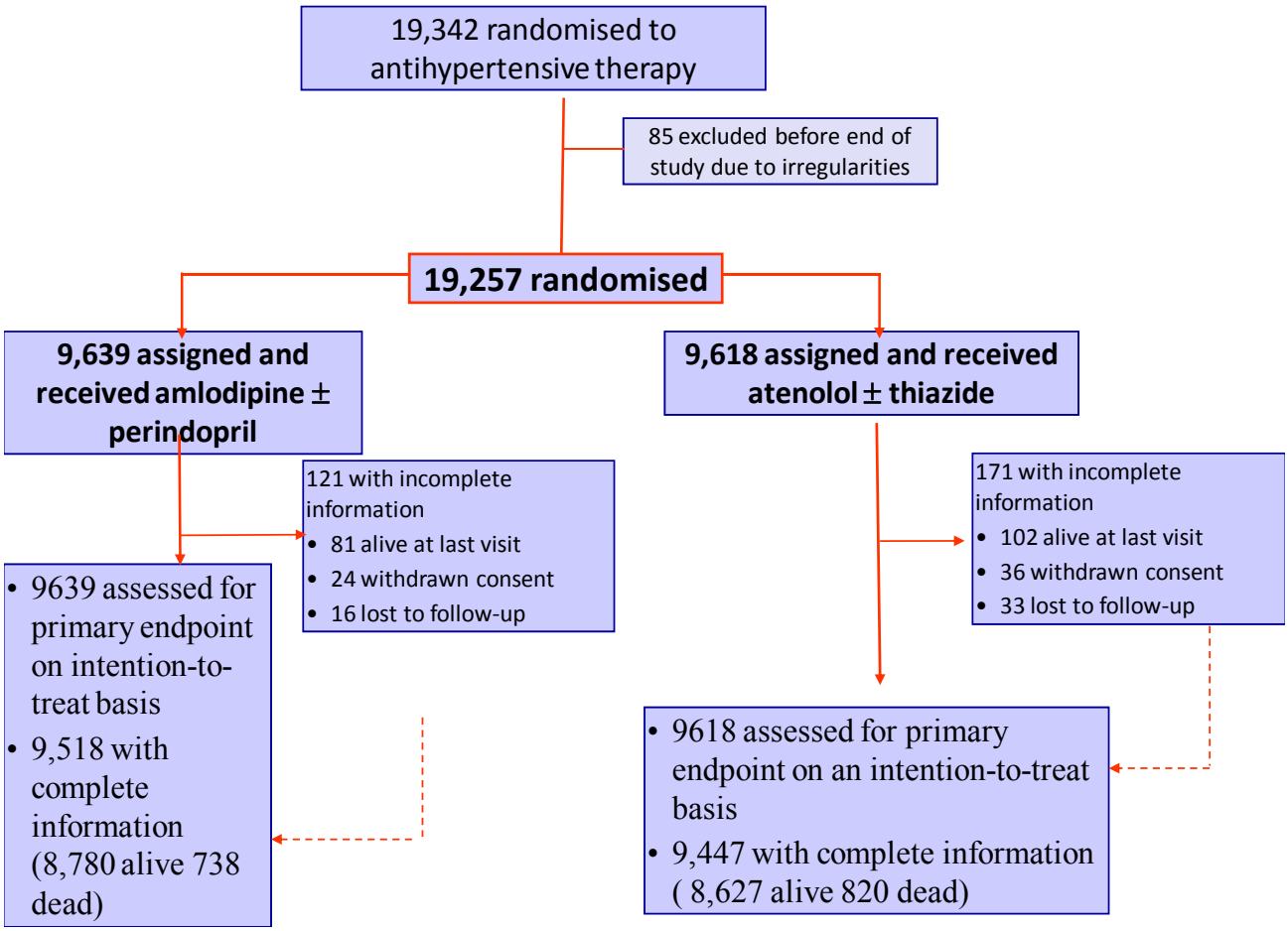


Figure 4.3 Kaplan Meier plots for the primary outcome, stroke and all-cause mortality in the ASCOT-BPLA

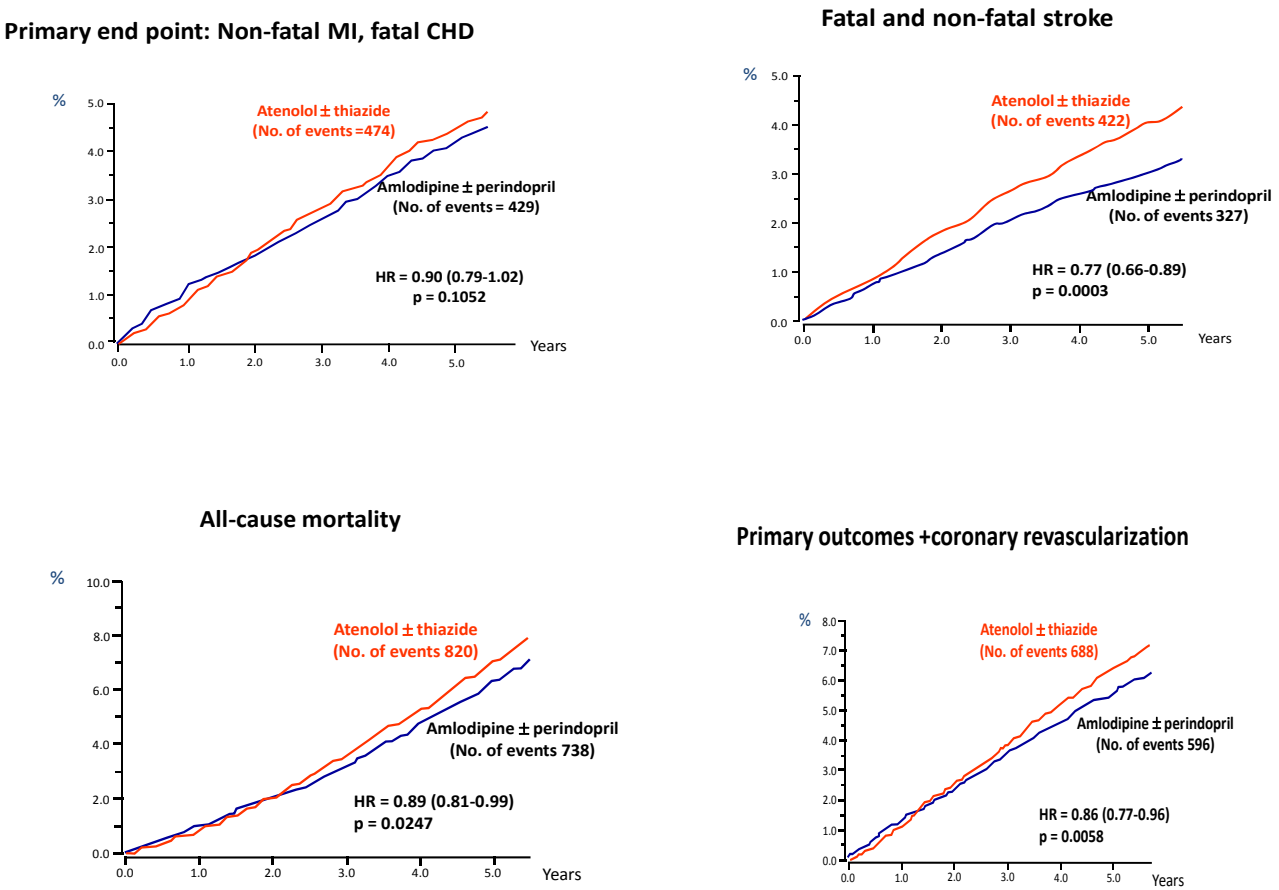


Figure 4.4 Hazard ratios associated with the allocation to amlodipine-based therapy, compared with allocation to atenolol-based therapy, for all pre-specified endpoints of the ASCOT-BPLA

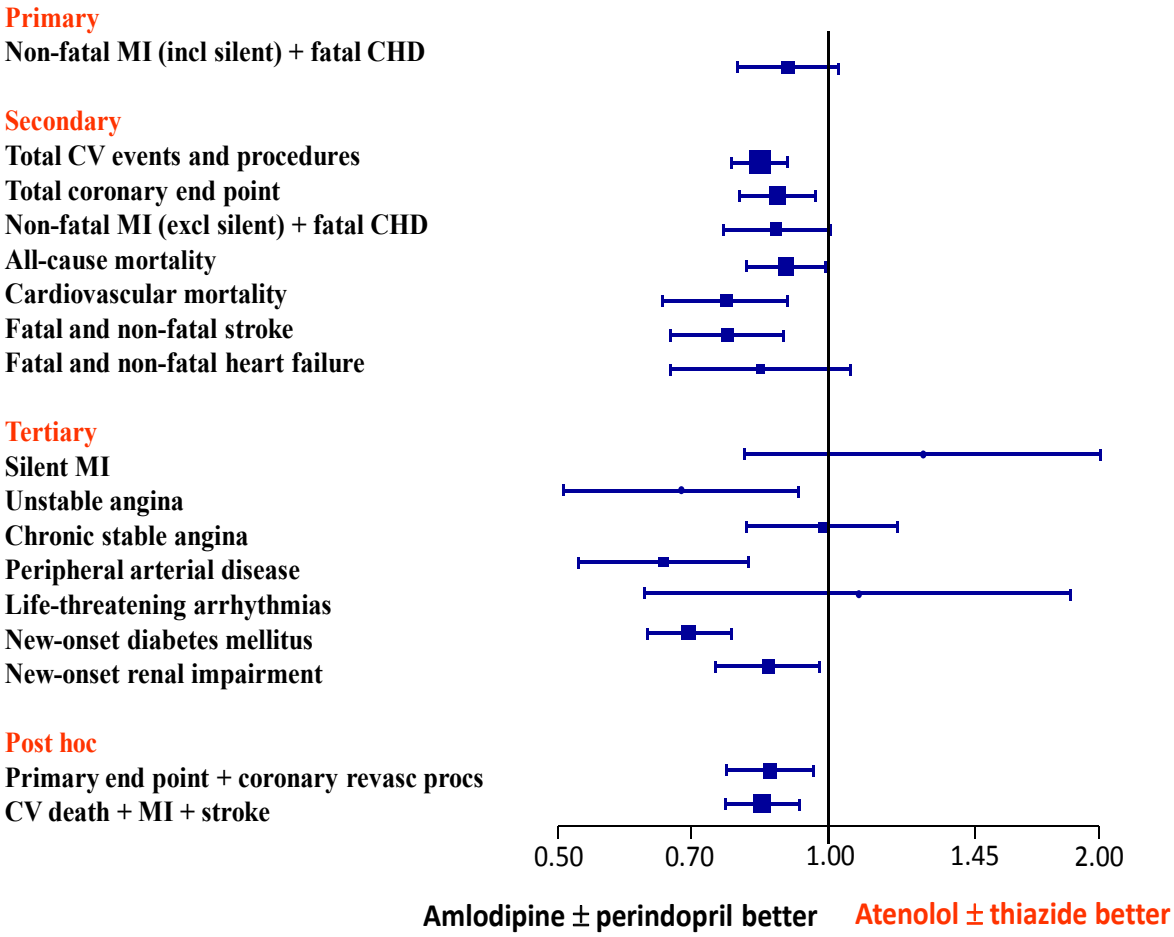
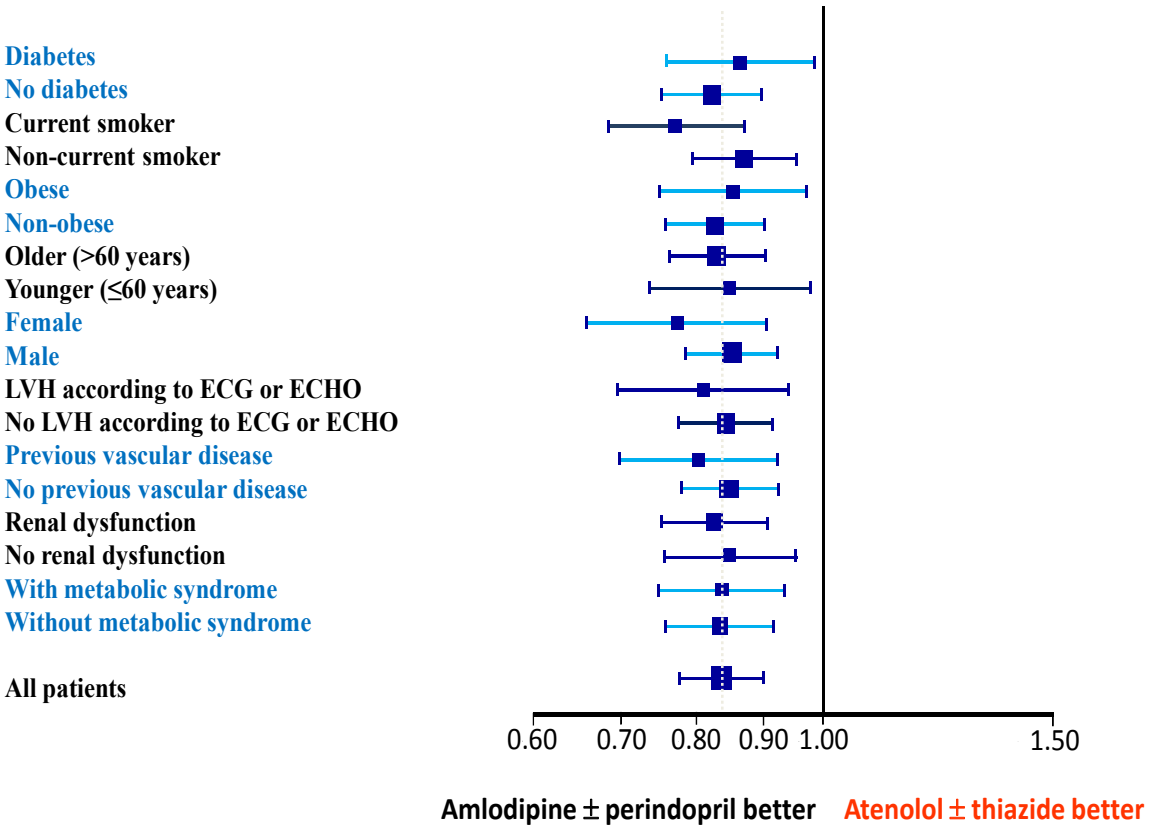


Figure 4.5 Total coronary events associated with allocation to amlodipine-based therapy, compared with the atenolol based therapy, stratified by the sub-groups of the patients in the ASCOT-BPLA



Chapter 5

STATISTICAL METHODS

Overview of statistical methods used

Chapter 5: Statistical methods

5.1 Summary:

Details of the statistical methods used in the four studies in this dissertation are included in their respective chapters (Chapters 6 to 9). In this chapter, I summarise how missing values were dealt with in the ASCOT-BPLA database and describe in more detail the statistical methods used in the subsequent chapters.

5.2 Missing values in the ASCOT-BPLA database

Of the 19257 evaluable patients in the ASCOT-BPLA database there was very little missing baseline data. For example, only 10, 2, and 1 subject had missing baseline values for weekly alcohol intake, years of education, and smoking, respectively. This tiny amount of random missing information does not have any impact on subsequent analyses. However, approximately 10% of all randomized individuals did not have fasting values for plasma glucose and/or fasting serum triglycerides at baseline. For the purposes of my analyses, these individuals were labelled as having missing values for plasma glucose and/or serum triglyceride. Since, the total number of patients with one or more missing baseline values was relatively small it was decided not to impute any values in the subsequent analyses. However, to exclude any possibility of selection bias, baseline characteristics of those with any missing (or non-fasting) values were compared with those with no missing (or non-fasting) values, in each of the analyses.

5.3 Model development: an overview

Cox proportional hazard models (206) were predominantly used in these analyses. This enabled me to relate explanatory variables (risk factors) to outcomes of interest using time to first event data. The advantage of using Cox models for survival analyses is that they are

unaffected by underlying event rates. However, they do make the assumption that the event rates for a patient sub-group remains proportional over the period of follow-up.

In the analyses described in Chapters 6 to 9, I have used the following approach to developing a primary (final) Cox regression model. Firstly I identified a base model, which included a priori confounding variables (such as age, sex, and ethnicity) and if required, a pre-specified covariate (the latter was only included in the model, if clinically relevant). Secondly, additional explanatory variables were added to this base model if they were found to be independent predictors, clinically relevant and/or improved the predictability of the model. These additional variables were identified, using forward or backward stepwise methods, and/ or on the basis of the findings of separately developed univariate models. Thirdly, the influence and added value conferred by the addition of each one of these potential explanatory variables to the base model was assessed, by comparing the base model with and without the variable of interest, using the likelihood ratio test (LRT).

If there was a significant correlation between the two identified explanatory variables, only one of them was added to the base model. The choice was made on the basis of the perceived clinical significance of the variable and the strength of its association with the outcome. In the case of co-linearity existing between a potential explanatory variable and a variable in the base model (i.e. a priori confounders or pre-specified covariate), the latter variable was retained in the model. The linearity of the relationship between the continuous explanatory variables and the risk of developing the outcome of interest was assessed using standard methods. If found to be non-linear, continuous variables were categorised using clinically relevant grouping/cut-offs (for example, alcohol intake was categorised as per published criteria for men and women). If such data was not available, then statistical techniques were

used to categorize the variable into appropriately balanced groups, based on the number of subjects or events (for example, quartiles or deciles). In a few cases, when a continuous variable showed evidence of non-linearity only at extreme values, the variable was retained as a continuous variable in the model, and an appropriate cut-off value was used to account for non-linearity at its extreme end.

In each primary model, the proportional hazards assumption was assessed both graphically and by using Schoenfeld residuals (207, 208). If the relationship between a variable and the outcome was found to be non- proportional, the reasons for non-proportionality were assessed using standard techniques.

Logistic regression models were developed in a similar way to the Cox models (as described above). Logistic regression models were developed for sensitivity analyses to ascertain the validity of output of the primary Cox model. In addition logistic regression models were developed if there were issues regarding the validity of the proportionality assumption in the final model. For example, if a variable in the model had a non-proportional relationship with the outcome of interest, but the overall model did not violate the proportionality assumption on global testing. In such cases, a logistic regression model with a log of time period of follow-up as a covariate was developed to compare the output of the primary Cox model with that of the logistic regression model. I have also used bootstrapping method to assess the internal validity of the model. For this, I used STATA command ‘bootstrap’ with 100 repetitions and either default (i.e. 100%) or 80% sampling frame (i.e. the number of sampled observations from the total study population). This technique makes no assumptions about the probability distribution of the outcome, and mimics the way the study data was sampled from the population frame, for example, for each new repetition a new sample is drawn with

replacement from the original (specified) data. Therefore, each repetition sample differs from other and these samples cumulatively are able to provide a mean confidence interval and standard errors, which reflects closely the population in the community (i.e. population frame) that the study population is derived from.

5.4 Risk estimation and risk score

The risk score for each patient was determined from the primary model by summing the products of the β coefficients derived from the primary model and the actual values of the variables in the model. β-coefficients for the continuous models were estimated using clinically relevant definitions for 'a unit increase' in the variable, instead of the conventional use of increase in per standard deviation (i.e. measures of spread). This was done as the risk score component contributed by continuous variable is unaffected by the definition of the unit's used, since the risk score contribution is product of corresponding β coefficient and the value of the variable divided by the unit used. The estimated probability of the outcome of interest after 5 years was estimated using the formula $1\text{-}S_o \exp^{(\text{risk score})}$. In this equation S_o is the baseline survival at 5 years and risk score is the sum of the product of β-coefficients derived from the Cox regression model and the value of the variables in the model ($\sum \beta_i X_i$). These risk scores were converted into 'user-friendly' integer scores by rounding the exact β coefficient derived from the final Cox model.

5.5 Assessment of model performance

Performance of the prediction models, particularly those used for risk estimation were assessed using well described criteria, including model discrimination and calibration (209-214) and are described in more detail below.

5.5.1 Measures of discrimination

The discriminative ability of a model is its ability to correctly identify those who will and will not develop the outcome of the interest during the specified period of observation. In chapters 6 and 9, I have used an observation period of five years to assess the discriminative ability of the risk prediction models. This period was chosen because the median duration of follow-up in the ASCOT-BPLA was 5.5 years. In my analyses, I have used several methods to assess the discriminative ability of the risk prediction models, including the area under the receiver-operating characteristics(a ROC) curves (215), Harrell's c-statistics, and integrated discrimination improvement (IDI).

The aROC is one of the most commonly used statistics, and is defined as a plot of sensitivity on the vertical axis against the plot of specificity on the horizontal axis (216). Mostly, aROC is used to assess the performance of a diagnostic test that has a binary response (yes or no), against the gold standard test. The value of aROC ranges from 0 to 1. A value of 0.5 equates to chance, and a value of 1 indicates perfect discrimination. A version of this statistical method also extends to survival analysis (215, 217), and that method was used in these analyses. However, even a modified version of this statistic, a ROC, is not without its limitations. Several studies have shown that, at times, a clinically important, independent risk factor may fail to reliably increase the value of aROC, despite increasing the predictability of the model (218).

In survival analysis, analogous to aROC is another statistics, Harrell's C-statistics (219, 220). This was used in two of the studies described in this dissertation (Chapters 6 and 9) to compare the discriminative ability of the models. The c-statistics describes the probability of concordance given similar comparability, where a pair of subjects is defined as concordant if their predicted survivor probability and survival times are in the same direction. A pair of

subjects are comparable if it can be determined (from the prediction model) which one survived longer. However, the use of this method will mostly favour the data from which it is derived, and therefore this statistic is prone to bias. Because of that, I have used bootstrap resampling (100 repetitions) to derive bias- corrected estimates of Harrell's C discrimination index, wherever needed or required.

In comparison to the aforementioned techniques, net reclassification improvement (NRI) and IDI are relatively new methods to assess and compare the discriminative ability of the risk models (221). NRI determines the proportion of individuals who are correctly reclassified into those who do and do not have an event over the period of observation, when a new function (bio-marker) is added to a risk model. In comparison, IDI is calculated by subtracting the average risk of an event among those with and without an observed event, separately for the two models, and then calculating the difference between the two models. The values of NRI and IDI are between 0 and 100%, and 0 and 1, respectively. The higher values of these indices imply a better performance of the model with a new function. I have used a modification of IDI(221) in the analyses described in Chapter 9. I have estimated 5-year-risks (probabilities) of developing an event predicted by each of the two models, and then calculated their respective risk difference (5-year- risk assigned by the model A minus that assigned by the model B). The calculated risk differences of subjects were further stratified by their respective observed 5-year outcome status (did and did not develop the event). If the observed status was the development of an event, the model which assigned a higher predicted risk was deemed to be better (i.e. the predicted risk was closer to the observed outcome), whereas, if there was no observed event (after 5-years), the model assigning a lower baseline risk was deemed to be superior at predicting the risk.

5.5.2 Measures of Calibration:

Calibration of the model measures the extent to which a model predicted risk, equals the actual risk observed in the data. I have used the modified Hosmer-Lemeshow $\chi 2$ statistics test (220, 222) to evaluate the calibration of my risk prediction models. I compared the plots of the actual (observed) and predicted (expected) 5-year outcomes. The observed outcomes were estimated using the Kaplan-Meier estimates for failure. Predicted outcomes were obtained from the risk models developed from the data. Each risk score's predictions were ranked and sorted into deciles and the mean of the predictions within each decile was compared to the observed (Kaplan-Meier) outcomes.

Ideally, a risk score will calibrate and discriminate well, however, a model that discriminates well but does not calibrate well can potentially be recalibrated to be more applicable in a given setting. Therefore, models that discriminate well are deemed worthier than those that calibrate well because there is no means of improving discrimination within a model while recalibration can potentially be improved (223).

5.5.3 Other measures used for comparison of model fit or performance:

I used likelihood-ratio chi-square (LR-chi)-statistic and Bayesian information criterion (BIC) (224, 225), as measures of model fit to compare the two models. LR-chi is a global measure of model fit, whereas BIC combines both model complexity (for example, the number of variables, and numbers of observations in the model), and global measure of fit (as measured by LR-chi statistic). Lower values of BIC represent a better fit, and BIC (unlike other statistics mentioned above) can be used to compare the performance of two models that are derived from same dataset, but not necessarily nested models.

Chapter 6

DETERMINANTS OF NEW-ONSET DIABETES AMONG HYPERTENSIVE PATIENTS: THE ROLE OF ANTIHYPERTENSIVE MEDICATIONS

Study 1: DETERMINANTS OF NEW-ONSET DIABETES AMONG 19,257 HYPERTENSIVE PATIENTS RANDOMISED IN THE ASCOT-BPLA TRIAL AND THE RELATIVE INFLUENCE OF ANTIHYPERTENSIVE MEDICATION

6.1 Summary

Both hypertension and type 2 diabetes mellitus are significant risk factors for cardiovascular disease (CVD), and frequently co-exist. Patients with hypertension have a two- to three-fold greater risk of developing new-onset diabetes compared with normotensive individuals. Observational studies have suggested that the increased predisposition of hypertensive patients to develop new-onset diabetes may be associated with antihypertensive drugs. These findings have important clinical implications particularly given the fact that most patients with high blood pressure require at least 2 antihypertensive medications to achieve the currently recommended blood pressure (BP) targets. Studies have suggested that the use of metabolically neutral (or beneficial) antihypertensive medications instead of those antihypertensive agents with diabetogenic potential—such as beta-blockers and/or diuretics, may prevent new-onset diabetes among hypertensive patients particularly if targeted at those patients at greatest risk. However, little is known about the determinants of new-onset diabetes among hypertensive patients. A small number of clinical trials, albeit with methodological limitations, have described the importance of baseline fasting plasma glucose (FPG) and obesity in predicting the risk of new-onset diabetes among hypertensive patients. However, to date, no study has developed a user-friendly, integer-based, risk score to help physicians easily and accurately identify those hypertensive patients with increased risk of developing diabetes.

The database of the BP-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA) was used to investigate these issues in a clinical trial setting. Multivariable Cox regression models were developed, using baseline variables to identify the independent predictors of new-onset diabetes, and determine individual risk scores.

The findings suggest that among non-diabetic hypertensive patients randomised in the ASCOT-BPLA, increased baseline FPG, body mass index (BMI), serum triglyceride and systolic blood pressure (SBP) were significant risk factors for the development of new-onset diabetes. In contrast, randomisation to the amlodipine ± perindopril[amlodipine-based] (in comparison to the atenolol ± thiazide [atenolol-based]) treatment, increased baseline high-density lipoprotein (HDL)-cholesterol and increased alcohol use and age above 55 years were significant protective factors. The risk of new-onset diabetes increased steadily with each quartile of the risk score, with a nineteen-fold increase among those in the highest quartile compared with those in the lowest quartile. There was no evidence of an interaction between risk quartile and antihypertensive treatment group, suggesting that the protective effect of amlodipine-based treatment was irrespective of the individual's baseline risk. The risk score developed has an excellent internal validity and discriminative ability.

In summary, this study provides evidence that treating hypertensive patients with an amlodipine-based regimen (in comparison with an atenolol-based regimen) significantly reduced the risk of new-onset diabetes. It further identifies, and describes, the relative importance of other predictors of new-onset diabetes in hypertensive patients including FPG, BMI, serum HDL-cholesterol and triglycerides. The model developed from these data allows accurate prediction of the risk of developing new-onset diabetes among hypertensive subjects. The development of a user-friendly risk score may help physicians choose appropriate antihypertensive drugs in a routine clinical practice setting. It could also be used as an effective tool to help physicians efficiently target preventative strategies to those hypertensive patients at highest risk of developing new-onset diabetes.

Study 1: DETERMINANTS OF NEW-ONSET DIABETES AMONG 19,257 HYPERTENSIVE PATIENTS RANDOMISED IN THE ASCOT-BPLA TRIAL AND THE RELATIVE INFLUENCE OF ANTIHYPERTENSIVE MEDICATION

6.2 Hypothesis

1. The risk of developing new-onset diabetes will be higher among those randomised to atenolol-based treatment compared with those randomised to amlodipine-based treatment in the ASCOT-BPLA.

2. It is possible to accurately identify from baseline data those hypertensive patients who are at a increased risk of developing new-onset diabetes during ASCOT-BPLA follow-up.

6.3 Background

Both hypertension and type 2 diabetes mellitus are significant risk factors for CVD, and frequently co-exist. Patients with hypertension have a two- to three- fold greater risk of developing new-onset diabetes compared with normotensive individuals (120). Furthermore up to 80% of patients with type 2 diabetes mellitus develop hypertension. Studies have shown that patients with hypertension have a clustering of metabolic risk factors, similar to those seen among patients with diabetes (226, 227). Based on these observations, and the fact that these disorders co-exist more commonly than would be expected by chance, it has been postulated that both diabetes and hypertension may share common underlying pathophysiological links (119, 227, 228).

Given the rapidly escalating prevalence of diabetes worldwide (229), it is important to identify the determinants of new-onset diabetes among high-risk populations, such as

hypertensive patients, to enable preventative strategies to be targeted most effectively. However, it is likely that the risk factors for new-onset diabetes may differ, either in their relative influence or strength of association, among hypertensive and normotensive individuals. It is also possible that among hypertensive patients there may be several novel predictors of new-onset diabetes that may be related to, or as a consequence of hypertension. These factors may not be clearly evident in community surveys. Indeed, observational studies among hypertensive populations have shown that the use of antihypertensive agents may variably influence the risk of new-onset diabetes among these populations (28-30, 131, 156). These findings have important clinical implications, given that most hypertensive patients require at least 2 antihypertensive medications to achieve currently recommended BP targets. Improved understanding of these issues would allow physicians to effectively target treatments to those who are at highest risk of developing diabetes. For example, a study estimated that if physicians chose metabolically neutral (or beneficial) antihypertensive medications instead of those with diabetogenic potential—such as beta-blockers and/or diuretics, there may be a reduction of 5.6 cases of new-onset diabetes per 1000 hypertensive patients per year (131). However, none of the studies to date have described a user-friendly risk score to help physicians accurately identify those hypertensive patients at highest risk of developing new-onset diabetes.

6.3.1 Diabetogenic potential of antihypertensive agents

There is rapidly accumulating evidence that conventional antihypertensive agents, such as beta-blockers (28, 230) and diuretics (231-235) are associated with an increased risk of developing new-onset diabetes. There is also some credible evidence that suggests that newer antihypertensive agents, which block the renin angiotensin system, such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), may reduce

the risk of developing diabetes among hypertensive patients (28, 29, 235-237). These observations have led to 2 prescribing guidelines changing their guidance on the use of beta-blockers (24, 238). The NICE-BHS collaboration now advocates avoiding monotherapy with beta-blockers, and places them among several fourth line options in their drug treatment algorithm. In contrast, the evidence to date has not influenced the prescription patterns or guidance on diuretic use (239, 240); as a result diuretics are still recommended as first-line agents in several commonly used guidelines (22, 23). Furthermore, the combination of diuretics and beta-blockers remains one of the most commonly used combinations, worldwide (8, 19-21, 241, 242).

6.3.1a Observational evidence of the diabetogenic potential of antihypertensive agents

The adverse metabolic effects of diuretics and beta-blockers—particularly impairment of glucose tolerance and the detrimental effect on lipid profile—have been known since the mid 1960's (133, 139, 243). However, their translation into increased incidence of diabetes was not recognised until several large observational studies reported their findings in the mid the 1990's (244-248)

Gress et al followed a population-based cohort of 12,550 subjects (aged 45 to 64 years) with no evidence of diabetes at baseline for an average duration of 6 years(244). They found that among the hypertensive patients in their cohort (n=3,804), the use of beta-blockers was associated with a 28% significant increase in the risk of new-onset diabetes after adjusting for age, sex, education, adiposity , family history and physical activity (hazard ratio [HR], 1.28 [95% confidence interval (CI), 1.04 to 1.57]). In contrast, there were no significant differences in the incidence of new-onset diabetes among those who were taking either ACE inhibitors, diuretics or calcium-channel blockers (CCB), compared with those hypertensives

who were not taking any drugs (244). Interestingly, whilst the use of diuretics was not associated with an increased risk of new-onset diabetes (0.91[0.73 to 1.13]), it was associated with a significant increase in fasting serum glucose during the first three years of observation (0.01 mmol/L, $p < 0.01$). In comparison, the use of ACE inhibitors and CCBs were associated with significant reductions in glucose levels (0.03 and 0.02 mmol/l, respectively), whilst beta-blockers had no significant effect on glucose levels after 3 years of follow-up. Clearly in this study, the reported glucose levels are not consistent with the findings of an increased risk of new-onset diabetes among hypertensive patients taking beta-blockers. These inconsistencies are likely to have arisen from several methodological and analytical limitations of these post-hoc analyses. For example, there was no information on either dose or duration of use of these medications during follow-up. Therefore it is possible that subjects may have changed their medications, lifestyle or both, which affected their blood sugar levels and hence risk of diabetes. Furthermore, whilst the glucose level was measured after 3 years of follow-up, the diagnosis of new-onset diabetes was made after 6 years of follow-up. This differential follow-up for the two outcomes may help to explain these inconsistent findings, as it is possible that patients changed their lifestyle or medications after the glucose findings at Year 3, such that they did not manifest with diabetes during the subsequent 3 years of follow-up. It is also possible in this observational study, that the prescription patterns of physicians may have been influenced by their perception of the patients risk of diabetes. For example, those patients who were considered by physicians to have a high risk of developing diabetes may have been prescribed medications, such as ACE inhibitors, while diuretics may have been prescribed for patients who were considered to have a low risk of developing new-onset diabetes. Moreover, this is an observational study, which by nature of its study design cannot adjust for all potential confounders, and has no allocated control group for comparisons.

A recent study assessed the incidence of new-onset diabetes among subjects from three large

prospective cohorts: The Nurses' Health Study (NHS) I & II, and the Health Professionals Follow-up Study (HPFS) (129). Overall 3,589 cases of incident diabetes were observed among 41,993 older women (NHS I), 14,151 younger women (NHS II) and 19,472 men (HPFS) with a history of hypertension. On multivariable analysis (adjusting for age, BMI, class of antihypertensive medications, physical activity, family history of diabetes and other medication use) those on beta-blockers were at a significantly higher risk of new-onset diabetes, compared with those who were not, in the 2 cohorts where information on beta-blockers was available (NHS-I: relative risk 1.32 [95%CI: 1.20 to 1.46] and HPFS: 1.20 [1.05 to 1.38]). Similarly, the use of thiazide diuretics compared with no thiazide use was independently associated with an increased risk of new-onset diabetes among older women in NHS-I (1.20[1.08 to 1.33]), younger women in NHS-II (1.45 [1.17 to 1.79]) and men in HPFS (1.36[1.17 to 1.58]), respectively. There was no association observed between the use of CCB or ACE inhibitors and the risk of new-onset diabetes among older women in NHS-1, nor was there any significant relationship between the use of CCBs and the development of new-onset diabetes among men in HPFS. It is important to note the limitations of these observational studies when interpreting these results. Firstly these are questionnaire-based cohorts, where ascertainment of hypertension, antihypertensive medication use, and the development of diabetes was self reported. Because of this, it is likely that individuals with asymptomatic diabetes will have been under-reported in these analyses. Secondly, there is also a possibility of bias in the diagnosis of asymptomatic diabetes. Since, the detection of asymptomatic diabetes is a function of the frequency of investigations, there is a real hazard that the type of antihypertensive agent prescribed, presence of co-morbid conditions and physician's discretion may have disproportionately influenced the frequency of routine investigations and hence the diagnosis of asymptomatic diabetes. Thirdly, there may also be some residual confounding, as like all observational studies these 3 cohorts could not control for unknown

confounders. Finally, these analyses did not adequately control for known confounders, for example, there was no adjustments for baseline BP, fasting glucose level, HDL cholesterol or triglyceride level.

Several other observational studies have also reported an association between the use of beta-blockers and/or diuretics and the risk of developing new-onset diabetes (245, 246, 248, 249). However, most of these observational studies, have been criticised because of small sample size (246, 248), lack of power (245, 248, 249), inadequate adjustment for confounders (129, 245, 248), self-reported ascertainment (129), selection bias and lack of, or an inappropriate, comparator group (248, 249).

In contrast to the findings of the above mentioned studies (section 6.3.1.a) there are a few observational studies that reported contradictory findings. One retrospective population-based cohort study used prescription of antihypertensive drugs (beta blocker, ACE inhibitor and CCB) as an exposure, among 76,176 previously untreated elderly (≥66 years) hypertensive patients. The authors reported there were no significant differences in the incidence of diabetes among the users of these 3 major antihypertensive drug classes (130). In a case-control analysis of a large prescription database, there were no differences in the diabetogenic potential among 4 of the major antihypertensive drug classes(beta blocker, diuretic, ACE-inhibitor, CCB) (250). In this study, the frequency of use of any of these antihypertensive agents was compared among 11,855 newly diagnosed (and treated) diabetic patients and 11,855 controls. The findings suggest that there was no evidence of a differential use of antihypertensive drug classes among cases and control. Both of these studies have several limitations: Firstly they have relied on the use of prescribing databases and therefore have no data to adjust for common confounders. Secondly they have used an extremely selective

population. Thirdly there may be bias in reporting of a diagnosis of diabetes. Fourthly the overall quality of the collected data may be open to criticism. For example, in the latter study, the prescription of hypoglycaemic agents was used as a surrogate to define diabetes. This implies that all those patients with diabetes and on life-style and dietary advice or insulin treatment were not included in this analysis, nor are undiagnosed (mainly asymptomatic) patients.

In summary, despite some conflicting findings, the majority of evidence from observational studies favours the hypothesis that the use of diuretics and/or beta-blockers is associated with an increased risk of the development of new-onset diabetes. However, there is no consistent evidence of a protective effect of ACE inhibitors or ARB's in these observational studies.

6.3.1b Clinical trial evidence of the diabetogenic potential of the antihypertensive agents

Over the last decade, several large-scale clinical trials have reported on the development of new-onset diabetes among their cohorts. Most of these post-hoc analyses have compared the incidence of diabetes between the two active treatment arms; however a few of them –mostly non-hypertension trials—have also compared the incidence of new-onset diabetes on active drug as compared to that on a placebo.

i) <u>Placebo –controlled trials:</u> Several placebo-controlled trials have evaluated the incidence of diabetes associated with the use of commonly prescribed antihypertensive agents as compared with the use of a placebo. Most of these studies were solely on hypertensive populations, but a few were also on high cardiovascular risk populations, with a significant proportion of hypertensive patients (235, 236).

In an initial analysis of the Systolic Hypertension in the Elderly Program (SHEP), among 4,736 participants with isolated systolic hypertension, the use of chlorthalidone (adding atenolol if required) as compared with placebo was associated with an increased, albeit statistically insignificant, risk of new-onset diabetes during the first 3 years of follow-up (8.6% [140 participants out of 1,631] vs. 7.5% [118 participants out of 1,578]; RR: 1.2[0.90 to 1.50], p=0.25) (234). Of note, in this analysis, published in 1996 the development of diabetes was defined using the WHO 1985 definition (FPG levels ≥ 7.8 mmol/L). However, in a subsequent up-dated analysis, using all available data until the end of the study and a lower FPG cut-off (FPG levels ≥ 7.0 mmol/L) on basis of the WHO 1999 definition, allocation to chlorthalidone therapy (compared with placebo) was indeed associated with a significant increase in the risk of new-onset diabetes (odds ratio 1.56 [1.30 to 1.95]) (251). Whilst these findings are consistent with other reports, it is possible that in both of these analyses there may be an underestimation of the effect size, because about a third of patients on the placebo arm were also receiving a diuretic—implying that the actual effect size would have been much greater if there was no cross-over of the study drug.

In the Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity (CHARM) program (235), 5,436 patients with heart failure and no history of diabetes received candesartan (n=2,715) or a placebo (n=2,721). During a median follow-up of 3.1 years, allocation to candesartan treatment, in comparison with placebo, was associated with a significantly reduced risk of new-onset diabetes (odds ratio 0.78 [0.64 to 0.96], p=0.020). However, it is difficult to attribute that the apparent differences in risk between the two arms are solely because of the use of candesartan (an ARB) in this trial. This is because there was an unequal use of diuretics in the two treatment arms, with those on placebo significantly more likely to be taking a diuretic than those allocated to the candesartan arm. This

differential usage is likely to account for some of the differences in the risk of diabetes between the two treatment arms. Another limitation of this study was that the ascertainment of new-onset diabetes was based on reporting by study-investigators (or study co-ordinators) rather than a systematic approach of serial measurements of fasting glucose or periodic assessment with oral glucose tolerance tests. It is therefore possible that there may be reporting bias, and an underestimation of the true incidence of new-onset diabetes. Notwithstanding this limitation, these findings are similar to those observed in the Study on Cognition and Prognosis in Elderly (SCOPE) trial (237). In SCOPE, compared with those allocated to placebo those allocated to candesartan therapy had a lower risk of developing new-onset diabetes (5.3% vs. 4.3% developed diabetes). However, notably, the associated relative risk reduction in this study was statistically insignificant (relative risk, 0.81[0.62 to 1.06]) (237), which is likely to be due to the extensive contamination by the use of diuretics and beta-blockers among those randomised to the two treatment arms, and the use of ACE inhibitors and other ARBs in the placebo arm.

In a post-hoc analysis of the Heart Outcomes Prevention Evaluation (HOPE) trial (236), among participants with a high cardiovascular risk, the use of ramipril (in comparison with placebo) was associated with a 34% significant reduction in the risk of new-onset diabetes (0.66 [0.51 to 0.85]). Although these results are consistent with other published reports, this post-hoc analysis has 2 major limitations. Firstly the development of new-onset diabetes was not a pre-defined end point, and secondly the diagnosis of diabetes was based on self-reporting by patients—hence, these findings are prone to ascertainment bias.

ii).Trials comparing active treatments: Over the last decade, several large-scale hypertension trials have compared the risk of developing new-onset diabetes in their active treatment arms.

The majority of these post-hoc analyses compared the risk of developing diabetes associated with allocated monotherapy (28, 29, 157, 230, 232). However, 2 trials compared the risk of new-onset diabetes among those allocated to 2 different treatment combinations (231, 252). Almost all trials compared the risk of developing diabetes between 'older' conventionally prescribed medications, such as diuretics and/or beta-blockers and 'newer' antihypertensive medications, such as CCB, ACE inhibitor or ARBs. However, one trial compared the risk of developing diabetes among those assigned to either a CCB or an ARB-based strategy (157).

a) *Trials comparing diuretic-based treatment*: Among the trials comparing the risk of diabetes associated with the use of diuretics in comparison with other antihypertensive agents, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is the largest to date (25, 233). In ALLHAT, 14,816 non-diabetic hypertensive patients at randomisation received either chlorthalidone (n=6,766), amlodipine (n=3,954) or lisinopril (n=4,096) monotherapy (233). After 4 years of follow-up, a significantly greater proportion of those allocated to chlorthalidone developed new-onset diabetes (11.6%), compared with those allocated to either amlodipine (9.8%; relative risk, 0.80 [0.64 to 0.99]) or lisinopril (8.1%; 0.77 [0.56 to 0.86]). However, in this trial diabetes was defined post-hoc on the basis of a single FPG reading ≥7.0 mmol/L. Moreover, only 38% of randomised patients had one or more glucose measurement recorded during the first 4 years of follow-up, to allow determination of their diabetic status. This implies that in these analyses there may be the possibility of misclassification and detection bias. However, these findings are consistent with previous reports.

In the Intervention as a Goal in Hypertension Treatment (INSIGHT) trial (232), 5,019 hypertensive patients with no previous diabetes were assigned to either longer acting nifedepine (n= 2,508) or a combination of hydrochlorthiazide and amiloride (n=2,511). The use of the diuretic combination, compared with the use of the CCB, was associated with a significantly higher risk of developing new-onset diabetes (5.6% vs. 4.3%; RR 0.77 [0.62 to 0.96]). However, in this trial the risk of developing diabetes was considerably lower in both treatment arms, compared with that seen among other trials of similar populations (25, 29, 253). However, the overall incidence of new-onset diabetes in INSIGHT was similar to that observed in the Nordic Diltiazem (NORDIL) study (254). In NORDIL, the use of a combination of diuretic and beta-blocker was associated with a relatively higher (but statistically insignificant) incidence of diabetes compared with the use of diltiazem (0.87 [0.73 to 1.04]). The failure to detect significant differences in the risk of diabetes between the two study arms could be because of the protocol driven use of beta-blockers and diuretics, as add-on drugs, in the diltiazem arm of the study.

b) *Trials comparing R*enin-Angiotensin system *(RAS) blocking agents*: Several trials have compared the use of RAS blocking agents with the use of diuretics or beta-blockers or a combination of both.

In the Captopril Prevention Project (CAPPP) (29, 255), among 10,985 non-diabetic hypertensive patients, 717 developed diabetes during a mean follow-up of 6.1 years. In an intention-to-treat analysis, compared with the thiazide diuretic and beta-blocker treatment regimen, the captopril-based treatment regimen was associated with a 14% significant reduction in the incidence of diabetes (0.86 [0.74 to 0.99]). The protection afforded by the use of captopril (ACE inhibitor) in comparison with the use of

diuretic-based treatment was more pronounced in the on-treatment analysis of CAPPP data, with a 21% reduction in the risk of developing diabetes associated with captopril-based treatment compared with the diuretic-based treatment (0.79 [0.67 to 0.94]). In the Losartan Intervention for Endpoint reduction (LIFE) trial (28, 256), compared with allocation to atenolol, allocation to losartan was associated with a 25% reduction in the risk of developing diabetes (0.75 [0.63 to 0.88]). In the African American Study of Kidney Disease and Hypertension (AASK) (230), African-American hypertensive patients with and evidence of renal involvement were randomly allocated to receive ramipril, metoprolol, or amlodipine treatment. In that study, among 1017 participants during a mean follow-up of 3.8 years, 14.5% developed diabetes. Compared with those allocated to metoprolol in this trial, those allocated to ramipril had about half the risk of developing diabetes (0.55 [0.36 to 0.78]).

These findings, taken together with the reports from ALLHAT, suggest that the use of an ACE inhibitor or an ARB is associated with a reduction in the risk of diabetes, similar to the findings of several placebo-controlled trials.

c) *Trials comparing newer vs. older antihypertensive treatment regimens*: A few trials have compared the risk of diabetes using combinations of newer versus older antihypertensive agents. In the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE) study (231), the majority (94%) of the 392 randomised hypertensive patients were previously untreated. Of these, during 1 year of follow-up, 8 patients developed new-onset diabetes among those randomised to the hydrochlorthiazide ± atenolol group (n=196) and 1 patient developed diabetes

among those randomised to the candesartan ± felodipine group (n=196) (0.13[0.02 to 0.99]). In this relatively short, small but methodologically sound trial, there were no add-on medications allowed, compliance with study medications was absolute, and frequent serial blood sugar and lipid profile measurements were taken for each individual. New onset of diabetes was a pre-defined end point, and was defined on the basis of WHO 1999 definition. These findings suggest that there were significant differences in the glucose and lipid profile between these 2 treatment groups. The thiazide-based treatment, in comparison with the candesartan-based treatment, was associated with a significant worsening in glucose (and lipid) levels, and an increase in insulin resistance. These findings are supportive and consistent with the findings of an increased risk of new-onset diabetes among those allocated to thiazide-based treatment.

In another recent trial, the International Verapamil SR-Trandolapril Study (INVEST) (257, 258), 16,176 patients, with stable coronary artery disease but without diabetes at randomisation, were assigned to either Verapamil-SR ± trandolapril-based treatment (n=8,098) or atenolol ± hydrochlorthiazide-based treatment (n=8,078). During a mean follow-up of 2.8 years, the incidence of new-onset diabetes was significantly lower among those assigned to verapamil-based treatment (7.0%, 569 patients) as compared with those assigned to atenolol-based treatment (8.2%, 665 patients) (0.85 [0.76 to 0.95]). These findings are consistent with reports from previous studies (28, 30, 230, 231). However, in the INVEST trial the patient population (i.e. those with stable coronary artery disease) is different from other studies that mainly recruited hypertensive patients with variable degrees of associated cardiovascular risk factors or

CVD, and because of this, patients in the INVEST trial may have been at a higher risk of developing diabetes.

d) *Trials comparing CCB vs. ARB*. A recent trial, the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) (157, 259), compared the incidence of diabetes among those allocated to either amlodipine (CCB) or valsartan (ARB). The findings suggest that compared with allocation to amlodipine, those allocated to valsartan had a significantly lower risk of developing diabetes (0.77[0.69 to 0.87]). These findings are consistent with the findings from the AASK study (230). In AASK, compared with those allocated to amlodipine, those allocated to ramipril were at 51% lower risk of developing diabetes (0.49 [0.31 to 0.79]). However, when further analyses were done on the AASK population, using the development of either diabetes or impaired fasting glucose as an end point, the relative-risk reduction associated with allocation to ramipril treatment was not statistically different than allocation to amlodipine treatment (0.76 [0.56 to 1.05], P=.09)

e) *Methodological issues*: There are several methodological issues pertaining to these studies. For example in both the ALLHAT and HOPE trials, the association between antihypertensive treatment regimen and new-onset diabetes was a post-hoc analysis. There was incomplete follow-up in some of the trials, for example, ALLHAT. In others there were issues related to the definition of new-onset diabetes (232, 235, 254, 257, 259). The results of several trials were contaminated by the use of beta-blockers or diuretics in both treatment arms (235, 254, 255), and in others the number of patients was too small to give adequate statistical power (231, 260). Finally 2 trials had an open-label blinded endpoint design that may have increased the likelihood of detection bias (29, 254).

6.3.1. c. Summary of evidence

Notwithstanding the methodological issues related to some of these analyses, the bulk of the findings suggest that there are indeed differences in the diabetogenic potential of various antihypertensive agents. Whilst the use of beta-blockers or diuretics or both has been associated with an increased risk of diabetes, the trial evidence consistently shows that the use of RAS blockers may afford some protection against the development of diabetes. In contrast, the data related to the use of CCBs are not consistent. For example, in INSIGHT, INVEST, NORDIL, and ALLHAT the use of a CCB was apparently protective in comparison with a diuretic or diuretic-based treatment regimen; however, in comparison with an ARB or ACE inhibitor, treatment with CCBs have been shown to significantly increase the risk of new-onset diabetes. Based on these findings, it has been estimated that compared with conventional therapy (beta-blockers ± diuretics), ACE/ARB-based treatment may reduce the risk of developing new-onset diabetes by 20%, and CCB-based treatment may reduce the risk by 16% (151). However, the accuracy of these crude estimations is questionable, because of the heterogeneity of these trials, the use of different comparators, and the methodological limitations summarised in section 6.3.1.b. Indeed, the methodological heterogeneity of these trials makes it difficult to summarize all the findings succinctly in a direct meta-analysis setting. However, Elliott et al have reported their findings of a network meta-analysis, which has allowed a relative comparison among different classes of antihypertensive agents, regardless of the heterogeneity in these trials (156). In their analysis, data from 22 clinical trials comprising of 143,153 non-diabetic participants were analysed for the outcome of new-onset diabetes. Their findings suggest that compared with the use of diuretics, the risk of new-onset diabetes is lowest for ARBs, followed by ACE inhibitors, CCBs and placebo. The risk of diabetes associated with the use of beta-blockers was similar to that of diuretics. The rank order remained the same even when placebo was used as a reference group, however, in this

case only the use of ARBs (odds ratio 0.75[0.61 to 0.91]) and diuretics (1.3 [1.07 to 1.58]) remained statistically significance. The odds ratios for ACE inhibitors (0.87 [0.75 to 1.01]), CCBs (0.97, [0.82 to 1.15]) and beta-blockers (1.17[0.98 to 1.40]) were not statistically significant. However, this type of analysis has its own limitations and makes several assumptions. Firstly this type of analysis assumes the evidence is consistent (e.g. all the included trials have evaluated the outcome similarly). However this network analysis included trials that differed in their definition of diabetes. Secondly, another assumption is that of homogeneity (e.g. the included trials have similar study designs and population characteristics). Again, in this network analysis the included trials had neither a similar study design nor were they conducted among similar populations. Thirdly, perhaps, the most important limitation of these findings is that the summary statistics assume comparison of a single drug in each arm of the included trials; however, in almost all trials included in this meta-analysis, there was widespread use of add-on antihypertensive medications. This would also influence the estimated summary statistics. Nonetheless, these findings are consistent with the findings of earlier meta-analyses, and are supported by the findings from other observational studies.

6.3.2 Other predictors of new-onset diabetes in hypertensive patients: the need for a risk score

The studies summarised in section 6.3.1 have established an independent role of antihypertensive therapy—particularly beta blockers and diuretics—in influencing the propensity of hypertensive subjects to develop new-onset diabetes. However, little is known about other baseline predictors of new-onset diabetes, and the importance of antihypertensive therapy relative to these variables. Furthermore, it is unclear whether among hypertensive

patients the relative influence and strengths of association of risk factors differ from those observed in community studies. (261-265).

A few clinical trials have previously evaluated the predictors of new-onset diabetes among hypertensive patients. In LIFE (28), a baseline increase of 1 mmol/l in non-fasting serum glucose was associated with a 63% increase in the risk of developing diabetes. Increasing BMI and SBP, and decreasing HDL-cholesterol and prior antihypertensive treatment were the other significant predictors of new-onset diabetes in this analysis. The findings of a post-hoc analyses of CAPPP were similar to those of LIFE (29), with the exception that there were no lipid measurements to analyze, and additional haemoglobin and age were found to be independent risk factors for new-onset diabetes. In contrast to the findings of LIFE and CAPPP, the multivariable Cox model used to analyse the INVEST data (257), found several other independent risk factors. Presence of left ventricular hypertrophy, previous stroke/ transient ischaemic attack or coronary revascularisation, history of hypercholesterolemia or use of lipid lowering agents, Hispanic ethnicity and greater BMI were found to be significant risk factors for the development of diabetes in this study. In contrast, older age was associated with a reduction in the risk of development of diabetes. Surprisingly, the baseline SBP, previous use of antihypertensive agents and the use of other medications were not found to be risk factors in these analyses. In INVEST the baseline data on laboratory-based biomarkers was not available for inclusion in these analyses.

From the data above, it is clear that there are several inconsistencies in the findings of the studies to date. These variations are mainly driven by differences in the quality of the available data, the study design and the patient characteristics. For example, in LIFE all patients had left ventricular hypertrophy at inclusion; whereas the presence of stable coronary

artery disease was an essential criterion for inclusion in INVEST. Therefore, it is not surprising that the presence of left ventricular hypertrophy was not found to be a risk factor in LIFE, whereas it was an independent risk predictor in the INVEST analyses. Similarly, coronary revascularisation was found to be a significant a significant risk factor in INVEST, but not in others. This could simply be because of differences in the patient populations, and/or that the data were not available in the LIFE or CAPPP analyses. Primarily, these findings differ because of the differences in the available data at baseline, for example, data on HDL cholesterol was not available in CAPPP and INVEST. Of equal importance, these 3 studies differed in their end-point definition of diabetes. In INVEST, diabetes was physician reported; in CAPPP the whole blood glucose levels were used to define diabetes using the WHO 1985 definition. In the LIFE analyses diabetes was defined on the basis of either the WHO 1985 (266) or the WHO 1999 definition (169).

Notwithstanding the inconsistencies and limitations in the existing literature, it is apparent from the available data that the predictors of new-onset diabetes among treated hypertensive patients are modifiable by the choice of pharmacotherapy and/or lifestyle modification. It is therefore conceivable that intensive management of these baseline predictors including SBP, BMI, fasting glucose and lipid levels may reduce the incidence of diabetes in high-risk populations. However, little is known about how to easily identify those hypertensive patients who are at a highest risk of developing diabetes. In a post-hoc analyses of LIFE (28), a diabetes risk prediction score was developed; however, the risk score was neither user friendly, nor it was applicable to the majority of hypertensive patients. Availability of a user friendly, easy to use, risk score or algorithm to identify those patients at risk of developing diabetes may facilitate the effective and efficient targeting of preventative treatment strategies in routine clinical practice.

6.3.3 Summary of the evidence: way forward?

In summary, these studies have shown that the propensity of hypertensive patients to develop new-onset diabetes is variably influenced by antihypertensive agents. Whilst, the use of beta-blockers and diuretics are associated with an increased risk of new-onset diabetes, drugs that block the renin-angiotensin system may reduce this risk.(30, 131, 156, 244). Despite this evidence, globally, both beta-blockers and diuretics are among the most commonly prescribed antihypertensive agents (19-21, 241, 242). This is, in part, because although several studies have shown adverse metabolic effects (including increased rates of new-onset diabetes) associated with these drugs, they have failed to demonstrate any associated increase in adverse cardiovascular outcomes (25, 26). This controversy notwithstanding, little is known about other baseline predictors of new-onset diabetes among hypertensive populations and the importance of antihypertensive therapy relative to these variables. Since most of these baseline predictors are modifiable by pharmacotherapy and or lifestyle modification, it is conceivable that improved management of these baseline predictors during follow-up may translate into a reduction in the risk of developing diabetes. However, at present, there are no easily available tools specifically designed for the treated hypertensive patient to enable easy identification of those who are more prone to develop diabetes.

The database of the ASCOT-BPLA (47, 48) provides an excellent opportunity to investigate these issues, and contribute to the current understanding of these matters.

6.4 Objectives

1. To compare the incidence of new-onset diabetes among those randomised to the two antihypertensive treatment regimens in the ASCOT-BPLA.

2. To determine the baseline predictors of new-onset diabetes among hypertensive patients randomised in the ASCOT-BPLA.

3. To assess the importance of antihypertensive therapy relative to other independent baseline predictors of new-onset diabetes.

4. To develop a risk score to identify those hypertensive patients at baseline, who are at highest risk of developing new-onset diabetes.

6.5 Materials and Methods

The details of the study design, methods used and the main results of the ASCOT-BPLA are described in Chapter 4, and have been previously published (47, 48). However, a brief summary of the details relevant to this study are given below:

6.5.1 Study population:

Hypertensive patients, aged 40-79 years, with three or more cardiovascular risk factors but without any previous coronary heart disease were randomised, using a prospective randomised open blinded endpoints design, to receive one of two antihypertensive regimens: atenolol adding a thiazide diuretic as required (atenolol-based regimen) or amlodipine adding perindopril as required (amlodipine-based regimen) to reach BP targets (n=19,257). The majority of these patients were directly or indirectly recruited from the general practices across Nordic countries, Iceland and UK/Ireland (48).

6.5.1.a.Analysis population: For the purpose of this analysis, all those with pre-existing diabetes (self-reported and receiving drug or dietary therapy) or those who were 'deemed' by the endpoint adjudication committee to potentially have (as yet undiagnosed) diabetes at baseline (based on a single recording of FPG $\geq$ 7.0 mmol/l or random glucose $\geq$ 11.1 mmol/l or presence of a combination of FPG $\geq$ 6.1 mmol/l and glycosuria at the randomisation or screening visit) (n=5,137) were excluded, to leave a residual population 'at risk' of diabetes (n=14,120). The latter criterion was chosen by the endpoint adjudication committee to avoid misclassification of as yet undiagnosed patients with diabetes as 'non-diabetic' at baseline, when further investigations with an oral glucose tolerance test or repeated fasting glucose levels may have revealed the presence of diabetes.

6.5.2 Procedures: After initial screening for the inclusion and exclusion criteria, subjects attended a randomisation visit after an overnight fast, when a detailed clinical examination, medical history, laboratory tests and an ECG recording were carried out. Subsequently, fasting blood samples were obtained at visits at 6 months, 12 months, and thereafter annually.

6.5.3 Outcomes: Development of new-onset diabetes was a pre-defined tertiary outcome in the ASCOT-BPLA. New-onset diabetes during follow-up was diagnosed on the basis of the WHO 1999 definition i.e. FPG ≥7.0 mmol/l and/or 2 hour post glucose levels ≥11.1 mmol/L. Two separate abnormal recordings were needed to confirm the diagnosis; however, one abnormal reading was acceptable in a clinically symptomatic individual (169). Each outcome was independently adjudicated by the ASCOT-BPLA endpoint committee.

6.5.4 Statistical Methods: STATA 9 software was used for all statistical analyses.

6.5.4. a. Descriptive analyses: Among 'at risk' individuals, baseline characteristics including data on demographic, medical history, clinical examination, laboratory measurements and ECG recordings were compared between those who developed new-onset diabetes and those who did not. Similar comparisons were performed after stratification by the two BP treatment regimens. All baseline variables were considered for inclusion in the multivariable models except for LDL cholesterol and serum creatinine. The LDL-cholesterol levels in the ASCOT-BPLA were estimated based on total cholesterol, HDL-cholesterol and triglyceride values (267); however LDL-cholesterol was excluded from any model building for the following reasons. Firstly there was collinearity between the estimated LDL cholesterol and the other baseline variables from which it was calculated. Secondly, in the presence of serum triglyceride >4.5 mmol/l, the indirect estimations of LDL-cholesterol are inaccurate, and

therefore were not estimated. In such cases, the LDL-cholesterol value was denoted as a missing value in the ASCOT-BPLA database. Thirdly, non-fasting values of triglyceride were not considered for estimations of LDL-cholesterol (see section 6.5.4.b). Therefore all values of LDL-cholesterol in these cases were also labelled as missing values. Because of these reasons, missing values and collinearity, LDL-cholesterol was not considered a priori for inclusion in the multivariable models. Similarly serum creatinine was a priori excluded from the models, because up to 20% of patients did not have these readings at the time of randomisation, and there was no pre-specified hypothesis supporting inclusion of this variable in these analyses.

6.5.4. b. Missing values: For purpose of these analyses, only fasting values of plasma glucose and triglyceride were used. Therefore, approximately 10% (n=1,428) of subjects who had non-fasting values of either triglyceride (n=1,392) or glucose (n=1,427) at baseline were excluded from the multivariable analysis. To assess whether these exclusions resulted in a selection bias, the baseline characteristics between those with and without fasting values were compared. Sensitivity models were developed that included all 'at risk' patients including those with non-fasting (or missing) values of triglyceride and/or glucose. In these models, dummy variables for glucose and triglyceride were included, with their respective values categorised as 0 and 1 to denote missing and non-missing values.

6.5.4. c. Univariate and multivariate analysis: The impact of baseline demographic, clinical and laboratory data on the development of diabetes was assessed using the Cox proportional hazards model (206). For each baseline variable a univariate proportional hazard model was used to estimate the hazard (risk) ratio (HR) and 95% confidence interval among the 'at risk' population. Three multivariate Cox regression models were developed,

separately, using forward stepwise selection ($p<0.05$ for inclusion) with age, sex and randomised BP treatment group as pre-specified covariates in each model. Model 1 included all 12692 patients with known, and if applicable fasting values of all variables; model 2 included patients with known (and/or fasting) values who were randomised to the atenolol-based treatment regimen (n=6321) and model 3 included patients with known (and/or fasting) values who were randomised to the amlodipine-based treatment regimen (n=6371). In each of these 3 models, all evaluable baseline variables were considered for inclusion, including age, sex, ethnicity, BP treatment allocation, BMI, smoking, alcohol intake, past history of vascular events, stroke/TIA, peripheral vascular disease, history of previous antihypertensive drug use, prior lipid lowering or aspirin therapy, the use of non-cardiovascular concomitant medication, presence of atrial fibrillation or other ECG changes, presence of left ventricular hypertrophy, systolic and diastolic BPs, heart rate, pulse pressure, total cholesterol, HDL-cholesterol, serum triglyceride, fasting glucose, number of cardiovascular risk factors and family history of early coronary artery disease.

The linearity assumption of the relationship between the continuous predictors and the hazard of developing diabetes was assessed using standard methods. Three continuous variables viz. age, FPG and BMI showed some evidence of non-linearity at extreme values. These variables were retained as continuous variables in the model with appropriate cut-off values to account for non-linearity (age <55 years, glucose <5 mmol/l, BMI >35 kg/m^2 were given the same risk as those with age = 55 years, glucose = 5mmol/l and BMI = 35kg/m^2) while using the rest of the measurement ranges as continuous variables. This method is more efficient than simply categorizing these variables, as it allows for the use of these variables as continuous variables, reflecting their true relationship with the outcome that may exist in nature.

The proportional hazards assumption was assessed both graphically and by using Schoenfeld residuals (207, 208). If the relationship between a variable and the outcome was not proportional, the reasons for non-proportionality were assessed. All the predictor variables were found to be proportional except baseline glucose. This was investigated by splitting the dataset by the time period of follow-up, and evaluating the relationship between baseline glucose and new-onset diabetes during those time-periods. Furthermore, I validated the results of the final Cox models by developing separate logistic regression models with log time of observation in the study as a covariate in the model. The results of the Cox models were accepted, if they were similar to that obtained by the logistic regression models. Further, assessments were carried by comparing the findings of the models, after removal of patients with any outlying influential values.

After validation and assessments, model 1 was accepted as the primary model to develop a risk score and to test any pre-specified interactions between the treatment group and other variables. Internal validity of the model 1 was assessed using bootstrap resampling with100 repetitions, and using 80% of the total population sample. An estimate of Harrell's C discrimination index, indicating the bias- corrected predictive accuracy of the model, was thus obtained.

6.5.4. d. Risk score The risk score for each patient was determined from the primary model by summing the products of the coefficients derived from the primary model, and the actual values of the variables in the model. The distribution of risk scores was then divided into quartiles of increasing risk. The uppermost risk quartile, compared with other risk quartiles, was associated with a considerable increase in hazard, and was therefore divided equally into two categories (4a and 4b) for presentation of the results. Calibration of the risk score model

was evaluated by comparison of the plots of the actual (observed) and predicted (expected) 5-year outcomes, and using the Hosmer-Lemeshow $\chi 2$ statistics test (220, 222). To assess whether the randomised BP treatment effect on the risk of new-onset diabetes differed with risk score category, the risk score was recalculated adjusting for treatment in the model but not including BP treatment in the risk score calculation. Finally, these risk scores were converted into 'user-friendly' integer scores for 5-year risks of developing new-onset diabetes by rounding the exact β coefficient from the Cox models. The estimated probability of new-onset diabetes within five years is $1-0.9999^{\exp(0.1*\text{risk score})}$.

6.6 Results

Of 19, 257 evaluable patients, 14,120 individuals were considered to be 'at risk' of developing new-onset diabetes. The mean age [standard deviation] of this sample was 62.8 [8.5] years and the majority were males (78%). 1,366 of these patients subsequently developed new-onset diabetes during an accumulated follow-up of 73,425 years (median follow-up 5.5 years; incidence rate 18.6 [17.6 to 10.6] per 1000 person years) (figure 6.1). Of these, 799 were allocated to the atenolol-based treatment group (incidence rate 22.1 [20.6 to 23.7] per 1,000 person year), and 567 were allocated to the amlodipine-based treatment group (incidence rate 15.2 [14.0 to 16.5] per 1,000 person year).

Of 12,692 patients who had no missing or non-fasting values of glucose and/or triglycerides, 1,212 developed diabetes during the 5.5 years of mean follow-up (705 among those allocated to atenolol-based treatment and 507 among those allocated to amlodipine-based treatment). The incidence rates for atenolol-based treatment and amlodipine-based treatment were unchanged from those reported in the 14,120 at risk population (see paragraph above).

6.6.1 Baseline characteristics

Table 6.1 describes baseline characteristics at randomisation among 12,754 people who did not develop diabetes, 1366 who developed new-onset diabetes, and 5,137 who were deemed to have diabetes at baseline. Among the 'at risk' population (n=14120), compared with those who remained non-diabetic, those who developed new-onset diabetes were younger, had higher mean BMI, serum triglycerides and BP levels, and had lower HDL-cholesterol levels.

Baseline characteristics in the 'at risk' population were well-matched among those randomised to the two BP-lowering regimens (Table 6.2). However, in each of the two

treatment groups, compared with those who remained non-diabetic, those who developed diabetes had an increased number of other cardiovascular risk factors at baseline, and were more likely to be younger with a higher BMI, FPG, pulse rate, diastolic BP and serum triglyceride levels and lower HDL-cholesterol levels (Table 6.2). However some differences were apparent between those who did and did not develop diabetes in each of the two BP-lowering treatment groups. For example, although systolic BP was raised among those who developed diabetes (compared with those who did not) in the two treatment groups, it was only statistically significant among those assigned to amlodipine-based treatment. Similarly in both treatment groups the frequency of current smoking was higher among those who developed diabetes compared with those who did not; however, the differences were only significant among those allocated to the amlodipine-based treatment.

6.6.1. a. Baseline characteristics among those with fasting values vs. missing or non-fasting values: Baseline characteristics, including demographic, clinical and medical history data, were compared between those with and without missing (or non-fasting) values at the time of randomisation. The findings suggest that there were no significant differences between the two groups. There were also no significant differences between the incidence rates of new-onset diabetes among those with and without missing (or non-fasting) values.

6.6.2 Risk factors for the development of diabetes among hypertensive patients

6.6.2.a. Univariate analyses: On univariate analysis (Table 6.3), patients allocated to the amlodipine-based regimen were 31% less likely to develop new-onset diabetes compared with those allocated the atenolol-based regimen (HR 0.69 [95%CI: 0.62 to 0.77]) and for each unit (per mmol/l) rise in HDL-cholesterol or total cholesterol the risk of new-onset diabetes

decreased by 61% (0.39[0.33 to 0.46]) and 8% (0.92 [0.88 to 0.97]), respectively. In contrast, for each 5 unit (kg/m^2) rise in BMI or 10 mmHg rise in baseline SBP the risk of new-onset diabetes increased by 42% (1.42 [1.37 to 1.46]) and 4% (1.04 [1.01 to 1.07]) respectively. Presence of micro-albuminuria, >3 cardiovascular risk factors, and higher levels of serum triglyceride, diastolic BP and heart rate at baseline were among other notable and significant risk factors for new-onset diabetes. However, the largest impact on the risk of new-onset diabetes was FPG level which was associated with a greater than 5-fold increase in risk for each 1mmol/l increase (5.24 [4.75 to 5.78]). The other significant determinants were the use of concomitant non-cardiovascular medication, total to HDL-cholesterol ratio >6, current smoking habit and male gender. Increasing age was protective, with a reduction in risk of 1% (0.99 [0.98 to 0.99]) for each increase in year of age at baseline.

6.6.2.b.Multivariate analyses : On multivariable analysis (model 1: Total =12,692, new-onset diabetes=1,212), adjusting for pre-specified covariates and other potential confounders, higher baseline levels of FPG, BMI, serum triglyceride, SBP and concomitant use of non-cardiovascular medication were significantly, and independently, associated with increased risk for the development of new-onset diabetes. In contrast, allocation to amlodipine-based treatment (in contrast to atenolol-based treatment), higher total and HDL-cholesterol levels, increased alcohol intake, and increasing age (per year) over the age of 55 years were significantly protective factors at baseline (Table 6.4).

The β-coefficients, Z-scores and p-values of each of the baseline variables used in the risk score are shown in Table 6.4. Larger values of the Z score (irrespective of the sign) indicate the strength of the variables as a predictor. Whilst, a negative sign indicates protective nature of the relationship, a positive Z-score indicates the causal nature of the relationship. Based on

these multivariable analyses, FPG was the most powerful predictor with risk increasing by 5.8-fold [5.23 to 6.43] for each 1mmol/l rise above 5 mmol/l. Risk increased by 49%(1.49 [1.38 to 1.62]) for each 5 unit increase in BMI (up to 35kg/m^2) and by 12% (1.12 [1.07 to 1.17]) for each 1 mmol/l increase in serum triglyceride level. For each 10 mmHg increase in SBP at baseline, there was a 7% (1.07 [1.04 to 1.11]) increase in the risk of new-onset diabetes. The use of concomitant non-cardiovascular medication was significantly associated with a 25%(1.25 [1.11 to 1.40]) increase in the risk of new-onset diabetes. In contrast, allocation to amlodipine-based treatment was the most significant protective factor, with a 34% (0.66 [0.59 to 0.74]) reduction in the risk of new-onset diabetes compared with those allocated to atenolol-based treatment. Increase in baseline HDL-cholesterol or total cholesterol by 1 mmol/l reduced the risk of new-onset diabetes significantly by 28% (0.72 [0.58 to 0.89]) and 11% (0.89 [0.84 to0.94]) respectively. Increasing age at baseline over the age of 55 years, and higher alcohol intake were the other significant protective factors (0.94[0.90 to 0.98] and 0.99[0.99 to 1.00], respectively) (Table 6.4). The findings of the sensitivity analysis, using a logistic regression model, were similar to these findings (data not shown). The results of the primary model were found to be essentially unchanged after removal of patients with any outlying values. When the dataset was split by the time period of follow-up, the absolute effect size of the of relationship between baseline FPG and the new-onset diabetes diminished over the period of follow-up, however, the relationship remained significant even among those who developed new-onset diabetes after 5 years of follow-up (Table 6.5).

On multivariable analysis, the predictors for new-onset diabetes among those randomised to atenolol-based treatment (model 2, Table6.6) and amlodipine-based treatment (model 3,Table 6.7) were essentially similar to those found on analysis of the primary model (model 1),

however some differences were apparent. For example, whilst FPG, BMI, total cholesterol, SBP, and age were significant predictors in the 2 BP treatment groups, raised serum triglycerides was a major predictor only among those randomised to the atenolol-based regimen (1.24[1.17 to 1.32]). Conversely raised HDL-cholesterol, alcohol intake, baseline heart rate and smoking were significant predictors only among those randomised to the amlodipine-based regimen. However when the differences between the two treatment groups were evaluated in the primary Cox model (model 1), there was no strong evidence of a significant interaction between allocated drug treatment and baseline triglyceride (p=0.09, after excluding an outlier), smoking (p=0.09), HDL-cholesterol (p=0.75), alcohol intake (p=0.25), and baseline heart rate (p=0.13). Of note, among these potential interactions only that between treatment allocation and serum triglyceride was pre-specified in the statistical analysis plan.

6.6.3 Risk Scores

Figure 6.2 illustrates Kaplan-Meier plots for the development of new-onset diabetes, stratified by quartiles of estimated risk score. The 5 year risk of new-onset diabetes increases steadily with increasing risk quartile. Compared with the lowest risk quartile, patients in the highest quartile had a nineteen-fold increase in the risk of new-onset diabetes (19.04 [14.27 to 25.41]), with a 5-fold and 2.5-fold increase in the risk among those stratified to the 3rd and 2nd quartiles, respectively. When the risk score was calculated without taking into account the effect of the allocated treatment, there was no evidence of an interaction between risk quartile and antihypertensive treatment group. Figure 6.3 shows that allocation to the amlodipine-based regimen (compared with the atenolol-based regimen) reduced the risk to the same extent in each risk quartile. The derived risk model had an excellent internal validity (estimated by boot strapping) and reasonably strong discriminative ability (Harrell's c-index

of 0.80). The risk model also has an excellent calibration, for each risk quartile there was no significant difference between the numbers of patients expected (i.e. estimated cases) to develop new-onset diabetes based on their risk scores probability, and the numbers of those who actually developed new-onset diabetes (observed cases) during 5-years of follow-up (Figure 6.4).

An easy-to-use integer-based risk table was developed using the output from the primary model by rounding off the beta-coefficients, to estimate the 5-year risk of developing new-onset diabetes (Table 6.8). Table 6.9 describes the 5 year probability (risk) of developing new-onset diabetes corresponding to the estimated risk score. Accordingly, those at lowest risk of developing diabetes had between two to five percent risk of developing diabetes during 5-years of follow-up (i.e. less than 1% per year), that contrasts with the 54% to 66% probability of developing diabetes during the 5 years of follow-up among those in the highest allocated risk scores. However, since the risk score distribution in this population followed a normal bell shaped curve, the majority of the patients had a risk score between 105 and 125, corresponding to an annual probability of developing diabetes between 0.8% and 2.5% (Figure 6.5).

6.7 Discussion

These analyses of baseline measures among over 14,000 hypertensive patients considered free of diabetes at the start of the ASCOT-BPLA (47) indicate that FPG, BMI and antihypertensive-treatment are the 3 most important determinants of new-onset diabetes among hypertensive patients. Other factors that are associated with the development of new-onset diabetes include, low HDL-cholesterol, serum triglyceride and systolic BP (Table 6.4). The risk model I have developed allows for the accurate prediction of new-onset diabetes over a 5 year period for an individual with hypertension and additional CV risk factors. The conversion of this risk model to an integer-based risk score may prove useful in routine clinical practice. It potentially allows the physician to easily identify those hypertensive patients at high risk of developing diabetes. This tool may potentially help target preventative strategies more effectively.

6.7.1 Fasting plasma glucose: The more than 5-fold increase in the risk of developing new-onset diabetes for each 1 mmol/l rise in FPG reported in this study is similar to that observed in the AASK study. In AASK, compared with those with FPG <5.6 mmol/l, those with FPG between 5.6 mmol/l to 6.9 mmol/L were at nearly a 5-fold greater risk of developing new-onset diabetes [3.47 to 6.94, $p<0.001$] (230). However, the effect size observed in the AASK study and my findings are significantly larger than that reported in earlier studies (28, 29). In LIFE and CAPPP an increase of 1 mmol/l in 'non-fasting' blood glucose was associated with only 63% and 52% significant increase in the risk of new-onset diabetes. The apparent difference in the effect size observed in my analyses and that seen in these earlier studies could be explained on the basis of my exclusive use of FPG levels, and the unambiguous, robust definition of diabetes with FPG cut-off ≥7.0 mmol/L (WHO 1999 definition) used. This contrasts with the use of 'non-fasting' glucose levels and the use of the earlier WHO

1985 definition of diabetes (FPG cut-off ≥7.8 mmol/L) in CAPPP, or a mixture of WHO 1995 and WHO 1999 definitions in LIFE — together these two factors would underestimate the true effect size. Indeed, the findings from the VALUE trial (259) support this argument. The VALUE trial used the WHO 1999 definition of diabetes, but glucose levels were not exclusively fasting. The effect size seen in the VALUE trial – more than a 2-fold increase in the risk of new-onset diabetes with each 1 mmol/L increase in non-fasting glucose levels— was in-between the two contrasting effect sizes seen in my study and those reported in CAPPP and LIFE.

In these analyses, the relationship of FPG with the risk of development of new-onset diabetes were linear and apparent from 5mmol/l onwards - a threshold for incremental risk which has previously been identified in an observational study of 13,163 normoglycaemic non-hypertensive individuals (268). In that study, a multivariate model adjusted for age, family history of diabetes, BMI, physical-activity level, smoking status, and serum triglyceride levels, identified a progressively increasing risk of new-onset diabetes from 4.83 mmol/L onwards. Indeed, the basement of the risk (i.e. a level from where onwards the risk increases) associated with fasting glucose at a FPG level of about 5 mmol/L was also found, in the Asia-Pacific Cohort study, in relation to the risk of CVD (269). In that study a continuous linear association was apparent between the risk of CVD and usual fasting glucose level above 4.9 mmol/L. Therefore, these reports are consistent with the findings of my analyses. However, my analyses are the first to establish among hypertensive patients that the risk of diabetes starts to increase at a FPG level of 5 mmol/L.

Another interesting finding of my analyses was that the risk of new-onset diabetes associated with baseline FPG progressively diminished with increasing follow-up time. This observation

is consistent with the finding that the relationship between baseline FPG and the risk of new-onset diabetes in the primary Cox model was non-proportional. However it did not affect these findings, as evidenced by the similar result found in my sensitivity analyses, where I incorporated log of follow-up period as a covariate in a logistic regression model. The risk of new-onset diabetes during the first year was more than 9-fold (9.71 [8.05 to 11.71]) which decreased to less than two-fold (but remained significant, p=0.007) after more than 5 years of follow-up (1.86 [1.19 to 2.90]). This trend, not only explains why there was a non-proportionality associated with FPG, but may also reflect the attrition of subjects susceptible to developing new-onset diabetes throughout the trial. Alternatively, it is likely that with an increasing duration of time, life-style and environmental factors may have disrupted the relationship between baseline FPG and new-onset diabetes. For example, in the Diabetes Prevention Project (270) among the high risk individuals with impaired glucose tolerance at baseline, the lifestyle intervention was associated with a 58% reduction in the risk of developing new-onset diabetes.

6.7.2 BMI: In my analyses, each 5 kg/m^2 increase in BMI was associated with a 1.5-fold increase in the risk of developing new-onset diabetes. This is consistent with the findings of other similar analyses (28, 29, 230, 232, 257, 259). The increase in BMI was the second-most important risk factor, which together with the increase in FPG, contributed to the bulk of the associated risk of developing diabetes. Indeed, the clustering of the 3 conditions: obesity, hypertension, and raised glucose is commonly present, and their co-existence is attributed to sharing one or more underlying pathophysiological processes (271, 272). Some authors identify insulin resistance as the reason for this common phenotypic presentation, sometimes defined as the metabolic syndrome; however, others argue that there may be other primary

mechanisms as yet undiscovered to explain the coexistence of these common conditions (273-275).

6.7.3 Amlodipine-based treatment: In my analyses randomisation to the amlodipine-based treatment regimen emerged as the strongest protective factor of all the variables evaluated. This finding is consistent with other trials using antihypertensive agents – in that a regimen based on a CCB to which an ACE inhibitor was added, was associated with significantly less new-onset diabetes than a regimen based on a beta-blocker to which a diuretic was usually added (131, 231). These findings are similar to another smaller study with just one year of follow-up, ALPINE.

The finding that the differential risk of new-onset diabetes between the two antihypertensive regimens in ASCOT-BPLA remained the same irrespective of the baseline risk (Figure 6.3), contrasts with results of the CAPPP Trial (29), but is consistent with findings of the LIFE trial (28). In CAPPP, those who were in the highest risk tertile were also those who had the greatest risk reduction associated with the use of captopril; however, in LIFE, the risk reduction associated with losartan, compared with atenolol, was equal in each risk quartile. Similarly, in my study, the risk reduction associated with amlodipine-based treatment (vs. atenolol-based treatment) was the same, regardless of the patient's baseline risk. This may suggest that every hypertensive patient should be treated with less diabetogenic antihypertensive medications (or a combination of these medications); on the other hand, it is also apparent that patients in the highest risk category compared with the lowest risk category have considerably higher risk (19-fold in this study). Therefore, in a scarce resource setting, where there are significant cost differences between treatment regimens, it may be equally justified to target those at high risk, as they contribute to the biggest disease load.

Given the evidence from previous trials (131, 156, 157) and the results of my analyses, I propose that in ASCOT-BPLA the 34% difference in the risk of new-onset diabetes between the two antihypertensive regimens may be explained by a composite of the adverse metabolic effects conferred by atenolol and thiazide, plus the protective effects afforded by perindopril, with amlodipine probably playing a neutral role. However recent analyses of the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study (276) in contrast to the HOPE trial (277) did not show a significant protective effect of ramipril against new-onset diabetes. In the DREAM study, using a 2X2 factorial study design, the differences in the primary outcome of a composite of death and new-onset diabetes associated with the use of ramipril vs. placebo, and rosiglitazone vs. placebo were evaluated among those with impaired glycaemia at baseline (278). During a median follow-up of 3 years, the use of ramipril 15 mg once daily as compared with placebo failed to demonstrate a significant protection afforded by ACE inhibitor compared with placebo; however the results were in right direction (0.91[0.81 to 1.03) and there was a significant improvement in reversal of impaired glycaemia and reduction of 2 hour post- glucose load—a pre-specified secondary outcome of the DREAM trial. Together these results suggest that ACE inhibitors may have beneficial effects on impaired glycaemia, albeit less than previously thought. Furthermore the DREAM study unlike others, had recruited patients at low cardiovascular risk whose renin-angiotensin system may not have been as active as those at higher cardiovascular risk, thus blunting the beneficial effects of renin-angiotensin system inhibition, and reducing the observed effect size. Thus this apparently ‘negative’ finding may be due to limited power to detect the differences between the two treatments in such a short duration of follow-up. Interestingly, the beneficial, albeit statistically non-significant, effect of ACE inhibitors in comparison with placebo is similar to the findings from a recent network analysis. However,

in that network analysis, compared with diuretics, ACE inhibitors had a significantly protective effect on the development of diabetes (156).

6.7.4 Systolic blood pressure: The finding that an increase in baseline systolic BP was associated with an increased risk of new-onset diabetes, favours the existence of complex relationships and pathophysiological links between hypertension and diabetes (119, 226-228)— such that both are risk factors for each other. The findings from my analyses are consistent with those in LIFE, which reported an 18% increase in the risk of new-onset diabetes for each 10 mm Hg rise in the baseline systolic BP. In another recent study on 1,754 hypertensive patients (mean age, 52 years; 43% women; average follow-up 3.4 years), uncontrolled BP during the trial (SBP≥ 140 mm Hg and/or DBP ≥90 mm Hg at last outpatient) was associated with a more than 2-fold increase in the risk of developing diabetes after accounting for age, BMI, baseline SBP and fasting glucose levels (279). This implies that, whilst the choice of a metabolically neutral or protective antihypertensive agent is important in reducing the risk of new-onset diabetes, it is equally (or perhaps more) important that the preferred antihypertensive regimen should reduce BP as effectively as the other available options. In this context, in the ASCOT-BPLA, compared with atenolol-based treatment, the amlodipine-based regimen was associated with a small but a significant SBP reduction of 2.7 mm Hg at the end of the study (203). This may therefore indicate that the reduction in the risk of diabetes associated with the amlodipine-based regimen, compared with the atenolol-based regimen, may partly be due to a better BP–lowering efficacy of this regimen.

6.7.5 Dyslipidaemia: The finding that baseline serum triglyceride and HDL-cholesterol levels are significant risk factors for the development of diabetes among a hypertensive sub-

population is consistent with earlier observations. Increasing levels of triglycerides have been previously shown to be a causal risk factor for new-onset diabetes (280-282). Similarly, raised HDL-cholesterol has previously been shown to be protective against the risk of new-onset diabetes. In the LIFE analyses with each 1 mmol/L increase in HDL-cholesterol level the risk of new-onset diabetes was reduced by about two-thirds. The findings of my analyses are consistent with the findings of these earlier analyses, and other reports in different population settings (283, 284). However, somewhat counter-intuitively, raised total cholesterol appeared to be protective in my analyses, although this too has been reported in other hypertension trials (28, 29). In the LIFE analyses, serum cholesterol was a protective factor only in their univariate analyses; however, in the CAPPP each 1 mmol/l increase in baseline total cholesterol, after adjusting for other predictors, was associated with a 12% significant reduction in the risk of diabetes. It could be argued that the apparently protective effect conferred by increasing levels of total cholesterol, after adjusting for other lipoproteins, is an artefact of the statistical model as both triglyceride and HDL-cholesterol are components of total cholesterol. However, it could also be argued that this observation is a true effect, given that the increasing levels of total cholesterol levels were protective in unadjusted analyses of the LIFE trial, and similar results have been seen in other non-hypertensive populations (283).

6.7.6 Age: Increasing age (over 55 years) was an independent protective factor for the development of new-onset diabetes in the ASCOT-BPLA. This counter-intuitive finding is consistent with the findings of several recent trials (257, 259), but contrasts with the findings of an older trial (29) . In the VALUE trial, each 10 year increase in age was associated with a 18% [12% to 25%] significant reduction in the risk of developing diabetes. Similar findings were seen in the INVEST analyses, with 10% risk-reduction for each 10 year increase in age.

In contrast, in CAPPP increasing age was associated with a small increase in the risk of new-onset diabetes (1.01[1.00 to 1.02]). Differences in population characteristics between these trials could provide an explanation for these inconsistent findings. Whilst, in the ASCOT-BPLA, VALUE and INVEST trials, randomised patients were older (mean age: 63, 67, and 66 years, respectively) and at a higher cardiovascular risk at baseline, the randomised subjects in the CAPPP were significantly younger (mean age, 52 years), and at a lower cardiovascular risk. These findings are also consistent with the findings of several observational studies (285, 286) which suggest that while the prevalence of diabetes continues to increase with increasing age, the incidence of diabetes plateaus after a certain age, particularly among high-risk patients. This observation may be explained on the basis of attrition of all those individuals who were susceptible as the age increases— a kind of survival bias.

6.7.7 Alcohol intake: My study is consistent with the findings from several other observational studies, in that alcohol intake was protective (287, 288). Carlsson et al in their systematic review found consistent evidence of a protective effect against the development of new-onset diabetes afforded by moderate alcohol intake. However, they did not find any evidence of a 'U' shaped relationship in their analyses. In contrast, another meta-analysis found that among heavy drinkers, there was a blunting of the protective effect. They further found that increasing alcohol intake after a certain level (i.e. alcohol intake ≥48 g/day) is associated with an increasing risk of developing diabetes (289), consistent with the presence of a 'U' shaped relationship between alcohol intake and development of diabetes. In contrast, the relationship between alcohol intake and the risk of diabetes was linear in my analyses. This may be because of a process of self-selection that happens among individuals taking part in a clinical trial. It is well described that people who participate in clinical trials are more likely to be healthier and aware of health-related issues, than those who do not volunteer for

participation (290, 291). Because of the general characteristics of those who drink heavily, it is likely that this group is least likely to opt in for a clinical trial, and may not be fully represented in the ASCOT-BPLA population.

6.7.8 Other medication usage: The increased risk of diabetes associated with the concomitant use of non-cardiovascular medications is a surprising finding. However, this association may potentially be a marker of the use of certain other diabetogenic medications, such as steroids or antipsychotics, among this broad category of medication usage. It is also possible that this variable is a surrogate marker for underlying chronic ill health, which in itself is a diabetogenic state. A recent review suggested that the presence of inflammation may have an important role in linking insulin resistance, obesity and diabetes (292). However, this contrasts with the findings of an apparent lack of any significant association between the risk of diabetes and presence of a chronic inflammatory condition such as rheumatoid arthritis in several observational studies (293-295). Notwithstanding these postulations, earlier analyses from hypertension trials have also found a significant association between the risk of diabetes and previous use of antihypertensive or lipid lowering agents (28, 257).

6.7.9 Risk score: The integer-based score developed from these analyses is the first diabetes risk prediction tool exclusively for use among hypertensive patients in a routine clinical practice setting. Previously the risk score developed from the LIFE population was neither user friendly nor had an algorithm that could be adapted for routine clinical use. Moreover, unlike the LIFE population where all patients had left ventricular hypertrophy, the ASCOT-BPLA population is more representative of hypertensive patients routinely seen in the community. Furthermore, the risk score I have developed has an excellent discriminative

ability (as estimated by associated Harrell's C statistic of 0.80), and a good calibration (as estimated by Hosmer-Lemeshow $\chi 2$ statistics test). This makes it an excellent tool for risk assessment; however, there are a few issues. First, it includes several laboratory measures. Traditionally, the use of laboratory measures in a risk-estimation tool adversely affects its usability and effectiveness, particularly amongst those in the community and primary care. However, laboratory variables included in this risk score are those that are routinely measured among hypertensive patients, and the requirements of these values will not be associated with any added costs, and is unlikely to affect its routine use. Second, in this risk score, I have not included any measure of physical activity (simply because they were not available). This may affect the accuracy of risk estimation; however, the lack of this measure will not affect relative categorisation of patients in the risk groups.

This (easy-to-use) risk score can potentially help clinicians take rapid decisions related to primary prevention of diabetes in routine practice, and its' findings are likely to be applicable to the majority of patients with hypertension in the community. For example, expected risk scores for the majority of hypertensive patients in the primary and secondary care are likely to be between 105 and 130. Therefore, depending on the baseline risk-score, treatment with metabolically neutral (or protective) antihypertensive medications could potentially lower the 5-year risk for new-onset diabetes by 2 to 10%. Furthermore, a routine use of this risk score may pro-actively encourage both patients and physicians to reduce their perceived 5 year risk of developing diabetes, particularly by focussing on the modifiable risk factors such as BMI, SBP and fasting glucose.

6.7. 10 Limitations and strengths:

Generalizability of these findings is an important limitation of these findings, because in the ASCOT-BPLA the majority of patients were men of white Caucasian origin. However, the vast majority of randomised patients in ASCOT-BPLA were recruited directly or indirectly from general practices in the Nordic countries and the UK. Moreover, compared with the patients included in several other recent trials (28, 157, 230, 232, 233, 277), the randomised patients in ASCOT-BPLA were fairly typical of the general hypertensive population (48). On the other hand, these findings require further validation among other ethnic groups. Furthermore, given the large sample size and hence power of these analyses, the clinical relevance of some of the less significant relationships needs to be considered when interpreting the results. For example, it can be argued that the significant relationship evident between the total cholesterol and risk of diabetes could potentially be a function of the greater power of these analyses to detect small, and sometimes, clinically irrelevant relationships. However, these findings have also been reported in other analyses. Another possible limitation of these analyses is that no information is available on physical activity levels of these participants, either on baseline or in-trial. These limitations contrast with considerable strengths of these analyses, including new-onset diabetes as pre-specified outcome, the use of only FPG values, and excellent internal validity of the risk models.

These analyses can also be criticised for seemingly arbitrary choice of cut-off values for 'per unit' rise of the continuous variables in the model. Conventionally 'per unit rise in standard deviation' is used as a cut-off 'per unit' value for the continuous variables, because the effect size (β-coefficient and/or hazard ratio) amongst the continuous variables in the model can be compared. In contrast, in these analyses I have used clinically relevant units to estimate the effect size (and β-coefficients). For example, to quantify the increase in the risk of NOD in these analyses (Table 6.4), I have used clinically meaningful values for 'unit' cut-off of per 10

mm Hg for SBP, and per 1 mmol/L for FPG and HDL cholesterol, instead of conventionally used per unit rise in standard deviation of 18 mm Hg for SBP, 0.6 mmol/l for FPG, and 0.4 mmol/l for HDL cholesterol, respectively. Therefore, it can be argued that the corresponding increase in the risk of NOD of 7% and 49% in these analyses (Table 6.4) is not comparable between the continuous variables in the model, mainly because of the use of different definitions of the 'per unit rise' for these variables. However, this argument is not applicable for interpretation of findings in my analyses. Firstly, I have used Z-scores (which a measure of strength of association) to compare the relative influence of these variables. Z-scores, by definition, remains unaffected by the cut-off units used to measure per-unit rise. This is clearly evident on comparing Z-scores in table 6.10 (where effect size is estimated using conventional 'per standard-deviation' rise, as a 'per-unit' definition for the continuous variables in the model) and table 6.4 (where clinically relevant cut-offs values are used to estimate the effect size). Secondly, the risk score estimated in these analyses is unaffected by the choice of 'per-unit' definition (whether clinically relevant cut-off or per unit increase in standard deviation).This is so, since risk scores are calculated by summing the product of β-coefficient with the value of the variable after taking into account the 'unit' used for estimating the beta-coefficient. For example, if the SBP value for a patient is 180 mm Hg, its contribution to the risk score (i.e. the product of β-coefficient and the value [per unit] of the variable) according to table 6.4 and 6.10 would be 0.067*(180/10) and 0.12*(180/18), respectively—which is exactly same at 1.2; confirming that the estimated risk scores remain unaffected by the units used to estimate β-coefficients.

Another criticism of these analyses is lack of external validation of the developed risk score--in particular, whether this risk score is valid among hypertensive populations in the community. Whilst this clearly is a limitation, it is likely that the use of this risk score in the

community would yield relatively accurate stratification of the risk of NOD among the majority of patients, particularly those who are male, have age >55 years, or are overweight—characteristics that define the patients in the ASCOT-population. Furthermore, there are several clear advantages of this risk score, including ease-of-use, an excellent internal validity and discriminative ability, and good internal calibration.

The conduct of several previous analyses relating to new-onset diabetes have been subject to methodological criticism (30, 131) such as being post-hoc, using different definitions of new-onset diabetes and use of non-fasting and/or whole blood glucose values, but most of these criticisms do not apply to the current study design and analyses. This study demonstrates the relative importance of antihypertensive therapy—after FPG and BMI—and, suggests that their judicious use will benefit all patients regardless of risk category. The development of a relatively simple risk score for predicting new-onset diabetes is the first such score for use in a hypertensive population. However, the risk score needs an external validation, and currently this is an important limitation to its routine use.

Further analyses evaluating whether worsening dysglycaemia and new-onset diabetes are associated with worsening cardiovascular outcomes are discussed in Chapter 7. The current analyses, together with those in Chapter 7, may inform policy decisions on prescribing for hypertensive patients, and possibly clarify earlier conflicting evidence on the relationship between new-onset diabetes and cardiovascular outcomes (25, 26, 296).

In summary, the present analyses provide robust evidence that treating hypertensive patients with a regimen based on amlodipine ± perindopril compared with a regimen based on atenolol ± thiazide diuretic significantly reduces the risk of new-onset diabetes, such that the number

needed to treat of 30 patients for just over 5 years to prevent one case of new-onset diabetes (95%CI 23 to 42). I have described a robust, discriminative model, which helps to accurately determine the risk of new-onset diabetes among hypertensive patients. Furthermore, I have highlighted the relative importance of various other independent predictors such as FPG, BMI, SBP, serum HDL-cholesterol and triglycerides, in the development of new-onset diabetes. Pending further definitive evidence related to cardiovascular morbidity and mortality with antihypertensive-associated incident diabetes, it seems at best unwise, except where compelling indications apply, to use beta-blockers and diuretics in combination, in preference to other combinations such as CCB plus an ACE inhibitor, particularly since the latter agents have been shown to be more cost-effective (238).

6.8 Conclusions

These analyses provide robust evidence that treating hypertensive patients with an amlodipine-based regimen in comparison with an atenolol-based regimen significantly reduces the risk of new-onset diabetes such that the number needed to treat of 30 patients for just over 5 years is required to prevent one case of new-onset diabetes [95%CI 23 to 42]. It further describes a stout, discriminative model, which helps to accurately determine the risk of new-onset diabetes among hypertensive patients, and highlights the relative importance of various other independent predictors including FPG, BMI, serum HDL-cholesterol and triglycerides, in the development of new-onset diabetes.

Chapter 6: Tables

Table 6.1: Comparison of baseline demographic, clinical and laboratory characteristics (percentage/ mean ± SD) according to glycaemic status at randomisation

BASELINE CHARACTERISTICS (N=19257)	AT RISK OF NEW-ONSET DIABETES (N=14120)		"DIABETES" AT BASELINE (N=5137)
	Remained non-diabetic(n=12754)	Developed diabetes (n=1366)	
Atenolol-based regimen (%)	49.0	58.5	50.1
Amlodipine-based regimen (%)	51.0	41.5	49.9
Age (years)	63.0±8.5	61.6±8.3	63.4±8.4
Male sex (%)	77.8	80.7	72.5
Europeans (%)	96.6	96.6	91.8
BMI (kg/m^2)	28.0±4.3	30.2±4.5	30.2±4.8
Current smoker* (%)	69.6	72.9	61.9
Alcohol intake (units/wk)	8.4±11.9	8.2±11.1	6.8±10.9
Family H/O early CAD (%)	30.7	31.4	18.3
H/O previous stroke or TIA (%)	11.9	10.0	8.9
H/O previous PVD (%)	6.3	6.2	6.1
Presence of LVH (%)	22.9	21.1	18.6
Presence of microalbuminuria (%)	61.0	65.8	61.6
TC/HDL ratio ≥ 6(%)	23.8	30.2	23.8
Total cholesterol (mmol/l)	6.0±1.1	5.9±1.1	5.7±1.1
HDL(mmol/l)	1.3±0.4	1.2±0.3	1.2±0.3
Triglyceride† (mmol/l)	1.7±0.9	2.1±1.1	2.1±1.1
FPG† (mmol/l)	5.3±0.6	5.9±0.7	8.6±2.8
Number of cardiovascular risk factors (cf 3 risk factors)			
4 risk factors (%)	30.9	33.1	37.0
>4 risk factors (%)	12.3	15.5	31.0
H/O previous anti-HT drug (%)	79.4	80.1	85.0
Non CAD concomitant medication (%)	56.4	60.2	65.8
SBP (mm Hg)	163.6±17.9	165.0±18.3	164.9±18.1
DBP (mm Hg)	95.3±10.2	96.4±10.7	92.5±10.3
Heart rate (beats per minute)	70.8±12.3	72.9±12.9	74.3±13.0

* Including those who smoked within 1 year

†Excluding those with non-fasting values of triglyceride and plasma glucose

Abbreviations: SD: Standard deviation, H/O, History Of; CAD: Coronary artery disease, TIA: Transient ischaemic attack, TC: Total Cholesterol, TG: Triglyceride, PVD: Peripheral vascular disease; LVH: Left ventricular hypertrophy, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 6.2 Baseline characteristics stratified by the treatment group and the development of diabetes (percent / mean± SD)

Baseline Characteristics	Atenolol-based regimen			Amlodipine-based regimen		
	Total (n=7046)	Developed diabetes (n=799)		Total (n =7074)	Developed diabetes (n=567)	
	Percent/mean±SD	Percent/mean±SD	p-value*	Percent/mean±SD	Percent/mean±SD	p-value
Age (years)	62.8±8.6	61.5±8.3	<0.001	62.9±8.5	61.9±8.2	0.006
Male sex (%)	77.9	79.9	0.156	78.2	81.8	0.028
Europeans (%)	96.6	97.1	0.589	96.6	95.9	0.569
BMI (kg/m^2)	28.2±4.3	30.3±4.5	<0.001	28.2±4.4	30.1±4.6	<0.001
Current smoker† (%)	69.7	71.1	0.354	70.1	75.5	0.003
Alcohol intake units/wk)	8.3±11.9	8.2±11.3	0.72	8.4±11.8	8.1±10.7	0.445
Family H/O early CAD (%)	30.8	33.2	0.123	30.7	28.9	0.338
H/O previous stroke or TIA (%)	11.8	8.9	0.006	11.6	11.5	0.904
H/O previous PVD (%)	6.3	6.4	0.962	6.2	6.0	0.841
Presence of LVH (%)	22.8	20.4	0.083	22.7	22.1	0.697
Presence of microalbuminuria (%)	61.8	66.7	0.002	61.2	64.6	0.084
TC/HDL ratio ≥ 6(%)	24.3	31.2	<0.001	24.6	28.8	0.017
Total cholesterol (mmol/l)	6.0±1.1	5.9±1.1	0.06	6.0±1.1	5.9±1.1	0.03
HDL(mmol/l)	1.3±0.4	1.2±0.3	<0.001	1.3±0.4	1.2±0.3	<0.001
Triglyceride‡ (mmol/l)	1.8±0.9	2.2±1.1	<0.001	1.8±1.0	2.1±1.1	<0.001
FPG‡ (mmol/l)	5.4±0.7	5.9±0.6	<0.001	5.4±0.7	5.9±0.7	<0.001
Number of cardiovascular risk factors (vs. 3 risk factors)						
4 risk factors (%)	31.2	32.8	0.008	31.1	33.5	0.016
>4 risk factors (%)	12.8	15.6		12.5	15.3	
H/O previous anti-HT drug (%)	79.8	80.4	0.66	79.2	79.7	0.754

Non CAD concomitant medication (%)	57.7	61.8	0.012	55.8	57.9	0.295
SBP (mm Hg)	163.6±18.0	164.6±18.3	0.107	163.8±18.0	165.5±18.3	0.017
DBP (mm Hg)	95.4±10.3	96.2±10.8	0.019	95.5±10.3	96.7±10.6	0.007
Heart rate (beats per minute)	70.9±12.3	72.5±12.5	<0.001	71.1±12.5	73.5±13.4	<0.001

Comparison between those who developed diabetes and those who remained non-diabetic on each of the antihypertensive-treatment group at the end of follow-up: Chi-square test or t-test, whichever applicable

† Including those who smoked within 1 year

‡Out of 14120 at risk patients, 1428 (10.1%) patients in all had non-fasting values of either triglycerides (n=1392: atenolol-based treatment (n=705) & amlodipine-based treatment (n=687)) or FPG (n=1427: atenolol-based treatment (n=725) & amlodipine-based treatment (n=702)) or both

Abbreviations: SD: Standard deviation; H/O, History of; CAD: Coronary artery disease; TIA: Transient ischaemic attack; TC: Total Cholesterol; TG: Triglyceride; PVD: Peripheral vascular disease; LVH: Left ventricular hypertrophy; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Table 6.3: Relationship of baseline variables with development of diabetes (Hazard ratios and 95% confidence interval) in univariate Cox regression models (only those with significant values are shown in the table)*

	HAZARD RATIO	95% CONFIDENCE INTERVAL	P-VALUE
Amlodipine-based treatment†	0.69	0.62-0.77	<0.001
Age (per year)	0.99	0.98-0.99	<0.001
Male sex	1.20	1.05-1.38	0.007
BMI (per 5 kg/m^2)	1.42	1.37-1.46	<0.001
Current smoker‡	1.18	1.05-1.33	0.007
Presence of microalbuminuria	1.22	1.09-1.36	0.001
TC/HDL ratio ≥6	1.35	1.21-1.52	<0.001
Total cholesterol (per mmol/l)	0.92	0.88-0.97	0.003
HDL (per mmol/l)	0.39	0.33-0.46	<0.001
Triglyceride (per mmol/l)§	1.29	1.24-1.33	<0.001
FPG§ (per mmol/l)	5.24	4.75-5.78	<0.001
Number of cardiovascular risk factors (vs.3 risk factors)			
4 risk factors	1.18	1.05-1.32	0.007
>4 risk factors	1.39	1.19-1.62	<0.001
Use of non CAD concomitant medication	1.17	1.05-1.3	0.005
SBP (per 10mm Hg)	1.04	1.01-1.07	<0.001
DBP (per 10mm Hg)	1.09	1.03-1.14	<0.001
Heart rate (per beat per minute)	1.01	1.01-1.02	<0.001

* The following variables were evaluated but were found to be non-significant: Race, alcohol intake, past history of vascular events, stroke/TIA and peripheral vascular disease, history of previous antihypertensive, lipid lowering and aspirin therapy, presence of AF or other ECG changes, and pulse pressure
† Compared with the those on atenolol-based regimen
‡Including those who smoked within 1 year
§Excluding those with non-fasting values (see footnote Table 6.2)

Abbreviations:-CAD: Coronary artery disease; TC: Total Cholesterol; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Hazard (risk) ratio

Table 6.4: Primary multivariate Cox proportional hazard regression model for the development of new-onset diabetes (Model 1, n=12,692, cases 1,212).

Baseline characteristics	Hazard ratio	95%confidence Interval	β-coefficient	z-score*	p- value	Contribution to risk score
FPG (per mmol/l above 5 mmol/l)†	5.80	5.24-6.43	1.758	33.55	<0.001	If FPG ≤5 mmol/l add 8.79 to the score , for FPG >5 mmol/l multiply the value with coefficient , and add
BMI (per 5 unit)‡	1.49	1.38-1.62	0.399	9.73	<0.001	If BMI <35 kg/m2 multiply the β-coefficient with BMI/5 and add, & for those with BMI≥35 add 2.814
Amlodipine-based regimen§	0.66	0.59-0.74	-0.412	-7.05	<0.001	Subtract β-coefficient if yes
Triglyceride (per mmol/l)	1.12	1.07-1.17	0.109	4.70	<0.001	Multiply β-coefficient with the value of triglyceride, and add
SBP (per 10 mm Hg)	1.07	1.04-1.1	0.067	4.19	<0.001	Multiply the coefficient with SBP/10, and add
Total cholesterol (per mmol/l)	0.89	0.84-0.94	-0.118	-3.97	<0.001	Multiply the coefficient with total cholesterol value and subtract
Use of non CAD medication (Yes/No)	1.25	1.11-1.40	0.22	3.69	<0.001	Add β-coefficient if yes
HDL Cholesterol (per mmol/l)	0.72	0.58-0.89	-0.329	-3.07	0.002	Multiply the β-coefficient with HDL value and subtract
Age >55 (per 5 year)**	0.94	0.90-0.98	-0.061	-2.77	0.006	if Age≤55 subtract 0.671 from score, and If Age> 55 multiply β-coefficient by Age/11, and subtract
Alcohol intake (unit/wk)	0.99	0.99-1.00	-0.006	-2.38	0.017	Multiply β-coefficient with units/wk, and subtract
Male sex	0.98	0.84-1.14	-0.025	-0.31	0.75	Subtract β-coefficient if yes

* Irrespective of sign, it indicates strength of association, and relative influence. Those with negative signs indicates protective influence in this model
† All those with FPG ≤5 mmol/l were given the same risk; hazard ratio is for every subsequent 1 mmol/l rise
‡ All those with BMI ≥35kg/m^2 were given the same risk of BMI=35 kg/m^2; hazard ratio is for every 5kg/m^2 rise in those with BMI <35 at baseline
§ Compared with those on atenolol-based regimen
ǀ Hazard ratio for every 10mm of Hg rise in SBP
**All those with age≤55 were given the same risk; hazard ratio is for every subsequent 5 year increase

Table 6.5: The Relationship (hazard ratio and 95% confidence interval) between baseline fasting plasma glucose (per mmol/L above 5 mmol/L) and the development of the new-onset diabetes, stratified by the time period of the new-onset diabetes.

Time period of the development of NOD*	Hazard ratio.	95% confidence interval	P-value
Follow-up period			
First year	9.71	8.05 to 11.71	<0.001
1-2 year	5.96	4.74 to 7.50	<0.001
2-3 year	5.92	4.55 to 7.70	<0.001
3-4 year	4.29	3.30 to 5.59	<0.001
4-5 year	3.90	2.88 to 5.27	<0.001
> 5 year	1.86	1.19 to 2.90	0.007

* Overall HR with FPG (per mmol/l above 5 mmol/l) was 5.80 [5.24 to 6.43]
NOD: new-onset diabetes

Table 6.6: Determinants of new-onset diabetes among those randomised to atenolol-based treatment in the ASCOT-BPLA (n= 6,321, cases =705)

Baseline Characteristics	Hazard Ratio	95% Confidence Interval	Z-score*	P-Value
FPG(per mmol/l above 5 mmol/l)†	5.59	4.89-6.40	25.09	<0.001
BMI(per 5 unit)‡	1.6	1.44-1.77	8.81	<0.001
Triglyceride (per 1 mmol/l)	1.24	1.17-1.32	6.69	<0.001
Total cholesterol (per 1 mmol/l)	0.87	0.81-0.94	-3.66	<0.001
Use of non CAD medication	1.31	1.12-1.52	3.38	<0.001
SBP (per 10 mm Hg)	1.07	1.03-1.12	3.26	<0.001
Age>55 (per 5 year)§	0.93	0.88-0.98	-2.49	0.01
Male Sex	0.92	0.76-1.11	-0.86	0.39

*Z score: derived from dividing β-coefficient with standard error, and indicates strength of association irrespective of sign

†All those having FPG ≤5 mmol/l were given similar risk as that of those with FPG 5 mmol/L

‡All those with BMI >35 kg/m2 were given same risk of BMI=35 kg/m2 since risk subsequently plateau

§Age≤55 is at baseline risk, hazards are for every subsequent 5 years rise above 55 years age

Table 6.7: Determinants of new-onset diabetes among those randomised to amlodipine-based treatment in the ASCOT-BPLA (n=6,371, cases = 507)

Baseline Characteristics	Hazard Ratio	95% Confidence Interval	Z Score*	P-Value
FPG[†](per 1 mmol/l above 5 mmol/l)	6.07	5.17-7.12	22.05	<0.001
BMI[‡] (per 5 unit**)**	1.40	1.24-1.59	5.32	<0.001
HDL Cholesterol (per1 mmol/l)	0.55	0.41-0.75	-3.85	<0.001
Heart rate (per 1 beat per min)	1.01	1.00-1.02	2.56	0.01
Alcohol intake (units/wk)	0.99	0.98-1.00	-2.46	0.01
SBP (per 10 mm Hg**)**	1.06	1.01-1.11	2.39	0.02
Current (or ex <1year) smoker	1.28	1.04-1.57	2.36	0.02
Total cholesterol (per 1 mmol/l)	0.9	0.83-0.98	-2.34	0.02
Age>55§ (per 5 year)[#]	0.98	0.91-1.05	-0.67	0.5
Male Sex	1.06	0.83-1.34	0.44	0.66

*Z score: derived from dividing β-coefficient with standard error, and indicates strength of association irrespective of sign

†All those having FPG ≤5 mmol/l were given similar risk as that of those with FPG 5 mmol/L

‡All those with BMI >35 kg/m2 were given same risk of BMI=35 kg/m2 since risk subsequently plateau

§Age≤55 is at baseline risk, hazards are for every subsequent 5 years rise above 55 years age

Table 6.8 An integer-based risk score to predict 5 year risk of developing new-onset diabetes.

										Score
Age	≤60	61-69	70-77	≥78						
	-7	**-8**	**-9**	**-10**						
Glucose	≤5	5.01-5.49	5.5-5.99	6-6.49	6.5-6.99					
	+88	**+97**	**+105**	**+114**	**+123**					
BMI	<19	19-20.9	21-23.4	23.5-25.9	26-28.4	28.5-30.9	31-33.4	33.5-34.4	≥35	
	+15	**+16**	**+18**	**+20**	**+22**	**+24**	**+26**	**+27**	**+28**	
SBP	<115	115-124	125-144	145-154	155-174	175-184	185-204	205-214	≥215	
	+7	**+8**	**+9**	**+10**	**+11**	**+12**	**+13**	**+14**	**+15**	
HDL	<0.75	0.75-1.24	1.25-1.6	1.7-2.1	2.2-2.6	2.7-3	>3			
	-2	**-3**	**-5**	**-7**	**-8**	**-10**	**-11**			
Triglycerides	<0.35	0.35-1.4	1.5-2.4	2.5-3.4	3.5-4.1	4.2-4.9	≥5			
	0	**+1**	**+2**	**+3**	**+4**	**+5**	**+6**			
T. Cholesterol	≤2.1	2.2-2.6	2.7-3.6	3.7-4.6	4.7-5.6	5.7-6.1	≥6.2			
	-2	**-3**	**-4**	**-5**	**-6**	**-7**	**-8**			
Alcohol(units/week)	<7.5	7.5-22.4	22.5-37.4	≥37.5						
	0	**-1**	**-2**	**-3**						
Randomised BP drug	Atenolol	**0**		Amlodipine	**-4**					
Non-CCD medication	No	**0**		Yes	**+2**					

Values beginning with '+' indicate extra points added to score and those values beginning with '– 'indicates points that are subtracted from the score

Table 6.9 Risk scores at baseline and corresponding 5 year probability (risk) of developing diabetes

Total risk score	5-year diabetes risk[§]
99	1.86%
100	2.05%
102	2.50%
104	3.04%
106	3.70%
108	4.50%
110	5.47%
112	6.64%
114	8.05%
116	9.75%
118	11.77%
120	14.19%
122	17.04%
124	20.41%
126	24.33%
128	28.86%
130	34.02%
132	39.83%
134	46.23%
136	53.13%
138	60.37%
140	67.71%

§ 5-year baseline survival probability: 0.9999996

Table 6.10: Modified model 1 to compare the effect size per standard deviation (sd) change in the determinant value (Model 1, n=12,692, cases 1,212).

Baseline characteristics	Hazard ratio	95% confidence Interval	β-coefficient	z-score*	p- value
FPG (per sd [0.6 mmol/l] above 5 mmol/l)†	2.87	2.70 -3.05	1.055	33.55	<0.001
BMI (per sd [4.4 kg/m2])‡	1.42	1.32-1.53	0.352	9.73	<0.001
Amlodipine-based regimen§	0.66	0.59-0.74	-0.412	-7.05	<0.001
Triglyceride (per sd [0.9 mmol/l])	1.10	1.06-1.15	0.098	4.70	<0.001
SBP (per sd [18.0 mm Hg]**)**	1.13	1.06-1.19	0.120	4.19	<0.001
Total cholesterol (per sd [1.1 mmol/l])	0.88	0.82-0.94	-0.130	-3.97	<0.001
Use of non CAD medication (Yes/No)	1.25	1.11-1.40	0.22	3.69	<0.001
HDL Cholesterol (per sd [0.4 mmol/l])	0.88	0.81-0.95	-0.131	-3.07	0.002
Age >55 (per sd [8.5 year])**	0.90	0.84-0.97	-0.104	-2.77	0.006
Alcohol intake (per sd [11.8unit/wk])	0.93	0.87-99	-0.076	-2.38	0.017
Male sex	0.98	0.84-1.14	-0.025	-0.31	0.75

sd: standard deviation

* Irrespective of sign, it indicates strength of association, and relative influence. Those with negative signs indicates protective influence in this model

†All those with FPG ≤5 mmol/l were given the same risk; hazard ratio is for every subsequent 0.6 mmol/l rise

‡ All those with BMI ≥35kg/m^2 were given the same risk of BMI=35 kg/m^2; hazard ratio is for every 4.4 kg/m^2 rise in those with BMI <35 at baseline

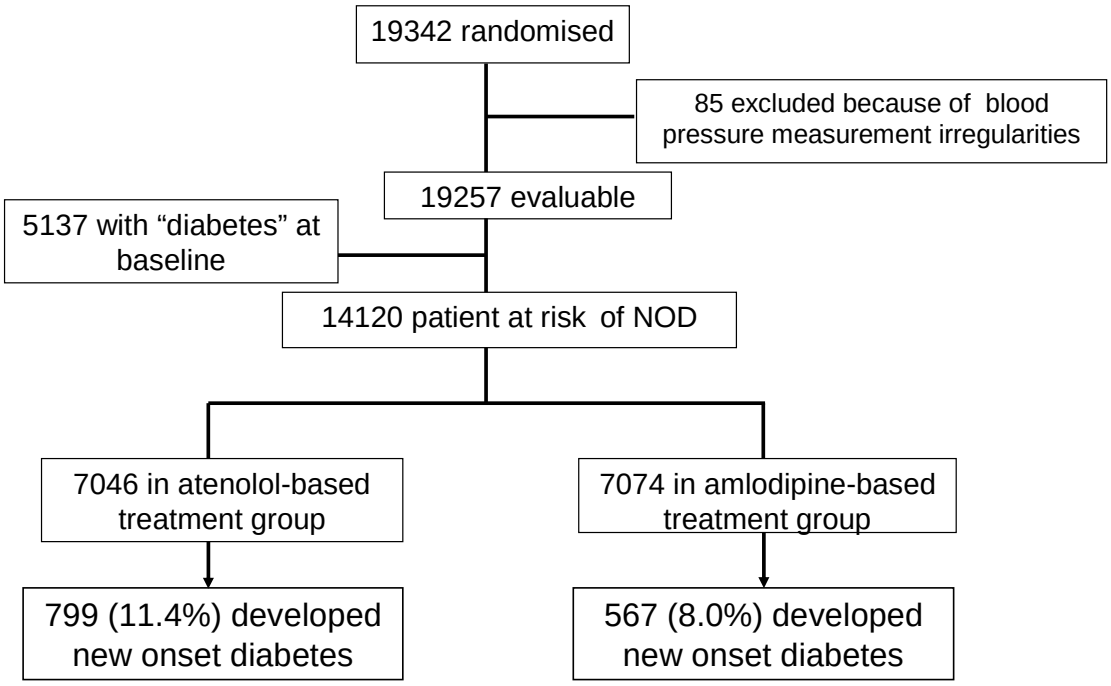
§ Compared with those on atenolol-based regimen

lHazard ratio for every 18 mm of Hg rise in SBP

**All those with age≤55 were given the same risk; hazard ratio is for every subsequent 8.5 year increase

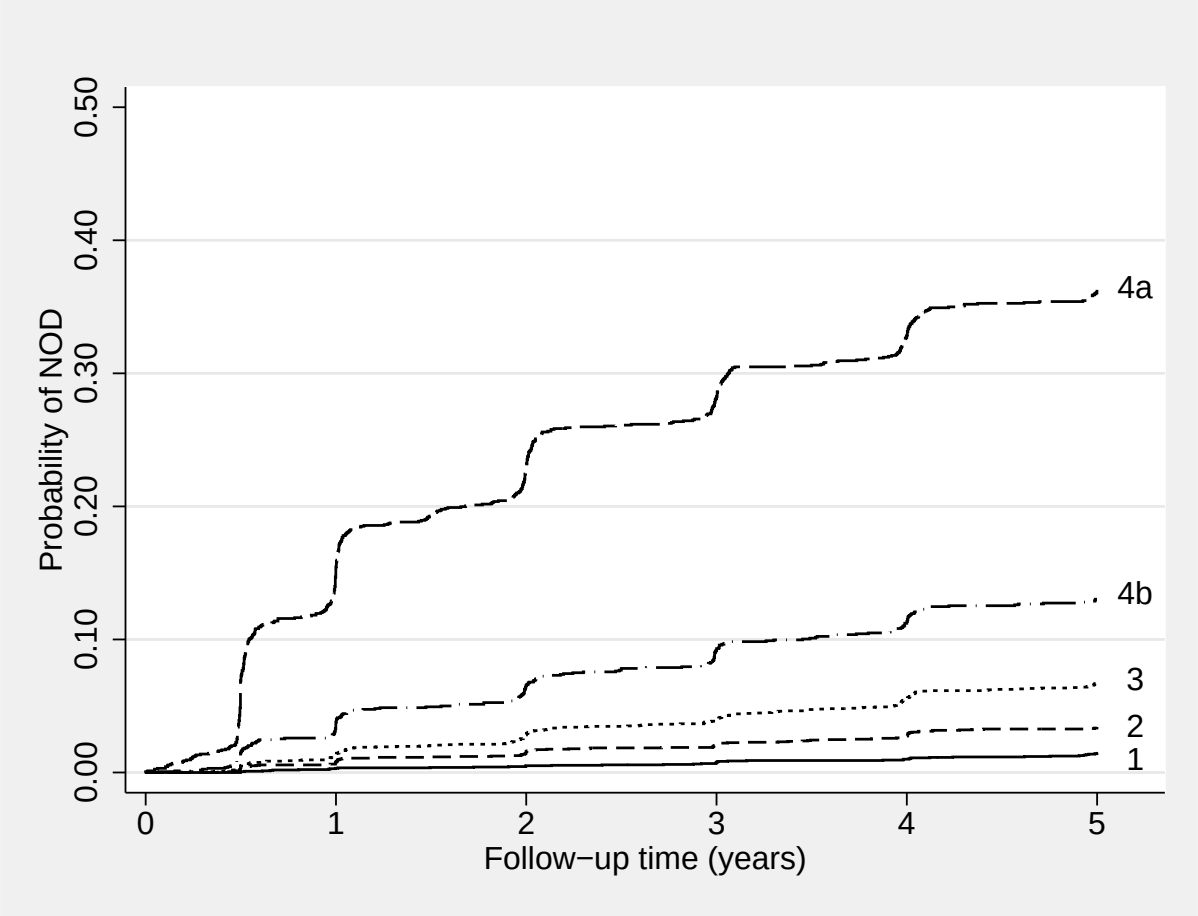
Chapter 6: Figures

Figure 6.1: New onset diabetes development according to the randomised treatment group in ASCOT-BPLA Trial



NOD: new-onset diabetes

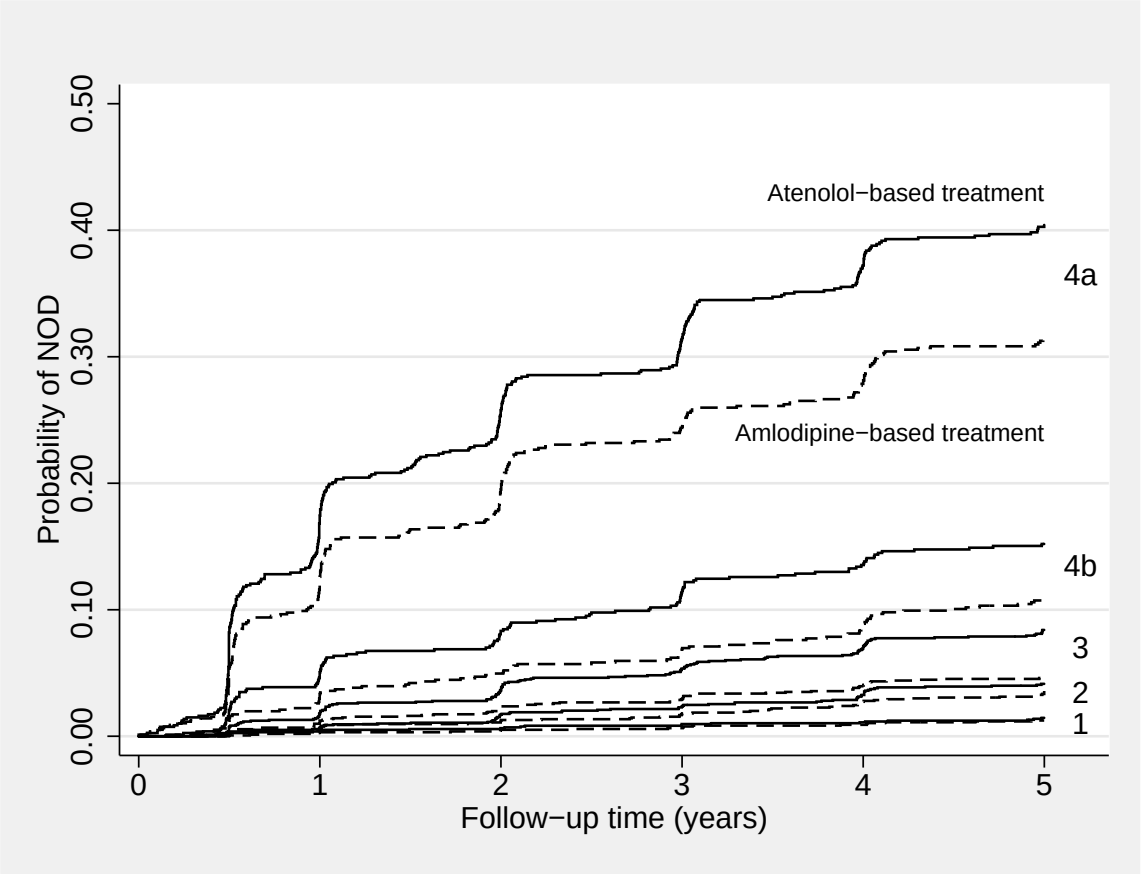
Figure 6.2: Kaplan –Meier graphs of incidence of new-onset diabetes stratified by quartiles of risk score with the uppermost quartile divided equally into two as 4a and 4b (cut off at 5-year follow-up).



Hazard Ratios and 95% confidence interval for each of the risk quartile with 1st quartile as the reference group: 2nd quartile HR= 2.5 (1.8, 3.5); 3rd quartile HR= 5.0 (3.7, 6.9); 4th quartile HR= 19.0 (14.3, 25.4) [4b quartile HR= 9.72 (7.14, 13.25); 4a quartile HR = 30.31 (22.64, 40.57)]. Corresponding risk scores for each of the quartile groups: 1st quartile = (<10.26); 2nd quartile = (10.26 - 10.85); 3rd quartile = (10.86 -11.62); 4th quartile= (≥11.63) [4b quartile = (11.63 -12.29); 4a quartile= (≥12.30)]

NOD: new-onset diabetes

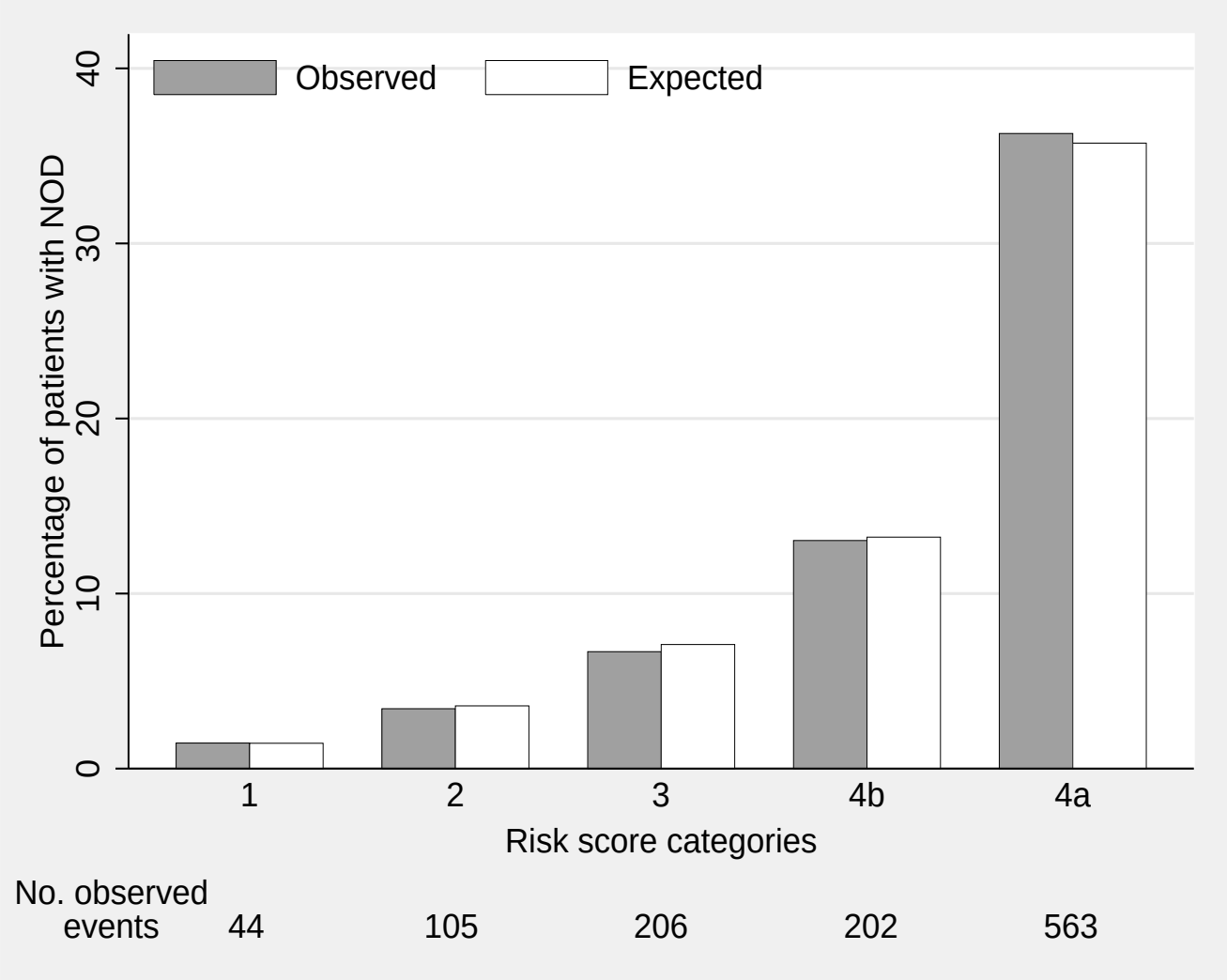
Figure 6.3: Kaplan-Meier graph of incidence of new-onset diabetes stratified by quartile of risk score* and the BP lowering treatment (cut off at 5-year follow-up)



Atenolol-based treatment =solid; Amlodipine-based treatment=dash

*Treatment adjusted for but excluded in the calculation of risk score

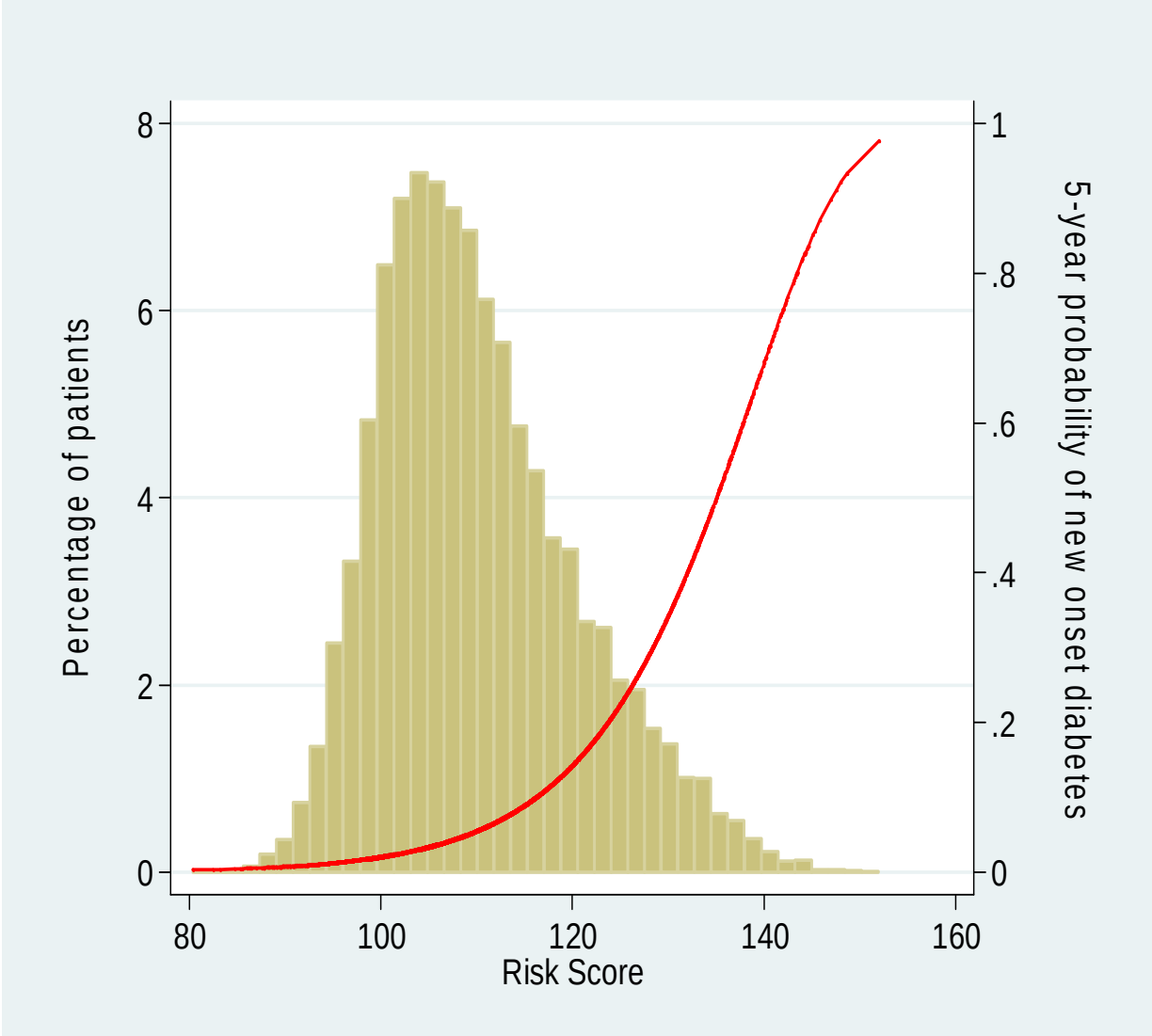
Figure 6.4 Observed and expected 5-year probabilities of the development of diabetes* by risk score quartiles (the upper most quartile divided into two: 4a and 4b) in ASCOT-BPLA



*Probabilities of observed and predicted events are for five years of follow-up

NOD: new-onset diabetes

Figure 6.5 Distribution of risk scores (in percentage) and the relationship with the 5 year probability of developing diabetes in the ASCOT-BPLA.



Chapter 7

OUTCOMES ASSOCIATED WITH GLUCOSE CHANGES, AND INCIDENT DIABETES DUE TO ANTIHYPERTENSIVE MEDICATIONS

Study 2: Relationship between Baseline And Cumulative Mean Fasting Plasma Glucose, Incident Diabetes At One Year, Blood Pressure Treatment Allocation And Cardiovascular Events And Deaths Among Hypertensive Patients In ASCOT-BPLA

7.1 Summary

Controversy exists whether the relatively small adverse effects on glucose metabolism and increase in incident diabetes associated with some of the antihypertensive medications, particularly beta-blockers and diuretics, translate into adverse cardiovascular events. This is an important clinical question, particularly given the fact that these two groups of antihypertensive agents are among the commonest prescribed medications, worldwide.

The database of the blood pressure (BP)-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA) provides an excellent opportunity to investigate these issues in a clinical trial setting. This database includes records of repeated metabolic measures on 19257 hypertensive patients during a median follow-up of more than 5.5 years. Cumulative mean glucose (CMG) was estimated for each individual by averaging all post-randomisation fasting plasma glucose (FPG) readings prior to the date of coronary heart disease [CHD] or stroke event or death. Logistic regression models using CMG or baseline FPG were developed for each of these outcomes, after adjusting for baseline a priori confounders including age, sex, ethnicity, smoking, BP-treatment allocation, body mass index (BMI), alcohol intake, total and high-density lipoprotein (HDL) - cholesterol and number of cardiovascular risk factors. Glycaemic status at the end of the first year after randomisation (i.e. normoglycaemia, impaired glycaemia or new-onset diabetes at 1 year, or pre-existing diabetes) was determined based on serial laboratory data, and using WHO definitions. New-onset diabetes was a pre-specified tertiary end-point of ASCOT-BPLA. Cox models were developed to assess the risk associated with allocated glycaemic status at 1 year for the development of a CHD or stroke event or death, or their combination (i.e. CHD plus stroke plus cardiovascular mortality). Sensitivity analysis included the development of separate logistic regression models, with glycaemic status during the complete study period as a pre-

specified covariate, and adjusting for a priori confounders and follow-up time to the event.

On analysis, CMG and FPG were both found to be independent and significant risk factors for cardiovascular outcomes and death in the ASCOT-BPLA. BP-treatment allocation was significantly associated with differential in-trial increase in CMG levels, and worsening of glycaemic status. Compared with those randomised to amlodipine ± perindopril (amlodipine-based) treatment, those randomised to atenolol ± thiazide diuretic (atenolol-based) treatment had a significantly higher mean CMG, and were significantly more likely to have impaired glycaemia or new-onset diabetes at the end of the first year of the trial (or the complete study period). Compared with those with normoglycaemia at the end of one year, those with impaired glycaemia, new-onset diabetes, and pre-existing diabetes had an increased risk of CHD, stroke and death; however, only the differences among those with pre-existing diabetes were significant. When glycaemic category was used as a continuous variable, a statistically significant trend was apparent, with a progressive increase in the risk of each of the 3 outcomes with each rise in glycaemic category. On sensitivity analysis, compared with those with normoglycaemia during the entire study period, those with impaired glycaemia, new-onset diabetes or pre-existing diabetes, respectively, had 43%, 53% and 62% significant increase in the risk of CHD, and 27%, 64% and 36% significant increase in the risk of stroke. No statistical difference in the risk of death was apparent among those in any of the 3 glycaemic categories, compared with those with normoglycaemia throughout the entire study period.

Taken together, these findings may partly explain the higher cardiovascular event and death rates observed among those randomised to the atenolol-based treatment regimen compared with those randomised to the amlodipine-based treatment regimen in the ASCOT-BPLA trial.

Findings of these post-hoc analyses further strengthen a small body of existing clinical trial and epidemiological evidence, suggesting that the antihypertensive-associated incident diabetes and glucose changes are indeed associated with the increased risk of adverse cardiovascular outcomes and death.

Study 2: Relationship between Baseline And Cumulative Mean Fasting Plasma Glucose, Incident Diabetes At One Year, Blood Pressure Treatment Allocation And Cardiovascular Events And Deaths Among Hypertensive Patients In ASCOT-BPLA

7.2 Hypothesis

1. Antihypertensive-associated increase in mean fasting glucose levels is associated with an increase in the risk of adverse cardiovascular outcomes among the hypertensive patients included in the ASCOT-BPLA.

2. At the end of the first year of treatment, compared with those with normoglycaemia, those with new-onset diabetes (within that period) have a greater risk of cardiovascular events and deaths during the remaining in-trial follow-up period.

3. There is a progressive increase in cardiovascular risk and deaths associated with worsening glycaemic status.

7.3 Background

It has been clear since the 1960's that diuretics and beta-blockers adversely affect glucose metabolism (133, 139, 297-300) However, recent reports from several large scale clinical trials have introduced new and sometimes conflicting data regarding the implications of these metabolic effects (28, 29, 47, 130, 131, 151, 231, 233, 301). Studies have suggested that there is a significantly increased risk of developing new-onset diabetes associated with the use of older antihypertensive agents, such as diuretics or beta-blockers compared with the use of 'newer' antihypertensive agents, such as calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARB's) (28, 29, 47, 157, 230, 233, 257, 277, 301). Since, the presence of diabetes is associated with a 2-4 fold increase in cardiovascular risk (302-304), it has been proposed that antihypertensive-associated incident diabetes may similarly confer increased cardiovascular risk, such that the decrease in cardiovascular risk caused by reduction in blood pressures is offset to an extent by the

increase in new-onset diabetes (305). Therefore, it has been postulated, that the discrepancy between the cardiovascular benefits observed in the earlier trials of BP-lowering, and those expected from observational epidemiological evidence (16, 17) for the same degree of BP-lowering is due to the associated adverse metabolic effects—including those on glucose metabolism—induced by the diuretic and beta-blockers used in those trials (18). This notion, together with extrapolations from indirect evidence (85, 306, 307), has led to changes in some (238), but not all (22-24, 308) prescribing guidelines. Indeed, despite these assumptions and changes in some guidance, both beta-blockers and diuretics continue to be used as first line agents, and remain among the most commonly prescribed antihypertensive agents, worldwide. This is, in part, driven by conflicting reports that have not shown any consistent evidence of cardiovascular harm associated with the development of antihypertensive-associated new-onset diabetes, particularly in the clinical trial setting (25, 26, 296, 309). For example, reports of post-hoc analyses from two trials have suggested that diuretic-associated incident diabetes is 'innocent', inducing no added cardiovascular toll (25, 26). In contrast, reports of several observational studies (296, 309, 310), and findings from one clinical trial (311), have shown that the cardiovascular risk associated with antihypertensive-associated new-onset diabetes is no different than that seen with diabetes developed in other settings (306, 307, 312, 313).

7.3.1 "Antihypertensive-associated diabetes is harmless"—evidence from clinical trials.

A few studies (25-27), despite showing increased rates of developing new-onset diabetes with the use of diuretics, have failed to demonstrate any discernible increase in cardiovascular outcomes associated with the diuretic-associated new-onset diabetes. Prominent among these studies are:

7.3.1.a Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT): Post-hoc analysis of the ALLHAT trial (25, 233), suggested that diuretic-associated incident diabetes is different from naturally occurring diabetes (25, 27), in that the glycaemic and metabolic changes are reversible and not associated with increased cardiovascular risk (143, 240, 314).

In the ALLHAT study (25), the authors compared the cardiovascular risk among those who developed new-onset diabetes in the first two years of follow-up, with those who did not. They further stratified the risks of cardiovascular events and death, according to the randomised treatment groups: chlorthalidone (a diuretic), lisinopril (an ACE inhibitor), or amlodipine (a calcium channel blocker). Furthermore, they evaluated the relationship between the change in glucose levels associated with the allocated therapy, and subsequent cardiovascular events.

Their findings confirmed that those allocated to chlorthalidone had a significantly higher incidence of new-onset diabetes (9.3%), compared with those allocated to lisinopril (5.6%) or amlodipine (7.2%) ($p < 0.008$ and $p < 0.001$, respectively). After two years of follow-up, allocation to chlorthalidone was associated with a significantly greater increase in fasting glucose levels (0.5 mmol/l), as compared with the other two treatment groups (0.2 mmol/L for lisinopril and 0.3 mmol/l for amlodipine). The authors reported the presence of inconsistent relationships between new-onset diabetes (within the first two years of follow-up) and subsequent risk of cardiovascular events or death. Compared with those who did not develop diabetes, those who developed new-onset diabetes had a significantly higher risk of CHD (hazard ratio [HR] 1.64 [95% confidence interval (CI): 1.15 to 2.33]), but no significant increase in risk of stroke (1.61[0.92 to 2.84]), death (1.31[0.95 to 1.81]) and heart failure

(1.37 [0.84 to 2.24]). Furthermore, in a sub-group analysis of those allocated to the chlorthalidone treatment group, a comparison of cardiovascular risk among those who developed diabetes and those who did not showed no significant difference in the risk of CHD (HR 1.46 [0.88 to 2.42]), death (HR 1.05 [0.66 to 1.67]), stroke (HR 1.83 [0.85 to 3.95]) and heart failure (HR 0.96 [0.46 to 2.00]). They also reported that the increase in 0.5 mmol/L fasting glucose levels during the first two years of chlorthalidone treatment was not significantly associated with an increased risk in cardiovascular events or death. Hence, on the basis of these analyses the authors concluded that there was no 'consistent' evidence that the diuretic-associated increase in incident diabetes was associated with an increased risk of cardiovascular events or death. These findings were, therefore, interpreted by some (25, 144) to suggest that diuretic-associated new-onset diabetes may be different than de-novo diabetes.(27, 240, 315),.

However, these analyses and their interpretation have been appropriately criticised because of several methodological shortcomings (305, 316, 317). For example, only 53% of the analyzed patients had one or more fasting glucose level recorded during the entire follow-up period; the misclassification of diabetic patients as non-diabetic was common and uncorrected, and the definition of new-onset diabetes was inadequate and based on a single reading of fasting glucose >125 mg/dl (6.9 mmol/l) (317). More importantly, the main conclusions drawn by the authors on the basis of these sub-group analyses among those with and without diabetes in the chlorthalidone arm are contentious, particularly as they do not have adequate power for such analyses (305, 316, 318). The lack of power is further evident from the wide confidence intervals associated with estimated hazard ratios in these sub-group analyses. Also, there were inconsistent findings among those allocated to the chlorthalidone arm and those allocated to the lisinopril arm, in that, among those developing new-onset

diabetes in the chlorthalidone arm, there was no significant increase in cardiovascular risk or deaths, whereas among those developing new-onset diabetes in the lisinopril arm the risk of CHD (2.23[1.07 to 4.62] and heart failure (3.66 [1.30 to 10.32]) was significant. Most importantly, overall, new-onset diabetes was associated with an increased CHD risk, and given that there were no significant interactions between the treatment allocation and the risk of cardiovascular events or death among those developing new-onset diabetes in each of the 3 treatment groups, the reported conclusions are debatable. These findings could equally be interpreted as being similarly applicable to those randomized to all three drug regimens, including chlorthalidone.

7.3.1 b Systolic Hypertension in the Elderly Program (SHEP) : Kostis et al (315) in their long-term mortality follow-up of the SHEP cohort (234, 319) reported that, after a mean total follow-up of 14.3 years(10 years after the trial closure), there was a 56% and 35% increase in the risk of cardiovascular- and all-cause mortality, respectively, among those who developed in-trial new-onset diabetes, compared with those who did not. However, among those allocated to chlorthalidone, the risks of cardiovascular mortality or death were statistically similar among those who developed new-onset diabetes during the trial period as compared with those who did not (HR 1.04[0.75 to 1.46] and 1.15[0.93 to 1.43], respectively). In contrast, among those allocated to placebo, cardiovascular mortality and all-cause death rates were significantly higher among those who developed diabetes during the trial as compared with those who did not. Based on these observational findings, the authors concluded that diuretic-associated new-onset diabetes runs a much milder course. However, these results could possibly be explained by the BP reduction of 11.3/3.4 mm of Hg that was seen among those on diuretic therapy at the end of the trial, compared with those allocated to placebo. Since in persons with diabetes, BP control is more effective than glycaemic control in

preventing cardiovascular complications (117, 320), it is likely that in the diuretic arm the incremental cardiovascular risk associated with a relatively small number of extra cases of new-onset diabetes was obscured by the considerable reduction in cardiovascular risk caused by significant BP reduction in the treatment arm, whether diabetic or not (305, 321). Hence, there was no noticeable increase in cardiovascular risk among those who became diabetic in the diuretic arm in this study.

7.3.2 Antihypertensive-associated diabetes increases cardiovascular risk: evidence so far

In contrast to the findings reported in section 7.3.1, a few studies have shown an increased cardiovascular risk associated with antihypertensive-associated incident diabetes (296, 311, 322, 323) and glucose changes (309). In a cohort study of 795 initially untreated hypertensive patients, with a median follow up of 6 years (range: 1 to 16 years), Verdecchia et al (296) observed the development of new-onset diabetes in about 6% (n = 43) of these patients. They reported that new-onset diabetes was associated with almost a three-fold (odds ratio 2.92 [1.33 to 6.41]) greater risk of cardiovascular disease (CVD), as compared with those who remained persistently free from diabetes. The cardiovascular event rates among those with new-onset diabetes were similar to those who had pre-existing diabetes. These findings are similar to those observed in other clinical settings. (306, 307) However, there were only 63 cardiovascular events in this observational study by Verdecchia et al, 2004. Moreover there were no controls or sufficient power, to assess the relationship between the use of antihypertensive medications (particularly diuretics or beta-blockers) and subsequent development of cardiovascular events.

In another population-based observational cohort, comprising 725 non-diabetic hypertensive men (322), 20% (n = 148) of patients developed new-onset diabetes during the follow-up of

up to 28 years. On survival analyses, those with new-onset diabetes, as compared with those who remained non-diabetic, had a significantly greater risk of stroke (HR 1.67 [1.1 to 2.6]), myocardial infarction (HR 1.66 [1.1 to 2.5]) and death (HR 1.42 [1.1 to 1.9]). The mean observation time from onset of diabetes to first event of stroke or myocardial infarction was 9.1 and 9.3 years, respectively. Development of new-onset diabetes was significantly and independently associated with beta-blocker treatment. However, this small observational study also had potential methodological limitations, including treatment bias and confounding. For example, in this study, it is likely that the use of diuretics was systematically avoided among those 'deemed' at a high risk of diabetes. Moreover, patients received several different antihypertensive medications, making it difficult to tease out the cardiovascular adverse effect of diabetes related to specific drugs. Interestingly, earlier analyses of this same cohort (after 16 years of follow-up) did not show any impact of beta-blocker and/or thiazide diuretic associated new-onset diabetes on the development of CHD (246). The authors attributed these apparent differences to the lesser number of events, and significantly lower power in the earlier analyses. Furthermore, they believe that their 'newer' findings suggest that the follow-up period may also be an important contributor, given the fact that there is a prolonged incubation period before the vascular damages associated with small hyperglycaemic changes manifest as cardiovascular outcomes.

In a recent report from the Valsartan Antihypertensive Long Term Use Evaluation (VALUE) trial (157, 311), the authors compared the risk of cardiovascular events and deaths among those with diabetes at baseline, those who subsequently developed diabetes, and those who remained non-diabetic during the mean in-trial follow-up of 4.2 years. Their findings suggest that patients who developed diabetes compared with those who did not, were at a greater risk of cardiac morbidity (defined as first event of myocardial infarction or heart failure) (HR

1.43 [95% CI, 1.16 to 1.77]), but not for stroke (HR1.04 [0.77 to 1.41]) or all-cause mortality (HR 0.61 [0.48 to 0.77) or cardiac mortality (HR 0.44[0.28 to 0.70]). The surprisingly protective effect of new-onset diabetes towards the risk of death during the study period was attributed to the escalation of treatment after the diagnosis of diabetes, with aggressive BP control and increased use of statins and aspirin. In a separate sub-group analysis, new-onset diabetes was also associated with a significantly increased risk of heart failure (HR 1.41[1.06 to 1.87], p=0.016) but not of myocardial infarction (HR 1.30[0.99 to 1.70], p=0.056). The former finding is supported by a recent report from the Ongoing Telmisartan Alone and In Combination with Ramipril Global End Point Trial (ONTARGET) (323), where development of the new-onset diabetes was associated with a 74% increased risk of developing heart failure requiring hospitalization (HR 1.74 [1.09 to 2.76]).

Despite supportive findings from the ONTARGET trial (323), the post-hoc analyses of the VALUE trial have several methodological issues. Firstly, the use of survival analysis is contentious because the authors used information from a future outcome (i.e. development of diabetes or not) in categorising patients at baseline, and have used this information of diabetic status as one of the baseline exposure variables in their statistical analyses. Therefore, it is likely that in the survival analysis, some of the cardiovascular events may have preceded the development of diabetes. The authors' reasonable justification for this approach was that patients prone to develop diabetes, such as those with impaired glycaemia, may have a high cardiovascular risk in the interim period before the diagnosis of new-onset diabetes. However, this does not detract from the fact that in survival analysis, outcomes cannot precede the exposure; perhaps the use of logistic regression models would have been more appropriate. Secondly, it is difficult to explain why in the VALUE trial the development of new-onset diabetes had differing consequences for coronary events and all-cause and cardiac

mortality: whilst, there was an increased risk of coronary events associated with new-onset diabetes, the new-onset diabetes was associated with an apparent reduction in the risk of all-cause and cardiac- mortality. It can be argued (as have the authors) that the apparently protective effect of new-onset diabetes on mortality rates were because of the aggressive risk factor management initiated after the diagnosis of the diabetes, however, if true, similar benefits should have been observed on cardiac events as well. This is because, if the measures instituted after the diagnosis of new-onset diabetes, are able to reduce the risk of death and the end-organ damage, they should have a similar protective effect on the risk of subsequent coronary events. Finally, the risk of new-onset diabetes in VALUE was 23% lower in those allocated to the valsartan arm compared with those allocated to the amlodipine arm; however, there were no significant differences in pre-specified cardiac morbidity or mortality outcomes between the two treatment arms. It could therefore be interpreted to mean that any adverse cardiovascular effect associated with the development of new-onset diabetes was clinically insignificant during the duration of trial.

7.3.3 Antihypertensive-associated glucose changes and cardiovascular outcomes

A few studies (25, 243, 296, 309, 324, 325) have evaluated the associations between antihypertensive- associated glucose changes and cardiovascular risk, and have found an inconsistent relationship.

Dunder at al (309) in their observational study of 1860 men reported that an increase in blood glucose was an independent risk factor for myocardial infarction among 502 men receiving antihypertensive agents (mainly beta-blockers and diuretics), but not among those without such treatments (n=1,358). They reported a 22% increase in the risk of myocardial infarction with each 10% rise in fasting glucose level from baseline. Another observational study (322)

among 6,886 hypertensive patients found that the use of diuretics (compared with other antihypertensive agents) was associated with significantly higher in-trial blood sugar levels, which in turn were associated with an increased risk of cardiovascular events. Compared with those in the lowest in-trial blood sugar stratum (<6.11 mmol/l), those in the highest in-trial blood sugar stratum (>7.75 mmol/l) had a 2-fold increase in CVD risk. Overall, and in each blood sugar stratum, the CVD incidence had a direct dose-response relationship with the use of diuretics; however, the differences were only significant among those with elevated in-trial blood sugar (> 7.75 mmol/L). Among those with in-trial blood-sugar > 7.75 mmol/L (the highest blood sugar stratum), the cardiovascular incidence rate was significantly higher among those who frequently used diuretics (31 per 1000 person years), compared with those with moderate (13.3 per 1000 person years, p=0.004) and rare (13.2 per 1000 person year, p=0.008) usage of diuretics. However, interestingly, the relationship between cardiovascular risk and diuretic-associated glucose changes became insignificant after adjustment for self-reported diabetes status.

In a post-hoc analysis of the largest hypertensive trial to date, ALLHAT (25) there was no significant increase in the risk of CHD, stroke or death associated with a diuretic-associated 0.5 mmol/l increase in glucose levels within the first two years of treatment. However, this analysis has several methodological limitations as previously discussed in Section 7.3.1.a, and the basis of these findings have been questioned (296, 317, 318). To date, no other hypertension trial has explored the relationship between antihypertensive-associated glucose changes and cardiovascular outcomes.

A few reports have suggested that diuretic-associated increases in glucose levels are transient (144, 240), and the adverse effect on glucose metabolism could largely be mitigated by the

use of potassium supplements (143, 147, 240, 326). Furthermore, a recent meta-analysis reported that intensive glycaemic control among diabetic patients did not reduce stroke or all-cause mortality, but did significantly reduce coronary risk (104). These findings conflict with reports from the long-term follow-up of other similar trials (that are not included in the meta-analyses above) , where intensive glycaemic control has been shown to reduce cardiovascular events and death among patients with diabetes (106, 109, 111, 117). Hence, the controversy regarding the impact of antihypertensive-associated glucose changes and cardiovascular risk persists, not only among patients with hypertension, but also in other settings.

7.3.4 Summary of the evidence: a critique

Despite several studies exploring the relationship between antihypertensive-associated glucose changes and/or incident diabetes and cardiovascular outcomes, the controversy still persists. The majority of the current evidence is consistent with the assumption that antihypertensive-associated incident diabetes (and glucose changes) is no different than naturally occurring 'de-novo' diabetes (or glucose changes), and has similar cardiovascular implications (305, 316, 318, 321, 326). However, the findings from the largest trial on hypertension, ALLHAT, and that with the longest follow-up, SHEP, have cast doubt on these assumptions. Some of the inconsistencies in the findings to date may have arisen from differences in the follow-up period, sample size, analytical methods used, study design, and quality of data.

The duration of follow-up in some of these trials (25, 311), and observational studies (246), may have been insufficient to demonstrate consistently the magnitude of increased cardiovascular risk associated with the small metabolic changes associated with the use of antihypertensive agents. Insufficient sample size to answer these questions is another reason for the conflicting reports. For example, it has been estimated that 385 to 449 hypertensive

patients need to be treated for four years with metabolically neutral or protective antihypertensive medications, instead of those with adverse metabolic effects, such as diuretics or beta-blockers, to prevent one cardiovascular event (327). Therefore, it is unsurprising that some of the sub-group analyses from ALLHAT, pertaining to the relationship between incident diabetes and cardiovascular outcomes were statistically insignificant. Notwithstanding these conflicting reports, it is unlikely that a well-planned large clinical trial, with a longer follow-up, will ever be conducted (in future)to resolve these controversies, mainly because of cost considerations. However, these important questions (in my view) could still be resolved by either the long-term mortality and morbidity follow-up of previously conducted large-scale hypertension trials, or by taking a different analytical approach on an existing large database of hypertensive patients.

I hypothesize that much of the inconsistencies in the findings to date may have arisen because previous analyses have defined new-onset diabetes as a dichotomous point of abrupt increase in cardiovascular risk. This approach (when used alone) does not take into account the increased cardiovascular risk associated with impaired glycaemia, nor the continuous linear relationship that exists between glucose and cardiovascular outcomes, as reported in several observational studies (315, 328) . Thus, comparing event rates among those with and without new-onset diabetes, particularly in clinical trial settings where the follow-up is limited and/or numbers of events are small, may have attenuated the real differences in event rates between diabetic, dysglycaemic and normoglycaemic individuals. Furthermore, I believe that using a single reading of FPG to reflect the ‘usual’ or ‘true’ glycaemic status of an individual is flawed. Firstly because of considerable intra-individual variability in FPG level; secondly FPG is dependent on the duration of fasting; thirdly when a single FPG is recorded in an epidemiological study, there is the possibility of misclassification bias if non-fasting glucose

levels are recorded as fasting. These factors, together, may have obscured the true relationship between fasting glucose and cardiovascular risk. Hence I propose that using a long-term marker of glycaemic status may be a more accurate and robust measure to reveal the true relationship between glucose levels (i.e. glycaemia) and cardiovascular risk, Indeed, studies have shown that glycosylated haemoglobin (HbA1c), an indicator of the average blood glucose over the preceding 3 months, has a consistent and linear relationship with cardiovascular risk (329-331), and hence is a more reliable indicator than fasting glucose alone. However, even HbA1c assays only denote the average blood glucose over a relatively short period of 8 to 12 weeks, and therefore, they may not consistently reflect an individual's 'usual' glycaemic status over a prolonged period in months or years (330, 332). Indeed, this was confirmed in a recent study by Kilpatrick et al (330): it was shown that compared with HbA1c, using mean blood glucose level (over prolonged period in years) to denote 'usual' glycaemic status was a significantly better predictor of cardiovascular risk. The authors went on to suggest that mean blood glucose may predict cardiovascular risk more accurately compared with the usual metrics for glycaemic control. This is further demonstrated in the Diabetes Control and Complications Trial (DCCT) (106, 107). In 1995 the authors of DCCT reported that intensive glycaemic control had no significant impact on cardiovascular events; however, 10 years later in 2005, after analysing a total of 17 years of follow-up, the same study group in their observational follow-up of DCCT, Epidemiology of Diabetes Interventions and Complications (EDIC) study, reported that intensive glycaemic control was associated with a 42% reduction in cardiovascular events (111). Kilpatrick et al have shown that use of mean blood glucose, instead of other glycaemic markers would have led to similar findings but well within the original follow-up period of DCCT, potentially having a large impact on the management of patients with diabetes.

However, to date, no study has assessed the cardiovascular risk conferred by antihypertensive-associated incident diabetes or dysglycaemia either using the analytical approach described above of using glycaemic categories in continuum, or mean blood glucose levels (preferably cumulative means or area-under curve) prior to the event. The database of ASCOT-BPLA (47, 48) provides an excellent opportunity to investigate these relationships and contribute to the current understanding of the impact of blood glucose and/or new-onset diabetes on cardiovascular risk.

7.4 Aims and objectives

1. To evaluate the relationships between baseline FPG, CMG, and antihypertensive treatment allocation among hypertensive patients in the ASCOT-BPLA.

2. To determine the risk of CHD, stroke and death associated with baseline FPG, and CMG levels prior to events.

3. To determine if an increase in CMG from the baseline glucose level is associated with an increase in cardiovascular morbidity and mortality among hypertensive patients.

4. To determine if different antihypertensive treatment regimens differentially influence CMG levels at the end of the study.

5. To compare among those with normoglycaemia, impaired glycaemia and new-onset diabetes after one year of in-trial treatment and those with pre-existing diabetes at randomisation the subsequent risk of CHD, stroke and death.

6. To investigate whether there is a linear relationship between worsening levels of glycaemic status (normoglycaemia, impaired glycaemia , new-onset diabetes and pre-existing diabetes) and subsequent cardiovascular risk.

7.5 Materials and Methods

The details of the study design, methods used and the main results of ASCOT-BPLA have been published (47, 48) , and are also described in Chapter 4. However, a brief summary of the details relevant to this study are given below:

7.5.1 Study population: All randomized patients with evaluable data were included in these analyses (n=19,257). Subjects were hypertensive patients with three or more cardiovascular risk factors, but with no pre-existing history of CHD. The majority of patients were recruited from general practices across the Nordic countries, the UK/Ireland (48).

7.5.2 Procedures: After initial screening for inclusion and exclusion criteria, subjects attended a randomisation visit after an overnight fast, when a detailed clinical examination, medical history, laboratory tests and an ECG recording were carried out. Patients were then randomised using the prospective randomised open blinded endpoints design to receive one of two antihypertensive regimens: atenolol adding bendroflumethiazide/K+ as required (atenolol-based treatment) or amlodipine adding perindopril as required (amlodipine-based treatment) to achieve BP targets (<140/90 mm Hg for those without diabetes at baseline, and <130/80 mmHg for those with diabetes). Subsequently, at each study visit antihypertensive drug therapy was titrated to achieve target BP, and information was recorded about adverse events and any new cardiovascular event or procedure, including the cause for any hospital admission. Fasting blood samples were obtained at 6 months, 12 months, and thereafter annually. Additional blood samples were collected at extra-visits, if clinically indicated. Anthropometric measurements were recorded annually.

7.5.3 ASCOT-BPLA Definitions: In the ASCOT-BPLA database, *diabetes at baseline* (n=5,137) (333, 334) was defined as the presence of one or more of the following criteria:

1. Self-reported history of diabetes with evidence of receiving either dietary advice or antihyperglycaemic medications including insulin (n=4,646);
2. One (or more) recording of FPG ≥7 mmol/L, or random glucose of ≥11.1 mmol/L at the time of screening or randomisation;
3. Presence of a combination of FPG ≥ 6.1 mmol/l and glycosuria at screening or randomisation.

The latter criterion was chosen by the endpoint adjudication committee to avoid misclassification of people who had described themselves as non-diabetic at baseline, but investigations with oral glucose tolerance tests or repeat fasting glucose levels had revealed the presence of diabetes. Indeed, the majority of patients in the latter category subsequently had at least one recorded FPG levels that was consistent with a diagnosis of diabetes. *Development of diabetes* during follow-up was diagnosed on the basis of the 1999 WHO criteria.(169). The WHO-IDF definition (335) was used to define normoglycaemia (FPG < 6.1 mmol/L and random [or 2 hour post glucose load] glucose level < 7.8 mmol/l) and impaired glycaemia (FPG between 6.1 to 6.9 mmol/l or random [or post glucose load] glucose level between 7.8 to 11.0 mmol/l).

7.5.4 Outcomes: The combination of fatal CHD and non-fatal myocardial infarction [hereafter termed as CHD], fatal and non-fatal stroke [stroke], and all-cause mortality [death] formed the 3 separate outcomes in my analyses. All 3 outcomes were pre-defined primary or secondary outcomes of ASCOT-BPLA, and were independently adjudicated by the endpoint committee. For some descriptive analyses, patients who had at least one of the three events were grouped together as those with ‘any specified outcome’ to differentiate from those who

had no such event during the study period. For the purpose of the sensitivity analyses, combinations of the 3 specified outcomes (or their parts) were used. All of these 'new' outcomes are also taken from the list of pre-specified outcomes of the ASCOT-BPLA.

7.5.5 Statistical Methods: STATA 9 software was used for all statistical analyses.

7.5.5 a FPG, CMG and cardiovascular outcomes:

For the purpose of these analyses, CMG levels were calculated for every individual, based on the serial recording of all fasting glucose levels (gathered either on a scheduled or an extra visit) until the date of exit from the study or prior to death. Separate estimations were also calculated to determine CMG levels prior to the date of each pre-defined cardiovascular outcome. Thereafter, mean baseline FPG, CMG and difference between the two glucose levels (mean CMG minus mean baseline FPG) were compared between those who did and did not have each of the 3 pre-specified outcomes, and also according to antihypertensive-treatment allocation. Mean area-under-curve (AUC) for mean fasting glucose until the exit from the study (or death) was estimated using the trapezoid method (332, 336). Graphical comparisons using mean AUC fasting glucose, at several time-points during follow-up, were performed between those randomized to the 2 treatment groups. Means were compared using t-tests or if applicable, one-way analysis of variance. Chi-square test or Fischer exact tests were used for categorical variables.

The incidence rates (per 1000 person years) were determined for each of the three outcomes, and were stratified according to the allocated treatment. To assess the impact of glucose levels on the development of these outcomes, several multivariable logistic models using CMG (or baseline FPG) were developed for each of these outcomes after adjusting for a

priori factors that were considered to confound the association between glucose and cardiovascular outcomes including age, sex, ethnicity, smoking, BP-treatment allocation, body mass index (BMI), alcohol intake, total and high-density lipoprotein (HDL) - cholesterol and number of cardiovascular risk factor at baseline. Other baseline characteristics were considered for inclusion in the model if they were found to be a potential confounding variable on univariate analysis or using the backward stepwise selection method ($p<0.1$). All of these additionally identified variables were considered for inclusion in the model, if they were not highly correlated with the a priori confounders or the pre-specified covariates (fasting glucose or CMG). In the case of a significant correlation between two identified potential confounders, only one was entered into the model, and was chosen on the basis of its perceived clinical significance or the strength of its association with the outcome. Continuous variables were only categorised if they were found to be non-linear, or because the groupings would be more clinically relevant or desirable. For each model, the CMG levels prior to the outcome of interest were used as a specific covariate.

7.5.5.b Glycaemic status, new-onset diabetes and cardiovascular outcomes

i. Glycaemic status allocation at 1 year:

After excluding all those who were 'deemed' to have 'pre-existing' diabetes, and those who developed new-onset diabetes within the first year of the randomisation, the normoglycaemic or impaired glycaemic status at 1 year was determined for the remaining patients under follow-up —based on serial recordings of fasting (and if available non-fasting) glucose levels— provided there was at-least one available recording of glucose level during that period.

Patients were assigned to one of the following 4 categories: [1] Normoglycaemia at 1

year, if all available fasting glucose levels (including those at screening or randomisation visit) were < 6.1 mmol/l, and non-fasting glucose levels were < 7.8 mmol/L. [2] Impaired glycaemia at 1 year, if any FPG reading during the preceding year was between 6.1 to 6.9 mmol/l or non-fasting (random) glucose reading was between 7.8 to 11.0 mmol/L. [3] New-onset diabetes at 1 year, (defined using WHO 1999 definition: FPG ≥ 7 mmol/l and/or 2 hour post-load [or random] glucose ≥11.1 mmol/l on two separate occasions). [4] Pre-existing diabetes at the time of randomization. Glycaemic status at the end of the first year of follow-up after randomization was chosen, because it allows adequate time and opportunity to correctly classify patients, and provides a relatively long follow-up (mean 4.3 years) to assess the risk of subsequent cardiovascular events.

ii. Baseline variables and missing values:

All baseline variables, including data on demographic, medical history, medication, clinical examination and laboratory investigations, were available for these analyses. However, only fasting values of serum triglyceride (n=17,472) and glucose (n=17,435) were reported at the randomisation visit in ASCOT-BPLA. The models containing baseline FPG and/or serum triglyceride values are therefore limited to those with fasting values available for both (n=17,430). Of all randomized patients, 3.2%, 1.3% and 0.5%, respectively, had missing baseline values for serum creatinine, alanine transaminase and potassium. No attempt was made to impute any data for these missing values, as the numbers were small. To exclude any possibility of a selection bias, baseline characteristics of those with any missing (or non-fasting) values were compared with those with no missing (or non-fasting) values.

iii. Analysis:

Baseline characteristics of those who had normoglycaemia, impaired glycaemia, new-onset diabetes after one year of follow-up or pre-existing diabetes at baseline were compared. To assess the risk associated with glycaemic status after 1 year of follow-up, separate multivariable Cox regression models were developed for each pre-specified outcome, after adjusting for a priori and other confounders. A priori confounders included: age, sex, race, smoking, systolic BP, BMI, BP-treatment allocation, total and HDL-cholesterol and number of cardiovascular risk factors. All other baseline variables were considered for inclusion in each of these models, if identified as a potential confounder after backward stepwise selection or if clinically relevant. Whilst developing each of these models, appropriate checks for linearity, and the proportional hazard assumption were carried out using standard statistical methods (207, 208). If found to be non-linear, continuous variables were categorised using clinically relevant cut-offs. A likelihood ratio test was used to compare the use of clinical categorisation of glycaemic status in the final accepted model with the use of glycaemic status as a continuous variable in that model. If there were no significant differences between the two models, the simpler model using glycaemic status as a continuous variable will be accepted to characterize the relationship between glycaemic status and outcomes. A Wald test was used to evaluate the linear trends within the glycaemic status categories. A combination of the 3 outcomes or their constituent parts (CVD death + myocardial infarction + stroke) was used to develop a Cox model for the sensitivity analysis.

There are 2 important limitations of the Cox regression model. Firstly, the use of an arbitrary cut-off of 1 year may lead to misclassification of those individuals who subsequently develop diabetes or impaired glycaemia. Secondly, it excludes those events

that may have occurred at or just prior to the diagnosis (or identification) of the glycaemic status (337, 338). Therefore, I conducted a sensitivity analysis taking into account all available information to ascertain glycaemic status throughout the study period, and all events occurring during the total study period. Logistic regression models were developed for each outcome separately, using glycaemic status during the study period as a pre-specified covariate, and adjusting for a priori confounders and follow-up time to event.

7.6 Results

During a median follow-up of 5.5 years, 903 CHD, 749 stroke and 1558 all-cause mortality outcomes were observed among the 19,257 randomized patients in ASCOT-BPLA (Table 7.1). In total, 13.5% (n=2,607) of all randomized patients had at least one of the three pre-specified outcomes (any specified outcome) during the study period. Those allocated to atenolol-based treatment, in comparison with those allocated to amlodipine-based treatment, had higher incidence rates for CHD, stroke and death outcomes (Table 7.1); The differences were statistically significant for stroke (rate ratio 1.30 [95% CI: 1.13 to 1.51], p<0.001) and death (1.12 [1.02 to 1.24], p=0.025), but not for CHD (1.11 [0.98 to 1.27], p=0.11).

7.6.1 Baseline fasting glucose, CMG, BP-Treatment allocation and cardiovascular outcomes:

Baseline FPG values were available for 17,485 patients, contributing 808 CHD events, 661 stroke events and 1,407 deaths during the total follow-up period (Table 7.2). There were no apparent differences in demographic and clinical characteristics among those with and without baseline fasting glucose values (i.e. missing values) (data not shown). Follow-up fasting glucose readings were available for 19,194 randomized patients, with each individual contributing an average of 7.4 [SD, 2.2] (range, 1 to 14) measurements. These serial fasting glucose readings were used to estimate CMG level prior to exit from the study (or death).

7.6.1.a Baseline fasting glucose, treatment allocation and cardiovascular outcomes

i. Baseline fasting glucose and allocated treatment: Mean [±SD] baseline fasting glucose levels were identical among those allocated to atenolol-based treatment (6.2 [±2.1] mmol/L) or amlodipine-based treatment (6.2 [±2.11] mmol/L) (p=0.856). Figure 7.1 shows the mean baseline fasting glucose, stratified by treatment allocation,

among sub-groups of patients who had no event, any pre-specified event, CHD, stroke or death outcome: accordingly, in each of these sub-group of patients, there were no significant differences in the mean baseline glucose levels among those allocated to the 2 treatment regimens.

ii. Baseline fasting glucose and outcomes: Table 7.2 shows the mean baseline glucose values among those who had an event and those who did not during the study period. Compared with those who did not have an event, mean baseline FPG levels were significantly higher among those who had any of the three pre-specified outcomes (or their combination). There was a mean difference in baseline plasma glucose of 0.33 [95% CI, 0.18 to 0.48] mmol/l, 0.32 [0.15 to 0.48] mmol/l and 0.31 [0.19 to 0.42] mmol/l between those who had a CHD, stroke or death event, respectively, compared with those who did not have any events.

iii. Multivariable logistic regression models: On univariate and stepwise analyses, several variables including previous history of vascular disease, serum triglyceride levels, low-density lipoprotein (LDL)-cholesterol, presence of atrial fibrillation, metabolic syndrome and diabetes were found to be significantly associated with the 3 outcomes, and were thus eligible for inclusion in the 3 models containing a priori confounders and baseline glucose levels. Of these factors, previous history of vascular disease, serum triglyceride level and presence of atrial fibrillation were included in the 3 models, to develop the respective primary evaluation models for each outcome. Presence of diabetes correlated with baseline glucose levels, and thus was not included in the primary models, but was included in separate sensitivity analyses models because of its clinical significance. Metabolic syndrome was not included in the primary evaluation models as its constituent components were already part of a

priori confounders or pre-specified variables. LDL cholesterol was not included in the primary evaluation models as it correlated with total and HDL cholesterol.

On multivariable logistic regression analysis, baseline fasting glucose was found to be significantly and independently associated with increased risk of CHD, stroke and all-cause mortality. There was a 6% increased risk of CHD (odds ratio 1.06 [1.03 to 1.10]) (Table 7.3) and death (1.06 [1.04 to 1.09]), and a 7% increased risk of stroke (1.07[1.04 to 1.11]) (Figure 7.2 and Table 7.3), with each mmol/l increase in baseline fasting glucose. In a sensitivity analysis, using a combination of the 3 outcomes, baseline fasting glucose was found to be a significant predictor for total cardiovascular morbidity and mortality (Figure 7.2). When each of these models were further adjusted for the presence of diabetes at baseline, there were some apparent differences in the findings. Baseline fasting glucose remained an independent and significant predictor of stroke (1.07[1.03 to 1.12]), cardiovascular morbidity and mortality (1.05 [1.02 to 1.09]), and death (1.07[1.03 to 1.10]), but not for the CHD alone (1.03 [0.99 to 1.07]). In another sensitivity analyses, there was no interaction between baseline fasting glucose and allocated treatment, with the relationship between baseline fasting glucose and the 3 outcomes (CHD, stroke, and all-cause mortality) remaining unaffected by allocated treatment, and vice-versa (interaction test p-values: 0.638, 0.939 and 0.313, respectively)

7.6.1 b CMG, treatment allocation and cardiovascular outcomes

i. Baseline FPG and CMG: Compared with mean baseline fasting glucose, CMG levels at exit from the study (or death) were significantly higher among all randomized patients (mean difference 0.16 [0.12 to 0.20], $p<0.001$). A similar increase in the

CMG levels from baseline were observed among the sub groups of patients with and without cardiovascular event or deaths (Figure 7.3), although the differences were only significant among the group with largest number of patients i.e. those without any events during the study period.

ii. CMG and treatment allocation: Figure 7.4 shows the area-under-curve for mean CMG levels during follow-up (median follow-up 5.6 year, interquartile range 5.1 to 6.1 years), stratified by treatment allocation. Those allocated to atenolol-based therapy showed a greater increase in CMG levels in comparison with those allocated to amlodipine-based therapy. Among those allocated to the atenolol-based therapy, there was a rapid initial increase in CMG levels, apparent immediately after randomisation, followed by a steady and progressive increase in CMG levels. In comparison, those allocated to amlodipine-based therapy had a steady, slower and lesser increase in CMG levels.

Compared with those on amlodipine-based therapy, those randomized to atenolol-based therapy had significantly higher CMG levels at the exit from the study (or death) (mean difference: 0.2 [0.1 to 0.3] mmol/l). Figure 7.5 shows that in each sub-group of patients (categorised on the basis of the presence or absence of events), those allocated to atenolol-based therapy had increased CMG levels compared with those on amlodipine based therapy; however, the differences only reached statistical significance among those with any event, no event, or CHD.

iii. CMG and outcomes: CMG levels were significantly higher among those who had a CHD, stroke or death outcome during follow-up, compared with those who did not (mean difference [95%CI]:0.3 [0.2 to 0.5], 0.2 [0.1 to 0.3] and 0.2 [0.1 to 0.3] mmol/l for CHD, stroke and all-cause mortality, respectively) (Figure 7.6).

iv. Multivariable logistic regression models: In addition to those variables identified a priori as confounders, previous history of vascular disease, serum triglyceride levels, and presence of atrial fibrillation were other baseline variables found to be significantly associated with the outcomes. These factors were thus included in the 3 pre-existing models comprising of a priori confounders, to evaluate the association between CMG and cardiovascular outcomes (primary evaluation models). These variables were also included in the models developed for the sensitivity analyses

- On multivariable logistic regression, CMG was independently and significantly associated with each of the 3 outcomes, with a 7% to 9% increase in risk for each mmol/l rise in CMG (odds ratio [95%CI]: 1.09 [1.05 to 1.13], 1.07 [1.02 to 1.11] and 1.07 [1.04 to 1.10] for CHD, stroke and all-cause mortality, respectively) (Table 7.4 and Figure 7.7). On further sensitivity analyses, including all cardiovascular events (i.e. cardiovascular mortality + stroke + myocardial infarction), each 1 mmol/l increase in CMG was associated with a 7% [OR: 1.02 to 1.09] increase in cardiovascular risk. The relationship between the three outcomes remained significant, when the models were further adjusted for the presence of diabetes at baseline, with a 6 to 8% significant increase in the risk of CHD [1.01 to 1.12], stroke [1.01 to 1.12], any cardiovascular event [1.03 to 1.10], or death [1.04 to 1.12] per 1 mmol/l increase in CMG. Furthermore, on testing for interaction, there was no influence of treatment allocation on the relationship between the CMG and each one of the three outcomes: CHD, stroke and all-cause mortality in separate Cox models (interaction test p-values: 0.590, 0.834 and 0.185, respectively).

7.6.2 Glycaemic status, BP-treatment allocation and cardiovascular outcomes

After 1 year of follow-up, 19,069 patients were still under follow-up (after excluding 171 deaths, 11 that were lost to follow-up within that period, and 6 with no available glucose records). Of these patients, 10,000 (52.4%) had normoglycaemia, 3,589 (18.8%) had impaired glycaemia, 398 (2.1%) were diagnosed with new-onset diabetes, and 5,082 (26.7%) had pre-existing diabetes.

7.6.2.a Baseline characteristics according to glycaemic status at 1 year

Baseline characteristics of those who developed new-onset diabetes or impaired glycaemia were compared with those who were normoglycaemic at 1 year, and also with those who had pre-existing diabetes (Table 7.5). Compared with those with normoglycaemia at 1 year, those with impaired glycaemia or new-onset diabetes had a higher baseline FPG, BMI, alcohol intake, systolic BP, alanine transaminase, and a lower HDL cholesterol, and were less likely to have a previous history of stroke/TIA or a vascular event. Patients who developed new-onset diabetes or had impaired glycaemia at1 year as compared to whose with pre-existing diabetes were more likely to be Caucasians, current smokers, and with higher weekly alcohol intake, systolic BP and lower fasting glucose levels at baseline; however, there were no significant differences in mean or distribution of other baseline characteristics.

7.6.2.b Treatment allocation and glycaemic status at 1 year

Compared with those with normoglycaemia at 1 year, those who developed new-onset diabetes, or impaired glycaemia, were significantly more likely to have been allocated to atenolol-based treatment (Table 7.5). Of the 398 patients who developed diabetes within the first year of follow-up, nearly 60% (n=237) had been allocated to atenolol-based treatment at randomisation. There was no difference in treatment allocation among those patients with pre-existing diabetes (Table 7.5).

7.6.2.c Glycaemic status at 1 year and cardiovascular outcomes

Figure 7.8 shows the incidence rates of CHD, stroke and death outcomes among those with normoglycaemia, impaired glycaemia, and new-onset diabetes at 1 year, and those with pre-existing diabetes. There was a clear trend of increasing event rates with worsening glycaemic status (Figure 7.8 and Table 7.6). On sensitivity analysis, using a combination of the 3 outcomes: CHD + stroke + death, the findings were similar (Table 7.6) with an apparent trend of increasing event rates with worsening glycaemic category.

On multivariable analysis, compared with those with normoglycaemia, those with impaired glycaemia, new-onset diabetes, and previous diabetes had a progressively increased risk of CHD (HR [95% CI]: 1.10 [0.90 to1.36], 1.11 [0.66 to1.87], and 1.41 [1.17 to 1.68], respectively); however, only the risk associated with pre-existing diabetes was significant (Figure 7.9). On further analysis, using glycaemic categories as a continuous variable, there was a significant linear trend with a 12% [5% to 20%] rise in CHD risk with each rise in glycaemic category (Wald test, p <0.001). Similarly, significant linear trends for progressive increase in risk with worsening glycaemic category were noted for the stroke outcome (1.07 [0.85 to1.36], 1.04 [0.55 to 1.96], and 1.31 [1.06 to 1.63], respectively), with a 9% [2% to 17%] increase in stroke risk with each rise in glycaemic category (Wald test, p=0.002) (Figure 7.10), and for the all-cause mortality outcome (1.07 [0.9 to 1.2] , 1.13 [0.78 to 1.64], and 1.19 [1.05 to1.36], respectively) with a 7% [3% to 13%] increase in the risk of death with each rise in glycaemic category (Wald test, p=0.013) (Figure 7.11). The findings were similar on sensitivity analysis, with a 10% [5% to 15%] significant increase in the risk of cardiovascular morbidity and mortality with each rise in glycaemic category.

7.6.2.d Glycaemic status during the total study period and the cardiovascular outcomes

In the multivariable logistic regression models, adjusting for time to first event and a priori confounders, those with impaired glycaemia or new-onset diabetes during the total study period had a significantly increased risk of CHD and stroke, but not for death (Table 7.7). Compared with those with normoglycaemia throughout the trial, those with impaired glycaemia, new-onset diabetes, and pre-existing diabetes had 43% [1.14 to 1.79], 53% [1.04 to 2.26] and 62% [1.29 to 2.04] significant increase in the risk of CHD; 27 % [1.01 to 1.60], 64% [1.11 to 2.44] and 36% [1.08 to 1.73] significant increase in the risk of stroke; and 16% [0.94 to 1.43], 7% [0.73 to 1.56] and 16% [0.93 to 1.44] statistically insignificant increase in the risk of death, respectively (Table 7.7). Progressive worsening of glycaemic category was linearly and significantly associated with a 16%, 11% and 16% increase in the risk of CHD, stroke and death, respectively, for each rise in glycaemic category.

7.7 Discussion

These analyses have evaluated the risk of CHD, stroke and death associated with baseline fasting glucose and CMG levels, and assessed the influence of BP-treatment allocation on subsequent CMG levels. The risk of cardiovascular outcomes or deaths associated with developing new-onset diabetes or impaired glycaemia was also assessed, as was the association between glycaemic status (determined on the basis of observations during the whole study period) and cardiovascular outcomes. The findings suggest that both baseline fasting glucose and CMG levels are significant and independent predictors of cardiovascular events and death. Allocation to atenolol-based treatment, compared with amlodipine-based treatment, was associated with a significantly greater increase in CMG levels, and worsening of glycaemic status. During the first year of follow-up a significantly greater number of patients developed new-onset diabetes or impaired glycaemia after allocation to atenolol-based treatment regimen, compared with the amlodipine-based regimen. In-trial worsening of glycaemic status (after 1 year of follow-up) was associated with increasing risk of CHD, stroke and death. There was a significant linear relationship between the glycaemic status at the end of the first year and cardiovascular risk. These findings were supported by a sensitivity analysis, in which patients with impaired glycaemia or new-onset diabetes at any point during the ASCOT-BPLA follow-up (i.e. till the end of the study period) were compared with those who remained normoglycaemic throughout the trial period, and were found to be at a significantly higher risk of CHD or stroke, but not of death. In conclusion, these findings suggest that allocation to the atenolol-based treatment regimen was associated with worsening glycaemic status and CMG levels, and these changes may have contributed to the observed increase in adverse cardiovascular events in this treatment arm. If true, this hypothesis could partly explain the apparent differences in the event rates between the two treatment regimens in ASCOT-BPLA (47), and may have important clinical implications,

specifically in informing the choice of first-/and second-line antihypertensive agents, or their combinations.

7.7.1 Baseline fasting glucose and cardiovascular outcomes

In these analyses, increasing levels of baseline FPG were associated with a significantly increased risk of cardiovascular outcomes and death. The increased risk of CHD, stroke and death associated with the increase in baseline FPG have been previously reported in several observational studies (309, 315, 325, 328). However, trial data evaluating the risk of cardiovascular outcomes and death associated with FPG in hypertensive populations are few (25).

In a recent meta-analysis (339) that included individual-level data on 698,782 people, there was a 'U' shaped non-linear association between FPG and vascular disease. Compared with a fasting glucose between 3.90 and 5.59 mmol/l, those with either a higher (≥ 5.6 mmol/L) or lower (< 3.9 mmol/l) FPG were at greater risk of vascular disease (339). In contrast, my analyses suggest there is a linear relationship between baseline FPG and cardiovascular events and deaths. This difference could be explained by differences in the study populations. For example, hypertensive patients included in ASCOT-BPLA were at moderate cardiovascular risk (1.6 % per year for any cardiovascular event), with a median FPG level at randomisation of 5. 6 mmol/L (interquartile range, 5.1 to 6.5 mmol/L); whereas, in the meta-analysis, the patient-level data was derived mainly from observational population-based studies, with subjects conceivably at lower cardiovascular risk. This argument is supported by observations from a sub-group analysis of the meta-analysis that reported a linear relationship among those with a FPG ≥5.6 mmol/L, with a 12% increase in CHD risk with each mmol/l increase in FPG. In yet another meta-analysis of 17 cohort studies (269), that included fasting

glucose data on over 237,000 individuals, there was a significant and linear relationship between fasting glucose levels, and ischaemic heart disease and stroke, with risk increasing linearly for each mmol/l rise in fasting glucose ≥ 5.0 mmol/L. In addition several recent studies have also shown a linear increase in the risk of stroke associated with FPG >5.6 mmol/l. Thus the findings of my analyses, that fasting glucose is an independent predictor for stroke and mortality, is consistent with the finding of previous studies (307, 313, 340-342) and meta-analyses (104, 269).

7.7.2 CMG, treatment allocation and cardiovascular outcomes:

The results of my analyses suggest that among all randomized patients in ASCOT-BPLA, CMG levels were significantly higher than baseline glucose levels. This increase was significantly greater, and mainly driven by, those randomized to atenolol-based treatment compared with those allocated to amlodipine-based treatment. CMG levels were also significantly higher among those who had an outcome compared with those who did not. These descriptive findings were supported by my multivariable regression analyses where an increase in CMG was associated with an increased risk of cardiovascular events and death. This is an important clinical finding, with potential implications for practice.

CMG in these analyses denote average glucose levels prior to the event, and function as a long-term marker of glycaemia. Persistent hyperglycaemia is associated with oxidative and endothelial damage and results in formation of advanced glycation end products (343)). These advanced glycation products are in turn associated with several activities including activation of macrophages, oxidation of low-density lipoprotein, potentiation of a pro-inflammatory state and acceleration of the process of atherogenesis (343, 344). All of these activities, independently or collectively, could lead to the development of a cardiovascular

event. Therefore, it is unsurprising that there was a significant association between CMG and cardiovascular events in these analyses. Theoretically, any long-term marker of glycaemia should be a better and more robust marker of end-organ damage, rather than a one-off fasting glucose value, particularly given the fact that one-off glucose values are affected by blood sugar inherent variability (345, 346), and the duration of fasting.

Consistent with our findings, previous studies (329, 331, 340, 347) evaluating the relationship between glycosylated haemoglobin (HbA1c) — a marker for short-term glycaemic control — and cardiovascular and all cause-mortality, have reported the existence of a significant and linear relationship between HbA1C levels and cardiovascular outcomes. (329). In a meta-analysis of 10 cohort studies, a 1% increase in HbA1c was associated with an 18% increase in the risk of CHD or stroke (331). However, despite the consistent reports of a relationship between HbA1c and cardiovascular outcomes, it is possible that HbA1C (which reflects glycaemic status over 8 to 12 weeks) may not accurately reflect an individual's average glycaemic status over a longer period of time. For example, in a comparison of AUC of mean blood glucose and HbA1c in the Diabetes Control and Complications Trial (DCCT) (330, 332, 348), there was a marked discrepancy between the two metrics of glycaemia, with patients having the same mean blood glucose but different HbA1c values, and vice-versa. In another recent analysis (330) of the relationship between time to first cardiovascular event and mean blood glucose, HbA1c, and standard deviation of blood glucose was assessed. The authors reported that mean blood glucose, and not HbA1c levels, had an independent and significant relationship with the risk of cardiovascular outcomes. Furthermore this relationship remained unaffected, and independent, after adjusting for HbA1c in the same model. These findings are similar to my findings, where I have found a significant association between CMG and the risk of cardiovascular events and death. It is notable that in my

analyses, CMG remains an independent predictor of cardiovascular risk regardless of the presence of diabetes.

The use of CMG in my analyses was an excellent tool to summate all the different in-treatment (or during follow-up) influences on glucose level, including those of antihypertensive agents. The substantial and significant increase in CMG levels associated with the use of atenolol-based treatment (as compared with amlodipine-based treatment) is unsurprising; given the findings of earlier smaller and short-term studies, where both thiazide diuretics (133, 139, 349) and beta-blockers (231, 243) have individually been shown to increase on-treatment glucose levels. A notable observation is that, immediately after the allocation of atenolol-based therapy, there was a rapid increase in CMG levels, more dramatic as compared with those allocated to amlodipine-based treatment (Figure 7.4). This rapid increase was possibly driven by the fact that BP-control among patients allocated to atenolol-based treatment was inadequate in the early part of the trial, and therefore required the addition of second-line agents (in this case diuretics), much sooner than those allocated to the amlodipine-based regimen. More importantly the CMG levels among those allocated to atenolol-based treatment continued to increase at a greater rate compared with those allocated to amlodipine-based therapy. This implies that it is not only the initial metabolic changes that are important, but the accumulative effect of the life-time accrued changes that may be of a greater concern. This interpretation is contrary to another belief that only acute metabolic changes associated with antihypertensive agents, particularly with diuretics, are important, and the influence of these adverse metabolic changes diminishes over time (25, 143, 144, 240, 314).

In my analyses there was an average difference of 0.3 mmol/L in CMG between those who

did and did not develop an outcome. Thus the difference of 0.2 mmol/L in CMG between the two treatment groups in ASCOT-BPLA assumes a greater clinical significance, and may contribute to explaining the difference in event rates between these two treatment groups. The difference in CMG levels between the two treatment groups, also needs to be interpreted in context of the other two observations in these analyses. Firstly that CMG levels progressively increased from baseline among all randomized patients, but more rapidly and to a greater extent among those randomized to atenolol-based treatment. Secondly there were no differences in mean baseline FPG levels among those randomized to the two treatment groups. On the other hand, when the influence of CMG on the relationship between allocated treatment and the 3 outcomes was compared— by comparing the hazard ratios and β-coefficients associated with the amlodipine-based treatment (vs. atenolol-based treatment) in models with and without CMG— I found no significant change in the effect size. For example, for the CHD outcome, hazard ratios [95% CI] and β-coefficients (standard error) associated with amlodipine-based treatment [vs. atenolol-based treatment] in the model with allocated treatment and CMG, and in the model with only allocated treatment were 0.89 [0.77 to 1.03] and -0.11(0.07), and 0.88 [0.76 to 1.01] and -0.13 (0.07), respectively. This observation may suggest that the differences in the cardiovascular and mortality outcomes apparent between the two allocated treatment groups in the ASCOT trial cannot be completely explained on the basis of differences in the CMG alone. However, these comparisons have limited power. Moreover, these models do not take into account the important differences in the peripheral and central BPs, lipids and BP variability between the two treatment groups (203, 350-352), and those may have an additive influence in differentiating the treatment effect between the two BP treatment regimens.

My findings are, in part, consistent with observations from another large hypertension trial,

ALLHAT (314) , but differs from them in the conclusions drawn. In ALLHAT, the change in glucose level within the first two years of follow-up was not significantly associated with an increase in CHD risk, except among those patients who were randomized to lisinopril. The inconsistent findings in this trial can be attributed to some methodological issues. For example, less than 40% of all randomized patients had baseline and 2 year FPG available to determine the change in blood sugar level. Moreover, these single measurements are likely to have been affected by intra-individual blood sugar variability, measurement accuracy and duration of prior fasting. More importantly, these glucose changes were not adjusted for changes in other related and confounding factors. In my analyses there were less than 1% missing values, and CMG was calculated based on an average of 7 blood sugar values. Thus CMG represents the average change in glucose in the period before the event, rather than the absolute change calculated on the basis of two recordings. I propose that this methodology will provide more accurate and robust results, as it takes into account immediate blood sugar changes preceding the event. The metric of mean blood glucose has been previously demonstrated to be a better predictor of cardiovascular risk (330, 353) than other markers of glycaemia, such as HbA1c. In keeping with our findings, an observational study by Dunder et al (309) found that increasing glucose levels on antihypertensive medications are associated with significantly increased risk of CHD.

7.7.3 Glycaemic status and cardiovascular outcomes and death:

During the first year of follow-up compared with those allocated to amlodipine-based therapy, those allocated to atenolol-based treatment had significant worsening of glycaemic status, with a significantly greater number of patients developing new-onset diabetes and impaired glycaemia. Furthermore, compared with those with normoglycaemia at 1 year, those with impaired glycaemia, new-onset diabetes (at 1 year) and previously established diabetes

had progressively increasing risk of cardiovascular event or death; however, only the risk associated with pre-existing diabetes was statistically significant. This finding, when seen in isolation, appears to be no different from that of ALLHAT (25), and other trials (311); however, my interpretation of these findings are completely different from those made by the authors of ALLHAT, and are more similar to the conclusions drawn by the authors of the VALUE trial (311). The partial similarity among the findings of all retrospective analyses of the hypertension trials (including ours) transpires because none of the sub-group analyses have adequate power (i.e. sample size) to tease out significant differences among glycaemic categories. Furthermore several of these trials have limited follow-up period, which together with the use of crude clinical categorisation of glycaemic status, limits their power further. Therefore, whilst the authors of the ALLHAT analyses interpreted their findings—mainly based on the negative findings in the chlorthalidone arm— as no consistent evidence of harm associated with new-onset diabetes among patients using diuretics; the authors of VALUE trial interpreted their findings as suggestive evidence of adverse cardiovascular outcomes associated with new-onset diabetes, which had been partly obscured (and therefore appeared inconsistent) because of the treatment changes initiated after the diagnosis of diabetes.

In my analyses I have additionally evaluated glycaemic categories in continuum for each of the 3 outcomes. The main assumption in doing this is that these glycaemic categories are arbitrary, and none of them have a discrete relationship with cardiovascular risk independent of others; rather there is a linear relationship between glycaemic categories and cardiovascular risk, with risk increasing with each increase (worsening) in glycaemic category. If these assumptions are true, then this strategy would enable investigation of these relationships, regardless of any constraints imposed by power, or short duration of follow-up. The results of my analyses suggest that the progressive worsening of glycaemic status at one

year was indeed linearly and significantly associated with increasing risk of CHD, stroke and death. These results also correlate well with the other findings from my analyses including CMG, BP-treatment and cardiovascular events which are also not limited by power considerations. These findings are also consistent with those from several previously published studies (329, 347).

Perhaps the most striking finding of my analyses, is that compared with those with normoglycaemia throughout the study period, those with impaired glycaemia, new-onset diabetes, and pre-existing diabetes have a significant, and progressively increasing risk of CHD, stroke and death. A strength of these sensitivity analyses is that it includes those events that are usually excluded in survival analyses, for example, those outcome events that occur prior to, or at the time of diagnosis (or identification) of new-onset diabetes (i.e. exposure). It has been well described in the literature that patients with diabetes may have an increased cardiovascular risk for a variable period preceding the date of the diagnosis (325, 337, 338, 342, 354-358) and indeed diabetes is often only diagnosed at the time of the clinical presentation with a features of target organ damage. Studies have shown that beta-cell dysfunction in patients may occur as much as 8 years prior to the diagnosis of diabetes, and during that period there is enhanced cardiovascular risk compared with those with no underlying beta-cell dysfunction or insulin resistance. Therefore, categorizing the glycaemic status of patients based on several observations during a reasonable time period prior to the diagnosis, may actually improve the power to detect obscure associations, particularly in the setting of a clinical trial with a limited follow-up.

If my interpretation of these data is correct then a study with a long-term follow-up, or with a large numbers of patients with new-onset diabetes, would be able to provide unequivocal

evidence of adverse cardiovascular outcomes associated with antihypertensive-associated diabetes (305, 322). In keeping with my findings, a small observational study (n = 795) (296) with a long-term follow-up (median 6 year, range 1 to 16 years) has indeed shown that antihypertensive-associated new-onset diabetes was associated with a 3-fold greater risk of CVD when compared with those patients persistently free from diabetes (296). However, the results of this observational study needs careful interpretation, particularly considering the small number of events (n = 63) and no control subjects. In contrast, the findings from the long-term evaluation of the SHEP trial showed no diuretic-associated increase in cardiovascular risk (26), however this analysis had several methodological shortcomings as previously discussed in section 7.3.1.b (305, 321).

In summary, I believe my analyses are innovative and robust and may help resolve some of the prevailing controversies in this field. My findings suggest that the antihypertensive-associated changes in glucose and glycaemic categories are associated with an increased cardiovascular toll. These findings, taken together, may also partially explain the observed differences in event rates between the two treatment regimens in the ASCOT-BPLA, particularly given the fact that the BP-differences between the two arms were small, and relatively inconsequential (203). These findings may have clinical implications, particularly in guiding the choice of first- and second-line antihypertensive agents.

7.7.4 Limitations and strengths

There are several limitations of these post-hoc analyses. There was only a limited follow-up of 4.3 years (median) after determination of glycaemic status. This constraint is similar to that experienced in other such analyses in a clinical trial setting; however, it is substantially less than that reported in observational settings (322). There were only 398 patients in the sub-

group of new-onset diabetes; hence this group did not have sufficient power to allow discrete determination of the antihypertensive-associated risk of CHD, stroke or death. This is clearly reflected by the wide confidence intervals of hazard ratios associated with new-onset diabetes. However, I have attempted to address this limitation by analysing CMG levels and glycaemic categories in continuum. Moreover, I conducted sensitivity analyses using glycaemic categories based on observations throughout the trial period. This added substantially to the number of potential evaluable events and thus substantially increased the power of the study to detect associations. All together these findings form a consistent theme, and contribute to the knowledge to date. Another possible limitation of this analysis is that it has used a selected population of hypertensive patients, and these findings may not be reflective of the general population. However, having said that, most patients in this study were recruited from general practices, and are fairly typical of the patients seen routinely.

In contrast to these limitations, there are several strong methodological and analytical strengths of this study. Unlike other studies, > 99% of patients had more than one recording of blood sugar available for analysis. New-onset diabetes was a pre-specified tertiary outcome in the ASCOT-BPLA and thus this outcome was clearly defined, systematically evaluated among all patients, and the diagnosis was further validated by the endpoint committee. This is a particular strength of these analyses, which contrasts with post-hoc definition and incomplete follow-up in ALLHAT, and physician reported definition of new-onset diabetes in VALUE. The use of the glycaemic categories in continuum is well supported by observations in other settings (104, 269, 331, 340, 359). Moreover, the use of CMG to assess the association between antihypertensive-associated glycaemic changes and cardiovascular risk adds considerable strength to these analyses. Hence, pending further evidence derived from a long-term evaluation of a large trial, these findings provide the most

comprehensive evidence to date to suggest that antihypertensive-associated glycaemic and\or glucose changes are associated with adverse cardiovascular outcomes. These findings may also explain the higher death and cardiovascular event rates observed among those randomised to atenolol-based treatment in ASCOT-BPLA. These findings further suggest that CMG may be a more sensitive and accurate predictor of cardiovascular events and death compared with crude clinical categorizations.

7.8 Conclusions

Both baseline FPG and CMG are independent and significant risk factors for major cardiovascular outcomes and death. BP-treatment allocation significantly influences CMG and glycaemic status, which could partly explain the difference in death and cardiovascular event rates observed between the two treatment groups in ASCOT-BPLA. There is a linear trend for increasing risk of cardiovascular morbidity and mortality with worsening glycaemic status. CMG may be a more sensitive and accurate predictor of cardiovascular event and death compared with crude clinical categorizations.

Chapter 7: Tables

Table 7.1: Number of coronary, stroke and death outcomes & event rates * according to allocated treatment regimen in ASCOT-BPLA

Outcomes		Overall (n=19257)	Atenolol ±thiazide (n= 9,639)	Amlodipine ± perindopril (n= 9,618)
CHD (NF MI + Fatal CHD)	No. of events (Rate [95%CI])*	903 (8.7 [8.1-9.2])	474 (9.1 [8.3-10.0])	429 (8.2[7.4-9.0])
Stroke (F/NF)	No. of events (Rate [95%CI])*	749 (7.2[6.7-7.7])	422 (8.1 [7.4-8.9])	327 (6.2 [5.6-7.0])
All cause mortality	No. of events (Rate [95%CI])*	1558 (14.7 [14.0-15.4])	820 15.5[14.5-16.6)	738 (13.9 [12.9-14.9])

* Per 1000 person years
F= Fatal; NF=Non-fatal; CHD= Coronary heart disease; MI=Myocardial Infarction

Table 7.2: Mean baseline fasting glucose* (Standard deviation) stratified according to subsequent incidence of cardiovascular event or death during median follow-up of 5.5 years in the ASCOT-BPLA

Outcomes	Total (n=17,435)	No event		Event		p-value†
	Mean(SD)	Number	Mean(SD)	Number	Mean(SD)	
Death	6.2 (2.1)	16028	6.2 (2.1)	1407	6.5 (2.6)	<0.001
CHD (NF MI + Fatal CHD)	6.2 (2.1)	16627	6.2 (2.1)	808	6.6 (2.6)	<0.001
Stroke (F/NF)	6.2 (2.1)	16774	6.2 (2.1)	661	6.5 (2.5)	<0.001
Any specified outcome ‡	6.2 (2.1)	15092	6.2 (2.1)	2343	6.5 (2.5)	<0.001

- * among 17,435 with fasting glucose values at baseline
- † using student's t-test.
- ‡ defined as those who had any of the 3 pre-specified outcomes: CHD, stroke, or death.

F= Fatal; NF=Non-fatal; CHD= Coronary heart disease; MI=Myocardial Infarction; SD: standard deviation

Table 7.3: Multivariable logistic regression model* investigating the risk (Odds) (95% confidence interval) of CHD associated with an increase in baseline fasting glucose (per mmol/l) after adjusting for a priori and other confounders

Baseline characteristics	Odds ratio	95% Confidence interval	p-value
Fasting glucose (per mmol/L) at baseline	1.06	1.03 to 1.10	<0.001
Age (per 1 year increase)	1.02	1.01 to 1.03	<0.001
Male	1.65	1.34 to 2.04	<0.001
Ethic group (referent group whites)			
Blacks	0.31	0.14 to 0.69	0.004
South-Asians	1.15	0.61to 2.14	0.669
Mixed	1.57	0.87 to 2.80	0.131
Current smokers/ex-smokers within 1 year	1.23	1.04 to 1.45	0.014
BMI (kg/m^2) (per unit)	0.99	0.97 to 1.01	0.255
Amlodipine-based treatment	0.87	0.76 to 1.01	0.064
Systolic BP (mm/Hg) (per mm Hg increase)	1.01	1.00 to 1.01	0.001
Number of cardiovascular risk factors (referent 3)			
4 risk factors	1.37	1.16 to 1.63	<0.001
5 or more risk factors	1.80	1.47 to 2.21	<0.001
Alcohol intake (units/week)(per unit increase)	0.99	0.98 to 1.00	0.007
Total cholesterol (per mmol/L)	1.28	1.19 to 1.37	<0.001
Atrial fibrillation (present vs. Absent)	1.31	1.00 to 1.72	0.054
HDL cholesterol (per mmol/L)	0.65	0.50 to 0.85	0.001
Triglycerides (per mmol/L)	0.89	0.81 to 0.97	0.011
Previous history of vascular disease† (present vs. Absent)	1.21	1.00 to 1.45	0.046

- *n=17,430 after excluding those with non-fasting glucose and triglyceride values, and those with missing values of any variables in the model.
- † excluding patients with previous CHD or recent stroke or TIA

Table 7.4: Multivariable logistic regression model* investigating the risk (Odds) (95% confidence interval) of CHD associated with an increase in cumulative mean glucose (per mmol/l) after adjusting for a priori and other confounders

Baseline characteristics	Odds ratio	95% Confidence interval	p-value
Cumulative mean glucose (per mmol/L)	1.09	1.05 to 1.13	<0.001
Age (per 1 year increase)	1.02	1.01 to 1.03	<0.001
Male	1.67	1.36 to 2.06	<0.001
Ethic group (referent group whites)			
Blacks	0.30	0.13 to 0.68	0.004
South-Asians	1.11	0.6 to 2.08	0.738
Mixed	1.55	0.86 to 2.77	0.141
Current smokers/ex-smokers within 1 year	1.24	1.05 to 1.46	0.01
BMI (kg/m^2) (per unit)	0.99	0.97 to 1.01	0.165
Amlodipine-based treatment	0.89	0.77 to 1.03	0.114
Systolic BP (mm/Hg) (per mm Hg increase)	1.01	1 to 1.01	0.001
Number of cardiovascular risk factors (referent 3)			
4 risk factors	1.35	1.14 to 1.61	0.001
5 or more risk factors	1.73	1.41 to 2.12	<0.001
Alcohol intake (units/week)(per unit increase)	0.99	0.98 to 1	0.008
Total cholesterol (per mmol/L)	1.29	1.2 to 1.38	<0.001
Atrial fibrillation (present vs. Absent)	1.34	1.03 to 1.75	0.031
HDL cholesterol (per mmol/L)	0.65	0.5 to 0.85	0.001
Triglycerides (per mmol/L)	0.89	0.81 to 0.97	0.01
Previous history of vascular disease† (present vs. Absent)	1.23	1.03 to 1.48	0.025

- *n=17,469 after excluding those who exited from the study and those with missing values of any variables in the model.
- † excluding patients with previous CHD or recent stroke or TIA

Table 7.5: Baseline characteristics among those stratified according to glycaemic status: normoglycaemic, impaired glycaemia, new-onset diabetes or pre-existing diabetes, at one year from randomisation in ASCOT (n=19,069)*.

Baseline characteristics (numbers)	Normoglycaemia mean(SD) or [%] (10,000)	Impaired glycaemia mean(SD) or [%] (3,589)	New-onset diabetes mean(SD) or [%] (398)	Pre-existing diabetes mean(SD) or [%] (5,082)
Demographics				
Age (years)	62.9 (8.6)	62.6 (8.2)	62.2 (8.2)	63.4 (8.4)
Sex (male [%])†	76.2	82.6	82.4	72.4
Caucasians (%) †	96.8	96.1	95.2	91.8
BMI (kg/m2)	27.8 (4.2)	29.1 (4.6)	30.1 (4.3)	30.2 (4.8)
Age at leaving full time education (%) †				
12-14 (years)	31.3	30.5	30.4	32.8
15-16 (years)	35.5	36.4	37.7	38.1
17-18 (years)	13.1	12.9	14.1	12.7
≥19 (years)	20.1	20.2	17.8	16.3
Current smoker or ex <1year (%)	69.1	71.8	69.6	61.9
Alcohol intake (per week) (%) †	8.0 (11.5)	9.6 (12.8)	8.3 (11.5)	6.8 (10.8)
Presence of LVH (%) †	23.1	21.9	21.1	18.5
Medical and treatment history				
H/O Stroke/TIA (yes/no) (%) †	12.0	11.2	8.8	8.9
H/O any vascular event (%) †	17.2	16.5	15.1	16.2
Previous lipid lowering treatment (%)	8.9	9.7	8.8	14.9
Previous aspirin intake (%)	18.8	18.9	18.6	20.0
Previous antihypertensive treatment (%)†	79.2	80.0	80.9	85.1
Diagnostic measurements				
Systolic BP (mmHg) †	163.4 (17.9)	164.3 (17.9)	168.4 (19.6)	164.9 (18.0)
Diastolic BP (mmHg) †	95.4(10.3)			
Fasting glucose (mmol/l) †‖	5.1 (0.5)	5.9 (0.6)	6.1 (0.7)	8.6 (2.8)
Total cholesterol (mmol/l) †	6.0 (1.1)	6.0 (1.1)	5.9 (1.1)	5.7 (1.1)
HDL-cholesterol (mmol/l) †	1.4 (0.4)	1.3 (0.4)	1.2 (0.3)	1.2 (0.3)
Triglycerides (mmol/l) †‖	1.7 (0.9)	1.9 (1.1)	2.1 (1.2)	2.1 (1.1)
LDL-Cholesterol (mmol/l) †‖	3.9 (1.0)	3.8 (1.0)	3.8 (1.0)	3.6 (1.0)
Serum potassium (mmol/dl) †‡	4.2 (0.4)	4.2 (0.5)	4.2 (0.5)	4.3 (0.5)
Alanine transaminase (mg/dl) †‡	28.9 (17.0)	33.4 (20.2)	37.0 (25.0)	36.2 (23.2)
Creatinine (mmol/l) †‡	98.6(16.6)	99.7(16.9)	98.1(15.5)	97.6(17.3)

Study treatment≠				
Randomised to amlodipine-based treatment group (%)†	51.3	47.8	40.5	49.8
Randomised to atorvastatin treatment group (%)	50.1	50.4	52.1	50.0

*those who were alive, and with at least one measurement of glucose value to stratify the glycaemic status.† *significant differences among proportions or means of the groups, using X^2-trend test or one-way analysis of variance*, whichever applicable; ‡: missing values at baseline : 0.5%, 1.3%, & 3.2% of patients had missing value at baseline for serum potassium, alanine transaminase and serum creatinine, respectively; ‖only fasting values of either triglycerides or glucose were considered, and non-fasting values were considered missing, therefore 9.2%, 9.5% & 11.1% had missing values for glucose, triglyceride and LDL-cholesterol; ≠ **i**ntention to treat

BMI, body mass index; BP, blood pressure; LVH, left ventricular hypertrophy

Table 7.6: Glycaemic status at 1 year and incidence rates (per 1000 person years) of cardiovascular and death outcomes in the ASCOT-BPLA

Event rates	CHD		Stroke		All cause mortality		CVD mortality +MI +Stroke	
	No of events	Rates* (95%CI)	No of events	Rates* (95%CI)	No of events	Rates* (95%CI)	No of events	Rates* (95%CI)
Normoglycaemia	322	7.15 (6.41 to 7.97)	286	6.37 (5.67 to 7.15)	661	14.42 (13.36 to 15.56)	652	14.76 (13.68 to 15.94)
Impaired glycaemia	131	8.14 (6.86 to 9.65)	109	6.78 (5.62 to 8.18)	255	15.56 (13.77 to 17.60)	252	15.94 (14.09 to 18.03)
New-onset diabetes	15	8.43 (5.08 to13.99)	10	5.60 (3.01 to 10.40)	29	16.04 (11.15 to 23.09)	26	14.79 (10.07 to 21.73)
Previously known DM	242	10.82 (9.54 to-12.27)	191	8.53 (7.40 to 9.83)	442	19.27 (17.56 to 21.15)	442	20.24 (18.44 to 22.22)

- * rates per 1000 person years

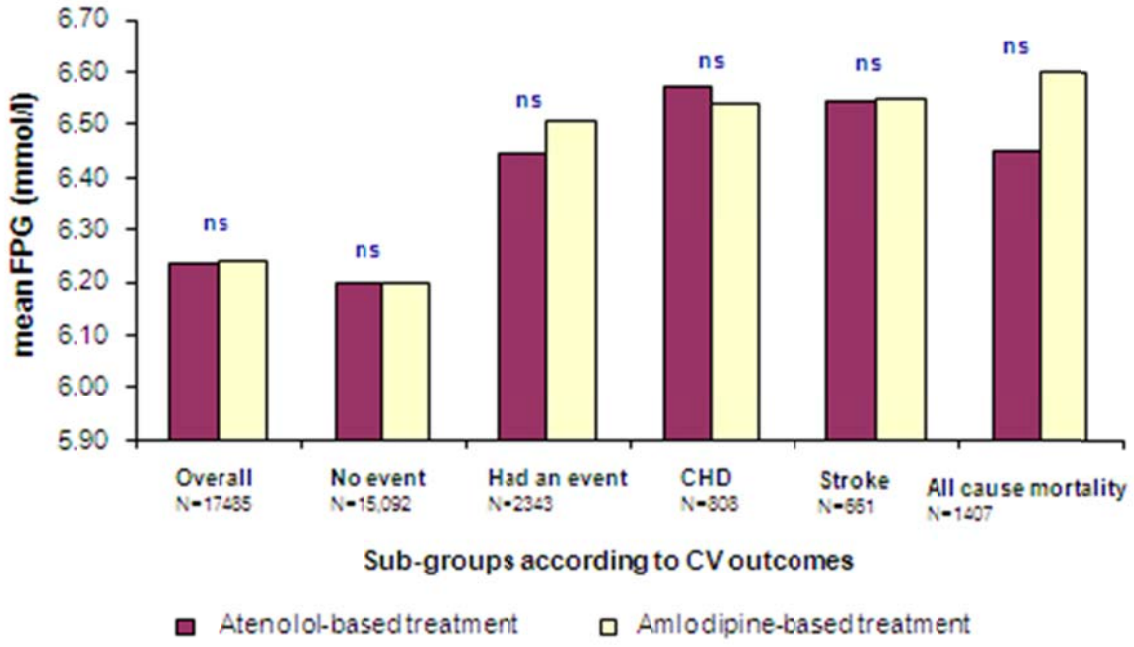
Table 7.7Risk (Odds ratio) of coronary, stroke, and deaths associated among those with impaired glycaemia, new-onset diabetes, and pre-existing diabetes during the total study period, compared with those with normoglycaemia throughout in the ASCOT-BPLA, using separately developed multivariable logistic regression models*.

	CHD	**Stroke**	**CVD mortality + MI + stroke†**	**Deaths**
	Odds ratio (95%CI)	Odds ratio (95%CI)	Odds ratio (95%CI)	Odds ratio (95%CI)
Impaired glycaemia‡	1.43 (1.14 to 1.79)	1.27 (1.01 to 1.60)	1.29 (1.07 to 1.55)	1.16 (0.94 to 1.43)
New-onset diabetes‡	1.53 (1.04 to 2.26)	1.64 (1.11 to 2.44)	1.35 (0.99 to 1.84)	1.07 (0.73 to 1.56)
Diabetes‡	1.62 (1.29 to 2.04)	1.36 (1.08 to 1.73)	1.30 (1.08 to 1.58)	1.16 (0.93 to 1.44)

- * adjusting for follow-up time to the event, and a priori confounders.
- † derived from the pre-specified outcomes after excluding non-cardiovascular mortality.
- ‡ Glycaemic status based on all available information throughout the trial period.
- There was a significant linear trend, with 16% (1.08 to 1.26), 11% (1.03 to 1.20), 8% increase (1.02 to 1.16) and 16 %(1.08 to 1.26) increase in the risk of CHD, Stroke, CVD morbidity and mortality, and death , respectively for each rise in the glycaemic category.

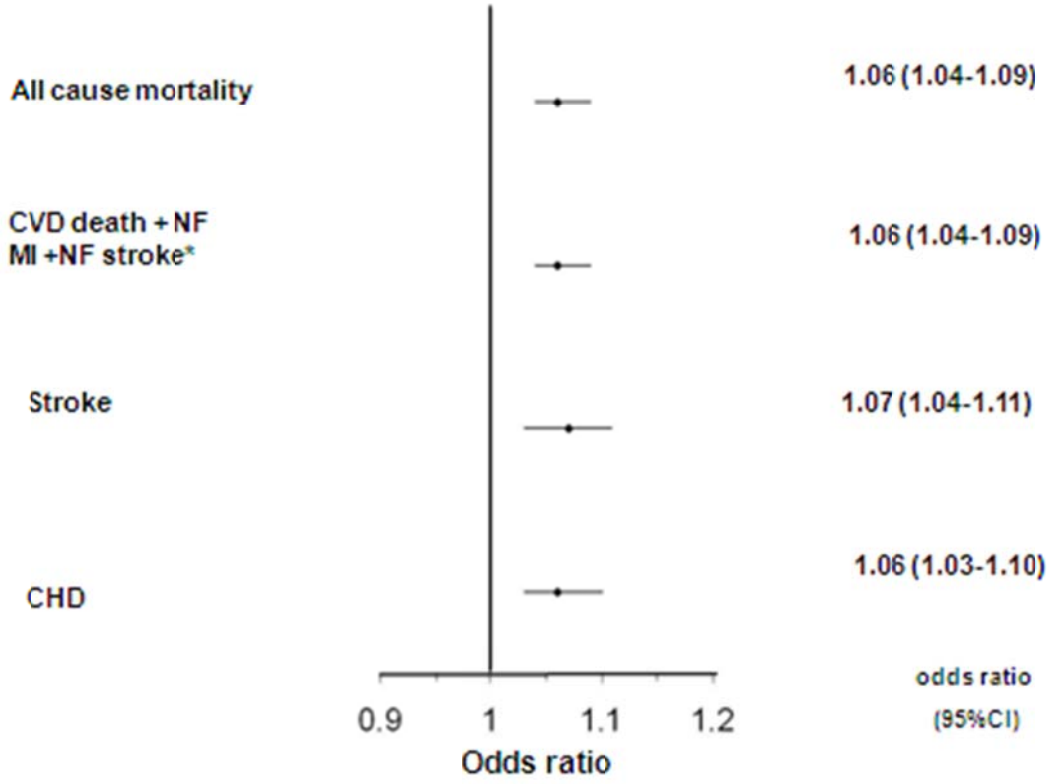
Chapter 7: Figures

Figure 7.1: Mean fasting glucose at baseline, stratified according to randomised treatment group, and presence or absence of a subsequent cardiovascular event.



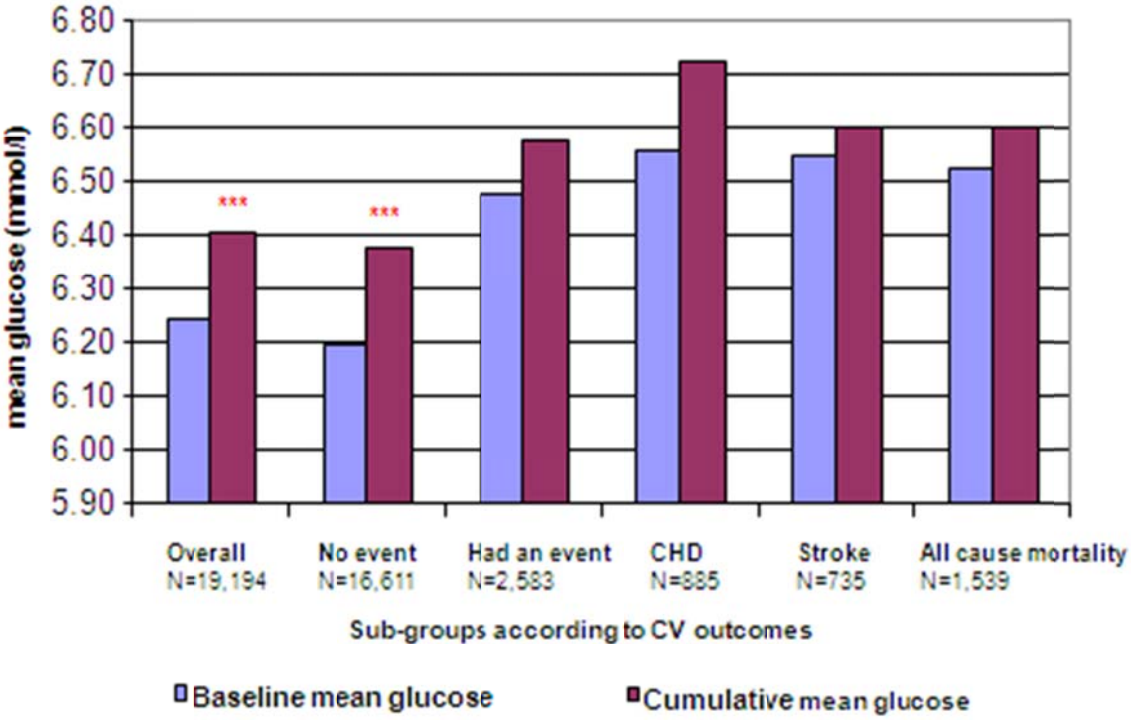
* Data evaluated among those with available fasting glucose value at baseline (n=17,485); ns: not statistically significant, t-test used to compare the two means; Had an event: first event of either CHD or stroke or death from any cause; CHD: Coronary heart disease includes both fatal coronary events and non-fatal myocardial infarction (primary outcome of the ASCOT-BPLA)

Figure 7.2: Risk (odds ratio) associated with each mmol/l rise in mean baseline fasting plasma glucose for each of the cardiovascular outcomes separately



- * Combination of the 3 pre-specified outcomes, but excluding non-cardiovascular deaths.
- Separate models for each outcome. All models were adjusted for a priori confounders (age, sex, race, smoking, systolic BP, BMI, BP-treatment allocation, total and HDL-cholesterol and number of CV risk factors) and other confounders found on univariate analysis (history of previous vascular disease, serum triglyceride levels, and presence of atrial fibrillation)
- NF: non-fatal; F: fatal; MI: myocardial infarction; CHD: fatal coronary heart disease including and non-fatal myocardial infarction; CVD: cardiovascular disease

Figure 7.3: Baseline- and cumulative mean glucose overall, and among various sub-groups



* T-test used to compare the two means; *** significant differences, p<0.001; Had an event: first event of either CHD or stroke or death from any cause; CHD: Coronary heart disease includes both fatal coronary events and non-fatal myocardial infarction (primary outcome of the ASCOT-BPLA)

Figure 7.4: Area-under-curve of cumulative mean fasting glucose during follow-up, stratified by allocated treatment regimen

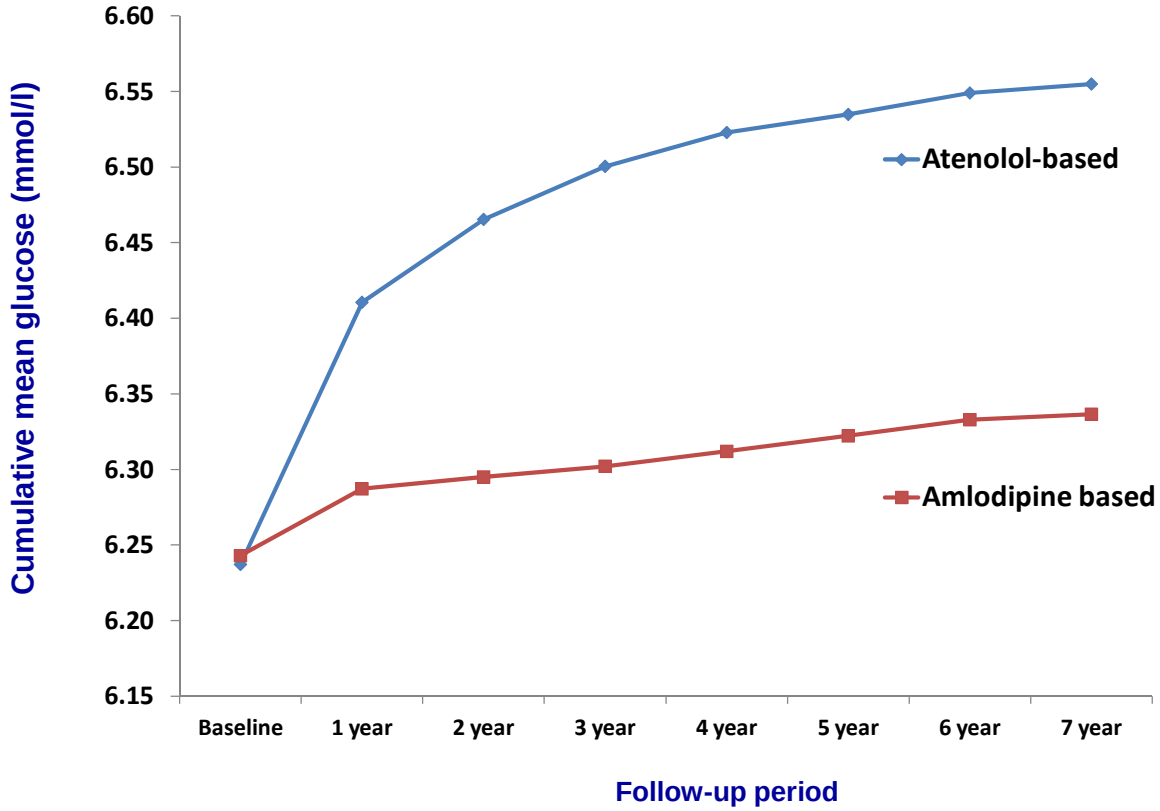
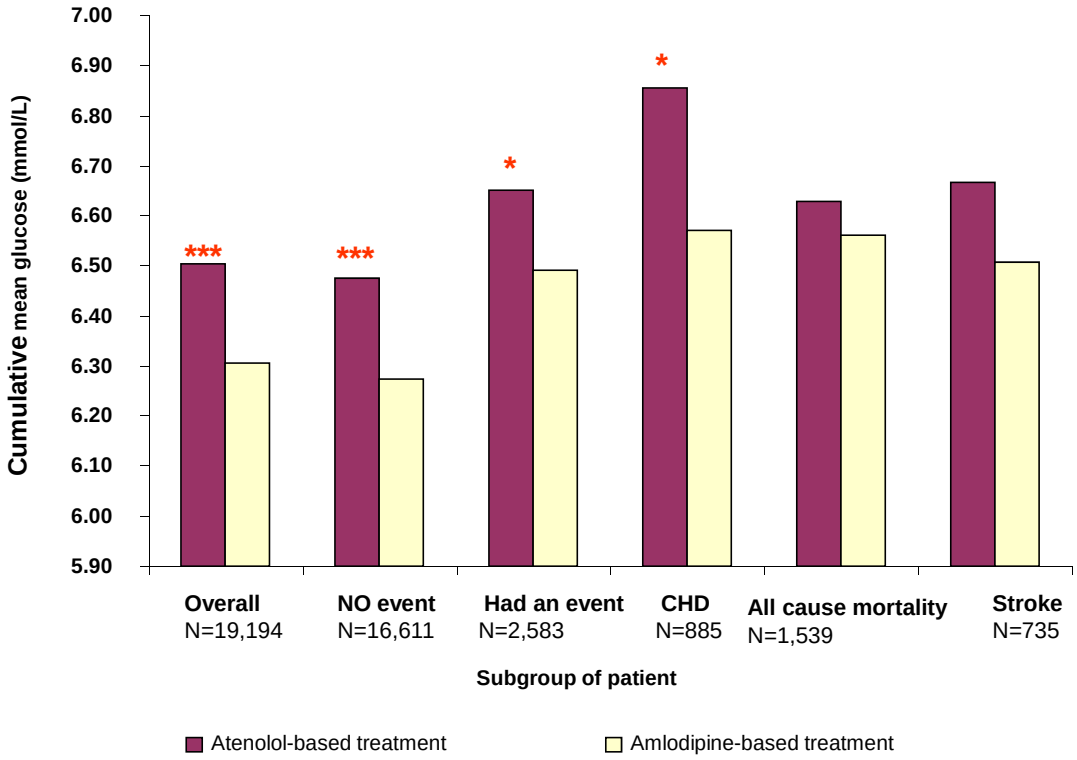
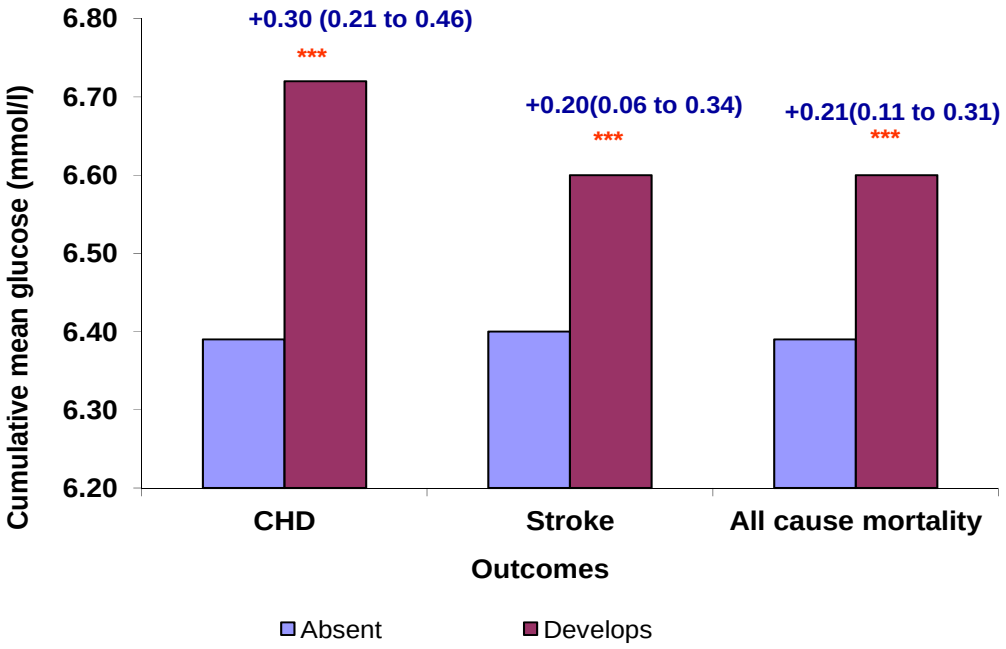


Figure 7.5: Cumulative mean glucose levels, stratified according to randomised treatment group, among all randomized patients* and sub-groups based on presence or absence of a subsequent cardiovascular event or death



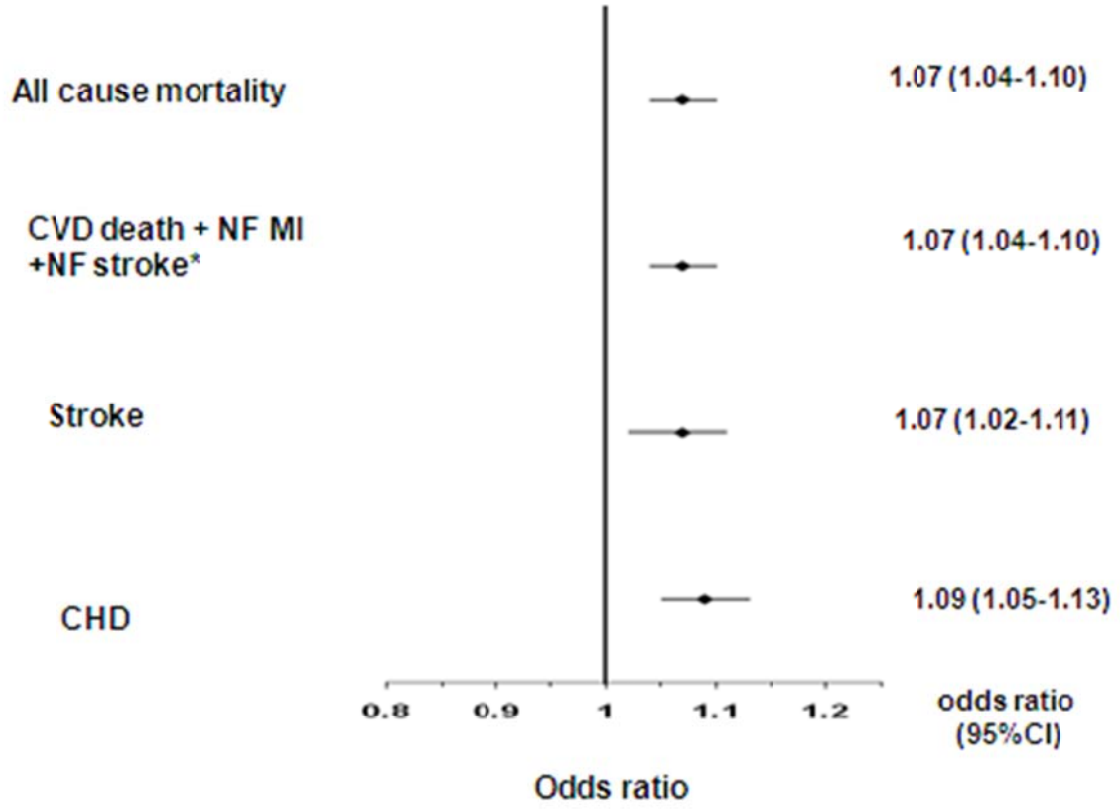
*p-value <0.05 & *** p-value <0.001— t-test used to compare the two means; Had an event: first event of either CHD or stroke or death from any cause; CHD: Coronary heart disease includes both fatal coronary events and non-fatal myocardial infarction

Figure 7.6: Cumulative mean glucose* and cardiovascular events or deaths



- * CMG levels prior to event compared with the CMG levels at the exit from the study
- *** denotes significant differences, p <0.001, on comparison of means using student's t-test.

Figure 7.7: Risk (odds ratio) associated with each mmol/l rise in cumulative mean glucose for CHD, stroke or death, or their combinations.



- Odds ratios are derived from the respective multivariate models, developed separately.
- All models were adjusted for a priori confounders (age, sex, race, smoking, systolic BP, BMI, BP-treatment allocation, total and HDL-cholesterol and number of cardiovascular risk factors) and other confounders found on univariate analysis (history of previous vascular disease, serum triglyceride levels, and presence of atrial fibrillation)
- * Combination of the 3 pre-specified outcomes, but excluding non-cardiovascular deaths.
- NF: non-fatal; F: fatal; MI: myocardial infarction; CHD: fatal coronary heart disease including and non-fatal myocardial infarction; CVD: cardiovascular disease

Figure 7.8: Incidence rates (per 1000 person years) of CHD, stroke and deaths, according to glycaemic status after 1 year from randomisation

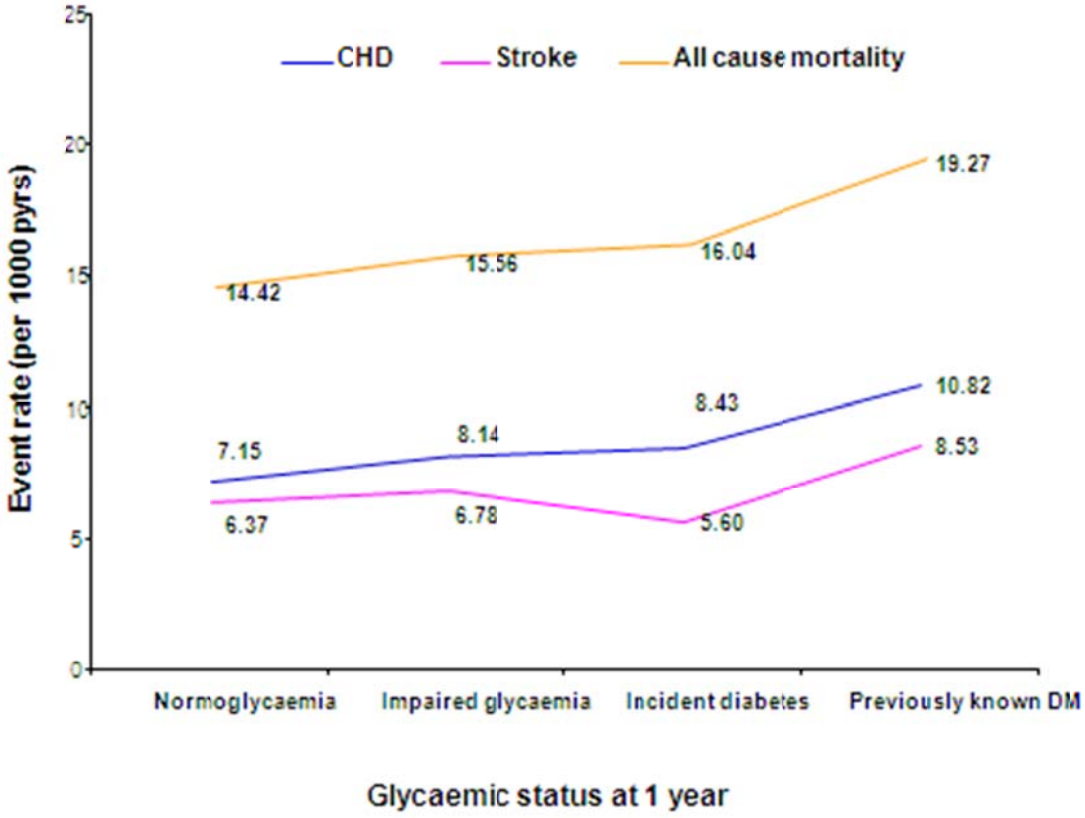
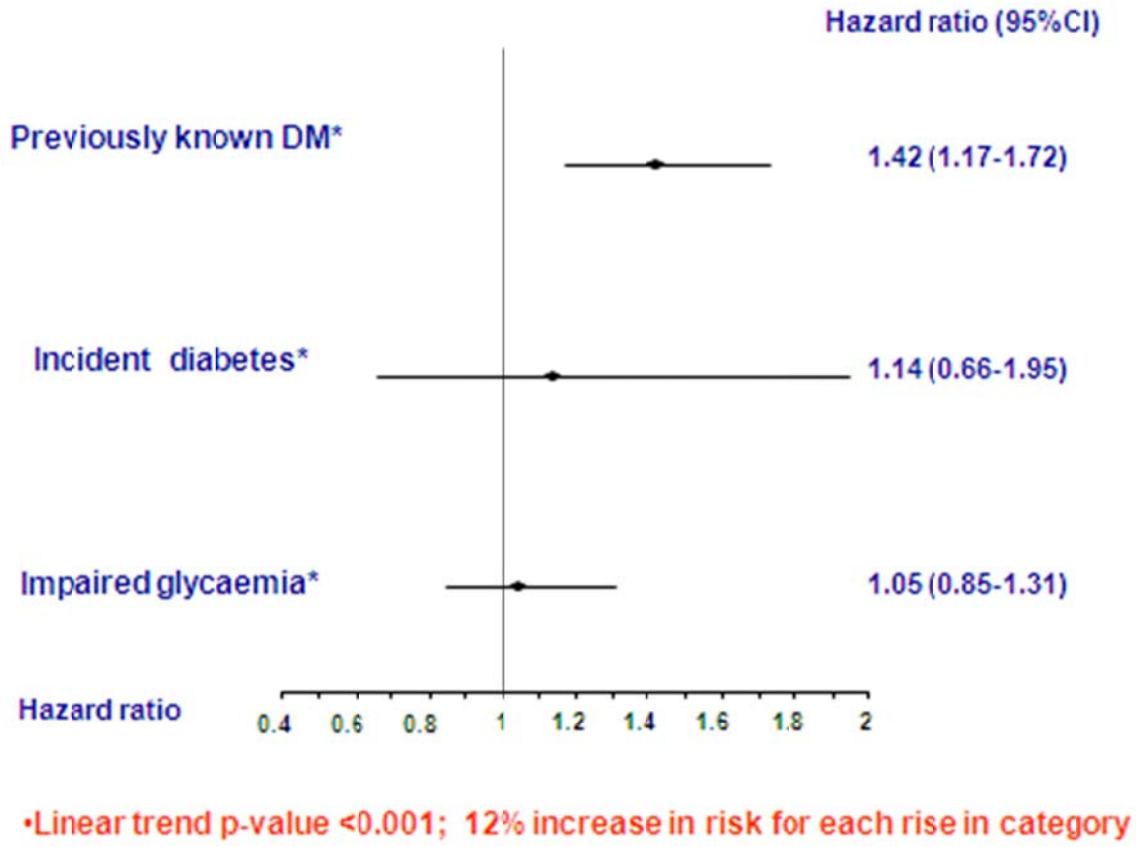
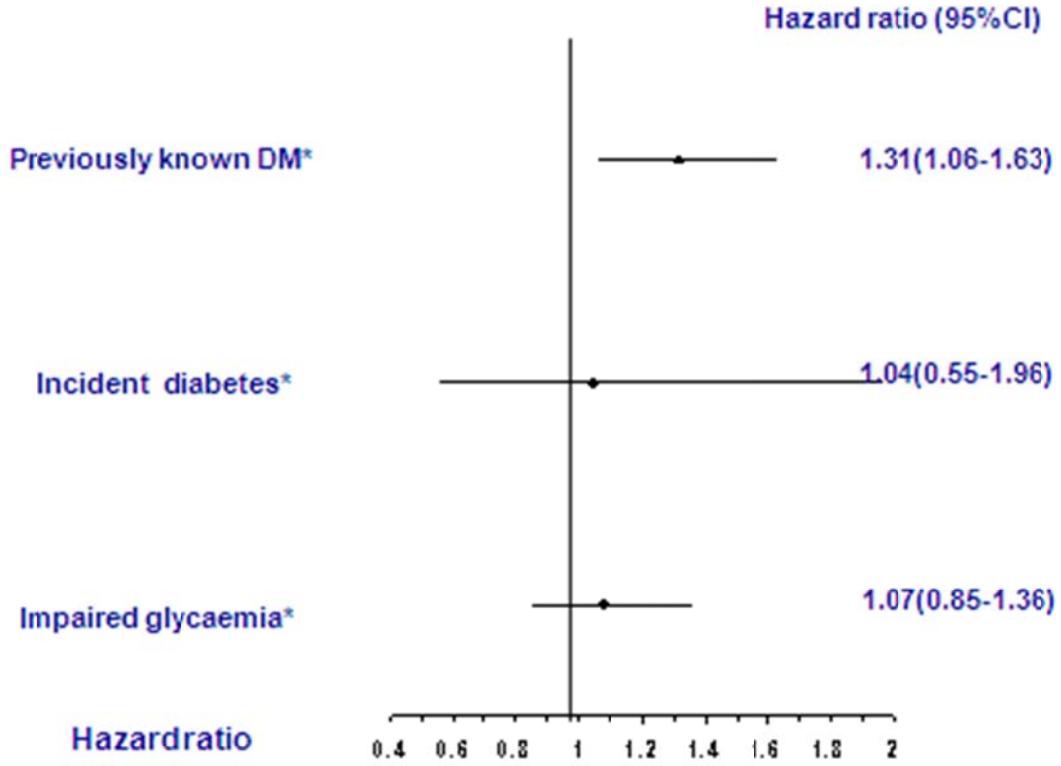


Figure 7.9: Risk (hazard ratio) of CHD associated with the glycaemic status at 1 year after randomisation



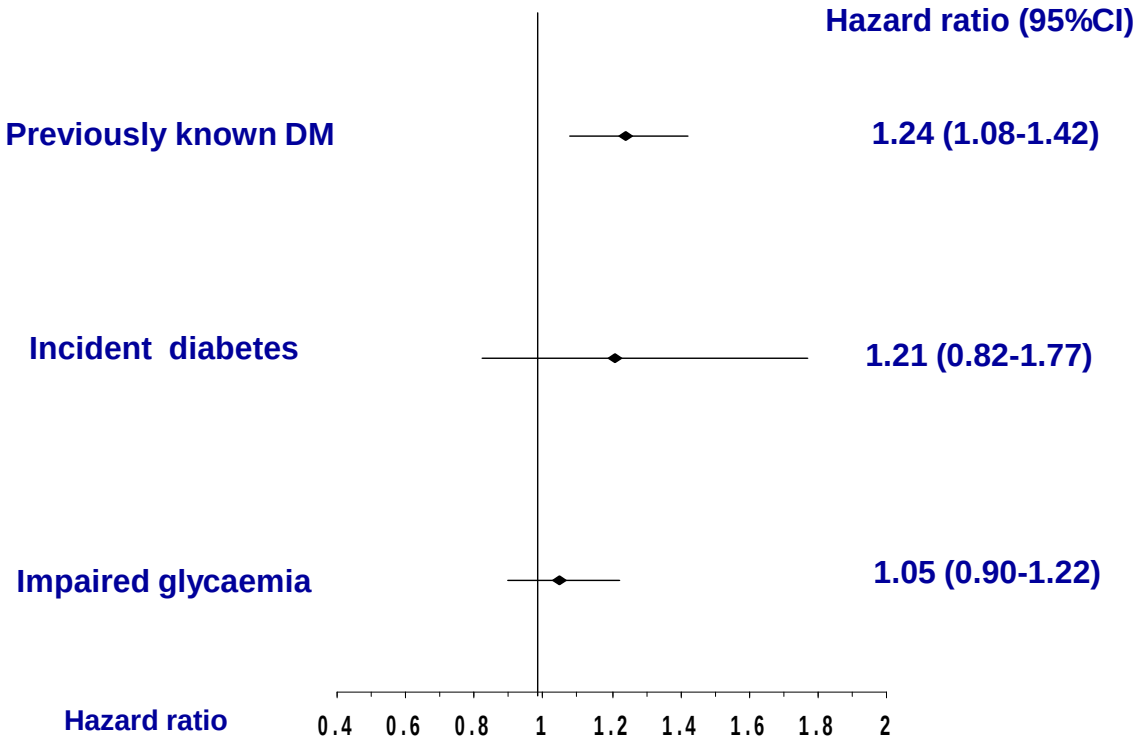
CHD: fatal coronary heart disease and non-fatal myocardial infarction.
*** Glycaemic status at 1 year.**

Figure 7.10: Risk (hazard ratio) of stroke associated with the glycaemic status at 1 year after randomisation



- *** Glycaemic status at 1 year.**

Figure 7.11: Risk (hazard ratio) of all cause mortality associated with the glycaemic status at 1 year after randomisation



7% increase in risk for each rise in category;
test for linear trend p-value=0.002

- **Glycaemic status at 1 year.**

Chapter 8

THE METABOLIC SYNDROME AND CARDIOVASCULAR OUTCOMES AND MORTALITY

Study 3: Role of the metabolic syndrome, as an independent predictor of cardiovascular outcomes and deaths, among hypertensive patients in the ASCOT-BPLA

8.1 Summary

The metabolic syndrome, defined as a clustering of cardio-metabolic risk factors such as dyslipidaemia, dysglycaemia, hypertension and obesity, is associated with an increased risk of incident diabetes, cardiovascular morbidity and mortality, and death. Recently the clinical usefulness of a diagnosis of the metabolic syndrome has been intensely debated. Whilst there are several contentious issues fuelling this debate, the foremost is whether the cardiovascular risk associated with the metabolic syndrome is greater than the sum of its individual components. Indeed, several studies have investigated this issue but have reported contradictory findings. The differences in the reported findings may partly be explained by differences in the study populations, the outcomes evaluated, and inadequate adjustment for potential confounders of the relationship between the metabolic syndrome and the evaluated outcome. Moreover, the uncertainty in the current literature is further compounded by the use of different definitions of the metabolic syndrome. To address these issues I have conducted a study to evaluate the association between different definitions of the metabolic syndrome and multiple outcomes including coronary events, strokes, and death in the same population. In the following analyses, I have used the database of the blood pressure (BP) lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA), to evaluate whether the metabolic syndrome is independently associated with cardiovascular outcomes and death, after accounting for the influence of its constituent metabolic components.

For the purpose of these analyses, the metabolic syndrome was defined using the original National Cholesterol Education Programme (NCEP)-Adult Treatment Panel (ATP)-III criteria (but replacing waist-circumference with body mass index [BMI] >30 kg/m^2) and also using 4 other definitions including the updated version of the NCEP-ATP definition and the International Diabetes Federation (IDF) definition. Three separate Cox models were

developed to assess the influence of age, sex, ethnicity, and the individual components of the metabolic syndrome on the association between the metabolic syndrome and 4 outcomes: [1] fatal coronary heart disease [CHD] plus non-fatal myocardial infarction [MI], [2] total coronary events, [3] stroke and [4] all-cause mortality.

Unadjusted metabolic syndrome (Model-1) was associated with a significantly increased risk of coronary outcomes (fatal CHD and non-fatal MI; and total coronary events) but not of stroke or all-cause mortality. After adjusting for age, sex and ethnicity (Model 2), the association between the metabolic syndrome and coronary outcomes became stronger and was also significantly associated with stroke and all-cause mortality. After further adjustment for the individual components of the metabolic syndrome (Model-3), the metabolic syndrome was no longer significantly associated with coronary outcomes, but was significantly associated with an increased risk of stroke and all-cause mortality. In each Cox model, the relationship between the metabolic syndrome and each outcome remained the same, regardless which definition of the metabolic syndrome was used. On sensitivity analyses, these relationships were also unaffected after excluding those with diabetes or with missing values at baseline; and after adjusting for the potential confounding influence of other conventional cardiovascular risk factors such as smoking and alcohol intake.

In summary, among hypertensive patients, the metabolic syndrome independent of its individual components was associated with an increased risk of stroke and all-cause mortality but not of coronary events. Additionally, these relationships were unaffected by the presence of diabetes, other conventional cardiovascular risk factors, and the use of different definitions of the metabolic syndrome. If these findings are replicated, they may have important implications for the optimal prevention of stroke and other cardiovascular endpoints.

Study 3: Role of the metabolic syndrome, as an independent predictor of cardiovascular outcomes and deaths, among hypertensive patients in the ASCOT-BPLA

8.2 Hypothesis

Among hypertensive patients, the presence of the metabolic syndrome confers an increased risk of coronary, stroke, and death outcomes independent of its constituent metabolic components.

8.3 Background

The metabolic syndrome, variously defined as a clustering of cardio-metabolic risk factors such as dyslipidaemia, dysglycaemia, hypertension and obesity (31-33), is associated with an increased risk of incident diabetes, cardiovascular morbidity and mortality, and all-cause mortality (34). In recent years, the clinical utility of the metabolic syndrome has been intensely debated. Indeed, during the last decade or so, there have been hundreds of publications related to this syndrome. However, in the following sections (8.3.1 to 8.3.4), I will focus the discussion on the following topics:

1. The evidence related to the role of the metabolic syndrome in the prediction of cardiovascular events and death.
2. The evidence related to the role of the metabolic syndrome in the prediction of cardiovascular events among hypertensive patients.
3. The evidence related to the use of different definitions for the metabolic syndrome and the disparity in findings.
4. The evidence related to whether the metabolic syndrome predicts the risk of cardiovascular disease (CVD) or death, beyond the cumulative contributions of its component risk factors.

Since the definition of the metabolic syndrome varies in several publications, and by several organisations (32, 33, 169-171, 173, 360) (see table 2.4), in the following discussion, unless specifically mentioned, the 'metabolic syndrome' will denote the diagnosis using the original definition proposed by the NCEP-ATP-III panel (90, 170) or its subsequent modification (33) (hereafter, termed as **ATP 6.1** and **ATP 5.6**, respectively).

8.3.1 The metabolic syndrome as a predictor of cardiovascular outcomes and death

Several studies have explored the relationship between the metabolic syndrome and the risk of cardiovascular events and death in different settings. The findings from the majority of these studies suggests that the metabolic syndrome is an independent risk factor for CVD and death, after adjusting for the influence of conventional cardiovascular risk factors, including age, sex, smoking, and low-density lipoprotein (LDL) – cholesterol.

The evidence among different age groups: The findings from several studies suggest that the relationship between the metabolic syndrome and cardiovascular outcomes is unaffected by the age of the study population. For example, in the Cardiovascular Health Study (CHS), among 2,175 elderly subjects (mean age, 73 years) (40), the presence of the metabolic syndrome at baseline, after adjusting for age, sex, family history of MI, smoking and LDL cholesterol, was associated with a 2-fold (hazard ratio [HR] 2.04 [95% confidence interval, 1.69 to 2.46]) increase in the risk of cardiovascular events. These findings are consistent with the findings from a population-based middle-aged cohort, The Kuopio Ischaemic Heart Disease Risk Factor Study (361), comprising of 1,209 men, aged between 42 to 60 years, with a median follow-up of 11.6 years (range, 9.1 to 13.7 years). In the Kuopio Ischaemic Heart Disease Risk Factor Study, compared with men without the metabolic syndrome, those with the metabolic syndrome, were at 3-times (2.9 [1.2 to 7.2) greater risk of fatal CHD, after

adjusting for age, smoking, LDL-cholesterol, and family history of CHD. In this cohort, the observed risk for CHD mortality was similar when using either the ATP or WHO definition of the metabolic syndrome.

The impact of gender: The findings from the majority of studies have suggested that the impact of the metabolic syndrome on cardiovascular events and death is similar among men and women (362-365). In contrast, a few studies have reported that the cardiovascular or coronary risk associated with the metabolic syndrome may be higher among women, as compared with men. In a pooled analysis of 11 European prospective cohorts (366), the relationship between the metabolic syndrome and cardiovascular- and all-cause mortality was evaluated among 6,156 men and 5,356 women, during a median 8.8 years of follow-up. In this study women with the metabolic syndrome (compared with those without) were found to be at slightly higher risk of cardiovascular mortality than men, after adjusting for age, blood cholesterol levels, and smoking (women, 2.78 [1.57 to 4.94]; men, 2.26 [1.61 to 3.17]). However in the same analysis there was no difference between men and women in the risk of all-cause mortality (women, 1.38 [1.02 to 1.87]; men, 1.44 [1.17 to 1.84]). The slightly higher risk of CVD mortality among women with the metabolic syndrome in this study was also evident in another study, where women with the metabolic syndrome (compared with those without) were at a considerably higher CHD risk, compared with men (women, 2.46 [1.99 to 3.03]; men, 1.86 [1.59 to 2.18]) (367). It is likely that the small (albeit statistically insignificant) differences in CHD risk seen between men and women in these studies may have been driven by the inclusion of diabetes as a component of the metabolic syndrome. Women with diabetes have a significantly higher CHD risk compared with men with diabetes (368). Thus including diabetes as a component of the metabolic syndrome may have differentially increased the CHD risk among men and women with the metabolic syndrome.

Indeed, this conjecture is well supported by the findings of a recent meta-analyses, including 21 studies (369). In that meta-analysis (where diabetes was also included in the definition of the metabolic syndrome), the increase in cardiovascular risk associated with the metabolic syndrome was more apparent among women as compared with men (relative risk, women, 2.10 [1.79 to 2.45]) and men, 1.57 [1.41 to 1.75])

In summary, the evidence to date is inconsistent, with some studies reporting a greater CHD risk amongst women with metabolic syndrome as compared with men with metabolic syndrome. Presence of diabetes, as one of the component of the metabolic syndrome, could potentially explain these conflicting findings; however, this hypothesis needs further elaboration in well directed, community based, studies.

Clinical trial-based populations: The impact of the metabolic syndrome on the risk of major cardiovascular events was evaluated among those randomized to the placebo arm of the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) (370). The findings suggested that the age-adjusted metabolic syndrome was associated with a 1.5-fold [1.2 to 1.8] and 1.4-fold [1.04 to 1.9] increased risk of major cardiovascular events in the 4S and AFCAPS/TexCAPS study, respectively. The increased cardiovascular risk associated with the metabolic syndrome in these 2 trials remained unchanged, after adjusting for the Framingham risk score at baseline. On further analyses, those with the metabolic syndrome, compared with those without, were at a significantly greater risk of a cardiovascular event, regardless of the estimated baseline Framingham risk (> or ≤ 20%). These findings imply that the metabolic syndrome is associated with an added cardiovascular risk, which is not entirely accounted for by those conventional risk factors measured in the Framingham risk score. Furthermore, the

increased cardiovascular risk associated with the metabolic syndrome remains regardless of an individual's baseline cardiovascular risk (370). Several other trials, among those with and without hypertension, have reported sub-group analyses on the efficacy of different treatment regimens among those with and without the metabolic syndrome (371). A detailed discussion of these studies is beyond the scope of this review, but in summary there were no major differences in the treatment efficacy of antihypertensive drugs or statins between those with and without the metabolic syndrome.

Role of the metabolic syndrome among those from different patient populations: Several studies have explored the role of the metabolic syndrome as a predictor of cardiovascular outcomes in different patient populations.

Among those with diabetes, a significantly high proportion of patients (between 75% and 93%) may have the metabolic syndrome (372, 373). However, despite this high prevalence, studies have not shown a consistent relationship between the metabolic syndrome and cardiovascular outcomes in this group. For example, in the Verona Diabetes Complications Study (373), among 946 patients with diabetes, the risk of CVD associated with the metabolic syndrome (prevalence, 93%) was evaluated during a mean follow-up of 4.5 years. The findings suggested that after accounting for the influence of age, sex, smoking habit, and glycaemic control, those with the metabolic syndrome, compared with those without, were at a 5-fold greater risk of developing CVD (4.89 [1.16 to 20.67]). This difference in the risk of CVD between the two groups: diabetes with the metabolic syndrome and diabetes without the metabolic syndrome is surprisingly high on two counts: First, diabetes itself is a risk factor for CVD, and the presence of the metabolic syndrome adding substantially to this risk is a bit unexpected. Second, given the high prevalence of the metabolic syndrome in this group, it is

likely that a number of the patients without metabolic syndrome may have some of the components of the metabolic syndrome; hence, the risk difference between the two (patients with diabetes with and without the metabolic syndrome) might be expected to be minimal. Indeed, these findings are in contrast to the findings of another study, the Casale Monferrato Study (372), among 1,565 elderly patients (>65 years) with type 2 diabetes . Nearly three-quarters of all patients included in this study had the metabolic syndrome at baseline (using the WHO definition). During 11-years of follow-up there were 685 deaths. The findings suggested that after adjusting for conventional cardiovascular risk factors, there was no significant difference in cardiovascular or all-cause mortality among those with and without the metabolic syndrome at baseline. The contrasting findings of these two studies may be explained on the basis of differences in the patient's characteristics and study design. For example, compared with those included in the Verona Diabetes Complications study, patients in the Casale Monferrato study were older (69 years vs. 63 years), with a longer duration of diabetes (11 years vs 9 years) and longer follow-up (11 years vs. 4.5 years). Both age and diabetes, together with duration of diabetes, are independent risk factor for CVD. Thus it is likely that the higher baseline age, longer duration of diabetes, and considerably longer duration of follow-up, among those in Casale Monferrato study may have over-ridden any small differences in the cardiovascular risk associated with the presence or absence of the metabolic syndrome, resulting in insignificant findings in this study. In comparison, among those included in Verona Diabetes Complications study, the lower baseline age, lesser duration of diabetes, and a short follow-up may have been insufficient to attenuate the differences in CVD risk between those with or without the metabolic syndrome.

In a study of patients who tested positive for the human immunodeficiency virus (HIV), there was a 3-fold increased risk of CVD among those with the metabolic syndrome compared with

those without (2.89 [2.34 to 3.59]). Similarly, among the post-MI patients in the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione) Trial (n=11,323), the presence of the metabolic syndrome, compared with its absence, was associated with a significantly greater risk of a cardiovascular events (29%, p=0.002) and death (23%, p=0.005) (374). In another study, among 461 patients with acute MI, the presence of the metabolic syndrome, compared with its absence, was associated with an increased risk of major adverse cardiovascular events, regardless of other cardiovascular risk factors, type of coronary vessel involvement and CRP levels (375). These findings suggest that even among those with high cardiovascular risk, the metabolic syndrome confers a further increase in the risk of the cardiovascular morbidity and mortality. However, in another study, the San Antonio Heart Study (SAHS), the findings among their high cardiovascular risk group were contradictory. In SAHS, among patients with pre-existing *CVD,* the presence of the metabolic syndrome was not associated with an increased risk of CVD or death (376).

The evidence regarding the role of the metabolic syndrome, as an independent predictor of CVD, among *hypertensive patients* is discussed in section 8.3.2.

Role of the metabolic syndrome among different ethnic groups: Several studies have explored the relationship between the metabolic syndrome and cardiovascular events among different ethnic groups. In the Atherosclerosis Risk in Communities (ARIC) study there was a wide variation in the prevalence of the metabolic syndrome among men and women of black-African (n = 3,621) and white Caucasian origin (n =10,881). In this study women of black-African origin had the highest prevalence of the metabolic syndrome and black-African men had the lowest. However, more importantly, despite differences in the prevalence of the metabolic syndrome among these sub-groups, the metabolic syndrome was associated with a

significant increase in the risk of CHD in each of these 4 groups, with the risk of CHD being highest among black African men (2.74 [1.72 to 4.38]) (377). Similarly, in the SAHS study, the incidence of cardiovascular events was evaluated among 928 non-Hispanic whites, and 2,013 Mexican-Americans. There were differences in the prevalence of the metabolic syndrome by ethnicity, with Mexican American women having the highest prevalence of the metabolic syndrome (30.9%), and non-Hispanic white women having the lowest prevalence (16.8%). However, despite the observed differences in prevalence, the metabolic syndrome was associated with a significantly higher risk of cardiovascular events, independent of the participant's ethnic origin (378). Similarly, in a study among 9,087 Japanese men (n=3,595) and women (n=5,492) the metabolic syndrome was a significant and independent predictor of ischaemic heart disease and stroke, after adjusting for age, sex, smoking, total cholesterol, alcohol intake and for women, menopausal status (363).

Long-term prediction of cardiovascular outcomes and death: Several studies have suggested that the metabolic syndrome is able to predict the longer-term cardiovascular risk, more accurately than the existing cardiovascular risk assessment tools, which usually predict for 10-year risk (37, 190, 379). In a community-based cohort of 2,322 men followed for up to 32 years, the metabolic syndrome at baseline was associated with a significantly increased risk of cardiovascular mortality (1.59 [1.29 to 1.95]) and total mortality (1.36 [1.17 to 1.58]), after adjusting for smoking, diabetes, hypertension, and serum cholesterol (380). These findings have important clinical implications because conventional cardiovascular risk assessment tools, such as the Framingham risk score, predict 10 year cardiovascular risk, and therefore, may underestimate the longer-term cardiovascular risk (37, 190, 379). For example, in a middle aged person, the use of the Framingham risk score, may provide a lower 10-year cardiovascular risk estimate, in comparison, the presence of metabolic syndrome in the same

person would invoke a longer term cardiovascular risk, and that may help initiate preventative strategies sooner. Indeed, the importance of the metabolic syndrome in predicting long-term cardiovascular risk is one of the key arguments in support of its continued role in clinical practice (37). In keeping with these findings, a new analysis from the British Regional Heart study assessed the risk of CVD associated with the presence of the metabolic syndrome among middle aged men, followed for up to 20 years. The findings suggested that compared with those without the metabolic syndrome, those with the metabolic syndrome had a significantly higher risk of CHD (relative risk, 1.57 [1.39 to 1.97]) and stroke (1.61, [1.26 to 2.06]); however when compared with actual events in this study, the CHD/CVD risk predicted by the metabolic syndrome was found to be inferior to that estimated by the Framingham equation (381). Despite a few inconsistencies in the current evidence, the consensus is suggestive of a possible role for the metabolic syndrome as an independent predictor of cardiovascular outcomes (34, 37, 382). However, it is as yet unclear, whether that is sufficient justification to support the continued use of the diagnosis of the metabolic syndrome in routine clinical practice (379).

Appraisal of the evidence to date: Studies have shown that the metabolic syndrome is associated with an increased risk of CVD morbidity and mortality of between 30% and 400%. This wide range in effect size may exist because most of the studies differ in their follow-up period, patients' characteristics, definition of the metabolic syndrome, and adjustment for other conventional cardiovascular risk factors. However, regardless of the apparent differences in the strength of the relationship, the evidence is consistent in support of the metabolic syndrome as an independent risk factor for CVD and death, regardless of the patient's ethnic origin, baseline risk, and presence of other conventional cardiovascular risk factors. This statement was further supported by a recent meta-analysis of 951,083 patients

from 87 studies (383), which found that the metabolic syndrome was associated with a significantly increased risk of CVD morbidity (2.35 [2.02 to 2.73), CVD mortality (2.40 [1.87 to 3.08]), all-cause mortality (1.58 [1.39 to 1.78]), MI (1.99 [1.61 to 2.46]), and stroke (2.27 [1.80 to 2.85]). In another meta-analysis, including 21 studies, those with the metabolic syndrome, compared with those without, had a significantly increased risk of all-cause mortality, CVD, CHD and stroke. Furthermore in this analysis the effect sizes were found to be higher when using the WHO definition of the metabolic syndrome as compared with the ATP definition (369).

In conclusion, there is consistent evidence to support a significant and independent relationship between the metabolic syndrome and several cardiovascular outcomes and death. This is unsurprising, given the fact that the constituent components of the metabolic syndrome, including obesity, impaired glucose metabolism, hypertension, and dyslipidaemia, all have an independent and continuous relationship with CVD risk (16, 35, 384-389). Perhaps a more important finding from these studies is that the metabolic syndrome, as a risk construct, is able to predict long-term cardiovascular risk independent of an individual's baseline risk. Another important observation is that the cardiovascular risk predicted by the metabolic syndrome is in excess of that predicted by conventional cardiovascular risk factors, such as age, sex, smoking and socio-economic status. Together, these findings imply that there may be a role for the metabolic syndrome, beyond that of the routinely used cardiovascular risk prediction tools in clinical practice.

8.3.2. The metabolic syndrome and CV outcomes among hypertensive patients

Only a few studies have evaluated the association between the metabolic syndrome and the risk of cardiovascular morbidity and mortality among hypertensive patients. In a study among

1,742 hypertensive patients (390), those with the metabolic syndrome, compared with those without, were at a 73% (1.73 [1.25 to 2.38]) increased risk of a cardiovascular event after adjusting for the influence of age, sex, smoking and total cholesterol. However, when those with pre-existing diabetes were excluded from the analyses, the associated cardiovascular risk was attenuated, although the relationship still remained positive and significant (1.43 [1.02 to 2.08]). Similarly, among hypertensive patients in the Losartan Intervention for Endpoint (LIFE) study (391), the metabolic syndrome was associated with a 1.5- and 1.7-fold increased risk of a cardiovascular event and cardiovascular mortality, respectively. These studies among hypertensive patients have a significantly smaller effect size as compared with similar community based studies, where the metabolic syndrome was associated with a 2 to 4-fold increase in CVD risk(392-394). This may be explained because among the hypertensive population, the baseline cardiovascular risk is higher as compared with those in the community. Moreover, since, hypertension was present in all patients—with and without the metabolic syndrome, it would reduce the effect size due to comparison of two groups at a higher gradient of risk.

8.3.3. The metabolic syndrome and cardiovascular outcomes: predictability of different definitions

The 3 most commonly used definitions of the metabolic syndrome are from the NCEP-ATP III, WHO and International Diabetes Federation (IDF) (32, 33, 169, 170, 360) (Table 2.4). In addition 2 more definitions of the metabolic syndrome, from the European Group for Study of Insulin resistance (EGIR) (171) and the American Association of Clinical Endocrinologist (AACE) (173), are occasionally used. The AACE definition is a modification of the NCEP-ATP criteria which refocuses the NCEP-ATP criteria from equal emphasis on all components to the requirement of an essential presence of altered glucose metabolism (i.e. a clinical

measure of insulin resistance) (see Table 2.4). In comparison, the EGIR definition is a modification of the WHO definition, keeping the same criteria but excluding all those with diabetes from the scope of this definition. All of these definitions, despite sharing similar (or the same) constituent components, differ from each other in their emphasis (either on a patho-physiological basis or the clinical usefulness of the metabolic syndrome), and/or the cut-off points of the component variables. This has led to several studies comparing how the relationship between the metabolic syndrome and cardiovascular outcomes varies when different definitions of the metabolic syndrome are used.

In a study comparing the ATP and WHO definitions of the metabolic syndrome (395), whilst the overall prevalence of the metabolic syndrome was similar (24% and 25% using the ATP and WHO definitions, respectively), the prevalence among a few sub-groups differed substantially. For example, among African-American men, the prevalence of the metabolic syndrome was 16% using the ATP definition and 25% using the WHO definition. However, the CVD risk associated with the metabolic syndrome was similar when using either of the two definitions, overall, and in the sub-groups. In another population-based study (396), consisting of 4,041 men and 3,812 women from 2 Finnish and 4 Swedish cohorts, comparisons of the risk of CHD and stroke were made using 4 different definitions of the metabolic syndrome: the original ATP, the modified ATP, WHO and IDF definitions. There were no major differences in the risk of CHD and stroke using each definition of the metabolic syndrome in both men and women. Similar findings were seen in an analysis of the SAHS data, where both the WHO and ATP definitions of the metabolic syndrome were significantly and similarly associated with an increased risk of CVD mortality (397). Meigs et al in their analyses reported that the cardiovascular risk associated with the metabolic syndrome, defined using different definitions, was similar and statistically significant (398).

In contrast to findings of the aforementioned studies (in section 8.3.3), there are a few studies where the use of different definitions of the metabolic syndrome resulted in substantial differences in the observed relationships between the metabolic syndrome and cardiovascular outcomes. In the CHS study, among elderly patients, the metabolic syndrome was significantly associated with an increased risk of CVD, when using the ATP definition but not when using the WHO definition. Similarly in another study, among 5,047 non-diabetic patients, 3 different definitions of the metabolic syndrome were used to compare the prevalence of the metabolic syndrome and predicted CVD (399). The findings suggested that the prevalence of the metabolic syndrome were similar (18.8%, 20.6%, and 21.9% based on the EGIR, ATP and IDF definitions, respectively), but in multivariable models, the CVD risk associated with the metabolic syndrome using the ATP and EGIR definitions was found to be significantly higher compared with the IDF definition (HRs 1.59 [1.25 to 2.03], 1.35 [1.05 to1.74] and 1.11 [0.86 to 1.44], respectively with ATP, EGIR and IDF definitions). In another study, the Finnish Diabetic Nephropathy (FDN) study (400), similar analyses were performed among patients with diabetes. The findings suggested that the metabolic syndrome, defined using the WHO definition, was associated with an increased risk of cardiovascular mortality, but this was not apparent using the IDF definition. In summary, most of the evidence favours that all definitions of the metabolic syndrome predict the risk of cardiovascular outcomes similarly; with the exception of a few studies suggesting the IDF definition may not predict CVD risk.

8.3.4. Does the diagnosis of the metabolic syndrome add value, beyond its individual components?

The studies summarised in section 8.3.2 have consistently shown that the metabolic syndrome, after adjusting for the confounding influence of other conventional cardiovascular

risk factors (such as age, gender, smoking, total cholesterol and LDL-cholesterol), remains a significant risk factor for cardiovascular outcomes and death. However, critics have often attributed these findings to the fact that all of the constituent components of the metabolic syndrome themselves have a separate, independent and continuous association with the risk of cardiovascular outcomes and death. Therefore, it is debatable whether the increased cardiovascular risk associated with the metabolic syndrome is in excess of the sum of its constituent components. Indeed this is a pivotal point in the ongoing debate surrounding the clinical utility of the metabolic syndrome.

Several studies have evaluated whether the cardiovascular risk associated with the metabolic syndrome is greater than the sum of its individual components, however their findings have been equivocal (40, 42-45). In a study using two community-based cohorts (the first consisting of those aged 50 years, and the second comprising of all those aged 70 years), the metabolic syndrome, independent of its individual components, was not associated with cardiovascular mortality in either age-group (44). A case-control study, using 393 patients with early-onset coronary artery disease (the cases), and 393 age, sex, and race matched control subjects, also found that the risk associated with the metabolic syndrome was no greater than the sum of the risks of its constituent parts (45, 401). In an observational study of 33,347 HIV-infected individuals, those with the metabolic syndrome at baseline, as compared with those without, were at a 3-fold (2.89 [2.34 to 3.59]) increased risk of developing CVD. However, on multivariable analyses, after adjusting for the influence of its individual components, the CVD risk associated with the metabolic syndrome was no longer significant (0.85 [0.61 to 1.17]) (42). These studies are supported by studies in several other community-based cohorts and surveys, that have also failed to demonstrate any additional cardiovascular

risk conferred by the presence of the metabolic syndrome, beyond that of (all or some of) its constituent components (393, 394, 402-405)

On the basis of these reports (42, 44, 45, 394, 405), most critics have questioned the clinical utility of the metabolic syndrome. However, a few important issues need to be considered to accurately interpret the findings from these studies. Firstly, in most of these studies there is a linear increase in the risk of cardiovascular outcomes and death, proportional with an increase in the number of constituent components of the metabolic syndrome, although often ignored in these individual studies, when taken together this evidence supports an additive effect of the components on the relationship between the metabolic syndrome and CVD. Secondly, several components of the metabolic syndrome remain hidden (and have therefore not been considered in these studies) either because they are not included in the definition of the metabolic syndrome, or they are not easily measured—for example, insulin resistance, elevated apolipoprotein-B, pro-thrombotic and pro-inflammatory state. Therefore, it is likely that that these factors (which also have an independent relationship with cardiovascular outcomes) may co- exist among those patients with an insufficient number of constituent metabolic components to have a clinical diagnosis of the metabolic syndrome (using standard definitions). This implies that these apparently 'non' metabolic syndrome patients, in reality may also have a high associated cardiovascular risk (because of the presence of known and unmeasured metabolic components), which would result in diminishing the observed differences between those with and without metabolic syndrome. Finally, the metabolic syndrome is a progressive disorder, and as this condition worsens over a period of time, the cardiovascular risk estimated at a given time-point may underestimate the actual long-term risk. Together all these factors, may attenuate the apparent differences in cardiovascular outcomes between those with and without the metabolic syndrome, in these short-term

studies. Therefore, whilst these studies have not reported any additional benefit from a diagnostic label of the metabolic syndrome, it is likely that these findings are far from conclusive.

Indeed, several other studies have reported that a diagnosis of the metabolic syndrome is indeed useful, and potentially adds more prognostic information than that obtained from its individual constituent components. For example, in the CHS study, after adjusting for the impact of its constituent components, the metabolic syndrome was associated with a 38% (1.38 [1.07 to 1.79]) greater risk of CHD compared with those without the metabolic syndrome (40). In another cohort study, the metabolic syndrome, compared with those without was associated with a significant increase in the risk of incident stroke after adjusting for the influence of its constituent components (406). These findings are also supported by those of a recent meta-analysis (43), which found that the metabolic syndrome, after adjusting for its individual components and additional cardiovascular risk factors including age, sex, and smoking, was associated with a 54% increased risk of CV events and death among mostly middle aged patients (43).

8.3.5: Summary:

The intense debate about clinical usefulness of the diagnosis of the metabolic syndrome could perhaps be summarized as follows. The simplicity of making the diagnosis, the ability to stratify the risk of an individual, and the positive public health messages arising from risk factor identification in a primary care setting, are among the positive aspects that support persisting with this diagnosis in routine clinical practice (37, 38). However, it is arguable that there is no consistent evidence that the diagnosis of the metabolic syndrome adds value to the cardiovascular risk stratification information provided by its individual components (35). The

apparent contradictions in the current literature can potentially be explained on the basis of a few methodological shortcomings in these studies. Furthermore these studies have used different patient populations, studied different outcomes and adjusted for different confounding factors making it difficult to compare their results.

Moreover, the fact that there is no consensus on the definition of the metabolic syndrome has compounded the uncertain validity of this syndrome. There are 2 main issues with the use of different definitions of the metabolic syndrome (31-33). Firstly, different definitions do not identify the same group of people. Second, a few studies have reported inconsistent relationships between the metabolic syndrome and cardiovascular outcomes, when using different definitions.

Given the aforementioned issues, it is likely that a study using different definitions of the metabolic syndrome to evaluate associations with multiple outcomes (including coronary events, strokes, and death), in the same population would provide more clarity. The database from the ASCOT-BPLA (47) provides an excellent opportunity to carry out such evaluations in a hypertensive population.

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8.4 Aims and objectives

1. To evaluate among hypertensive patients whether the association between the metabolic syndrome and coronary events, stroke events, and all-cause mortality is independent of its constituent components.

2. To compare among hypertensive patients the association between 5 different definitions of the metabolic syndrome and coronary and stroke events and all-cause mortality, after adjusting for the constituent components of each definition.

8.5 Materials and Methods

The details of the study design, methods used and the main results of the ASCOT-BPLA trial are described in chapter 4, and have been previously published (47, 48). However, a brief summary of a few details relevant to this study are given below:

8.5.1 Study population: participants

In ASCOT-BPLA, hypertensive patients, aged between 40 and79 years, arising mainly from family practices in the Nordic countries and UK/Ireland, who had at least three of the following cardiovascular risk factors: male sex, age 55 years or older, microalbuminuria or proteinuria, smoking, ratio of plasma total cholesterol to high density lipoprotein (HDL)-cholesterol of 6 or higher, or family history of premature CHD, type 2 diabetes, peripheral arterial disease, previous stroke or transient ischaemic attack were eligible for randomization if there was no current or past history of CHD or presence of a cerebrovascular event within the previous 3 months. Other exclusion criteria included fasting triglycerides greater than 4.5 mmol/L, heart failure, uncontrolled arrhythmias or any haematological or biochemical evidence of an end-organ damage, such as renal or liver failure, or haematological malignancy (48).

8.5.2 Procedures:

After an initial run-in period, all eligible patients were then randomised using a prospective randomised open blinded endpoints design to receive one of two antihypertensive regimens: atenolol adding a thiazide diuretic as required (atenolol-based regimen) or amlodipine adding perindopril as required (amlodipine-based regimen) to reach BP targets.

At the time of randomisation (and or screening) visit, a detailed baseline clinical assessment, measurements of BP, weight and height, and laboratory tests including fasting plasma glucose (FPG), and lipid profile were carried out. Patients were followed up after 3 months, 6 months, 12 months, and thereafter annually. At each visit, BP measurements were taken, study medications were titrated as required, and data on any adverse event or pre-specified outcome was collected. Routine fasting blood investigations were carried at a 6 months, 12 months and thereafter at annual visits.

8.5.3 Definitions:

The metabolic syndrome: **definitions**

The primary definition of the metabolic syndrome used in these analyses was from the NCEP-ATP-III (31, 407), hence forth known at ATP 6.1. For the purposes of these analyses, BMI >30 Kg/m^2 was used instead of waist circumference in defining metabolic syndrome as waist circumference was not measured in ASCOT-BPLA.

Using this definition, the metabolic syndrome was considered to be present if any three of the following risk factors were present at baseline.

I. Systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mm Hg or on antihypertensive therapy. Since the presence of hypertension was a necessary inclusion criterion of the ASCOT study, every randomised patient had this risk factor.
II. Fasting serum triglyceride ≥ 1.7 mmol/l.
III. HDL-cholesterol ≤ 1.03 mmol/l for males, and 1.29 mmol/l for females
IV. BMI >30 kg/m2
V. FPG ≥ 6.1 mmol/L or presence of diabetes.

In addition, we considered the following four other definitions of the metabolic syndrome in these analyses:-

1. The modified ATP 6.1 definition (33) [hence forth known as ATP 5.6]. The criteria were similar to those specified in ATP 6.1, with the exception that the cut-off for FPG was lowered to ≥ 5.6 mmol/L.
2. The International Diabetes Federation definition (32) [hence forth known as IDF]. The criteria are summarised in Chapter 2, Table 2.4. In this analysis, I have used BMI > 30 kg/m2, as an essential criterion, regardless of ethnicity. The other criteria are as defined in the original definition (see chapter 2, table 2.4)
3. A modification of ATP 6.1 by changing the fifth criterion to 'only' FPG ≥ 6.1 mmol/l, and removing the option of 'or presence of diabetes' from this criterion [hence forth known as ASCOT 6.1].
4. A modification of ATP 5.6 by changing the fifth criterion to only FPG ≥ 5.6mmol/l, and removing the option of 'or presence of diabetes' from this criterion [hence forth known as ASCOT 5.6].

The latter two definitions (ASCOT 6.1 and ASCOT 5.6) were included to explore the impact of reducing some of the increased cardiovascular risk conferred by the presence of diabetes at baseline.

8.5.4.Outcomes:

The pre-specified outcomes for these analyses were fatal CHD plus non-fatal (symptomatic or silent) MI, total coronary events, fatal and non-fatal stroke [stroke], and all-cause- mortality. Of them, the outcome of fatal CHD plus non-fatal MI was also the primary outcome of the ASCOT-BPLA, and the other 3 outcomes were pre-specified secondary outcomes in the ASCOT-BPLA. Because of that, data on all 4 outcomes was rigorously collected during the

study period, and each of these outcomes was independently adjudicated by the end-point committee of the ASCOT-BPLA. In addition to these 4 pre-specified outcomes, I have used some additional outcomes in some sensitivity and exploratory analyses, which were either constituent components of, or combinations arising from these four pre-specified outcomes. For example, for some models I have used non-fatal MI, fatal CHD or cardiovascular mortality as separate outcomes. All 3 of these outcomes are constituent components of the 4 pre-specified outcomes in these analyses. Furthermore, I have also combined some components of the 4 pre-specified outcomes to develop an additional post-hoc outcome, which is a combination of cardiovascular mortality plus non-fatal MI plus non-fatal stroke (see Figure 8.1).

8.5.5 Statistical Methods:

STATA 9 software was used for all statistical analyses.

Analysis population: All patients randomised in the ASCOT-BPLA (n=19,257) were included in these analyses.

Missing values: For purpose of these analyses, only fasting values of serum triglyceride (n=17,472) and glucose (n=17,435) were considered, and non-fasting values were denoted as missing values. Patients with these missing values were nonetheless considered for the allocation of the metabolic status at baseline, based on other available values. However, in multivariable models, by default, the population was limited to those with no missing values for any variable entered in the model (n=17,430). No attempt was made to impute any data for these missing values, as the numbers were small. To exclude any possibility of a selection bias, baseline characteristics of those with any missing (or non-fasting) values were compared

with those with no missing (or non-fasting) values.

Descriptive analyses: All eligible patients were assigned as having the metabolic syndrome at baseline or not on the basis of each of the five definitions: ATP 6.1, ATP 5.6, IDF, ASCOT 6.1 and ASCOT 5.6 used in these analyses (see section 8.5.3). Prevalence of the metabolic syndrome was estimated separately using each of these 5 definitions, and stratified by gender.

Baseline characteristics for those assigned as having the metabolic syndrome (using ATP 6.1) were compared with those without. Event rates (per 1000 person years) for each of the pre-specified outcomes according to the baseline metabolic status were determined. Kaplan Meirer curves and Nelson-Aalen cumulative hazard plots according to metabolic status (using all five definitions) were examined for each of the pre-specified outcomes.

Primary analyses: Three separate Cox proportional models (206) were developed for each of the 4 pre-specified outcomes (and, if needed for specific clinical reasons or comparisons with findings from the other studies, also for the other additional outcomes [see section 8.5.4]) to estimate respective hazard ratios (HRs) and confidence intervals (CIs) using the ATP 6.1 definition of metabolic syndrome. Model 1 comprised the unadjusted metabolic syndrome; In Model 2 the risk associated with the metabolic syndrome was adjusted for age, sex & ethnicity, and in Model 3, Model 2 was further adjusted for the influence of all the individual components of the metabolic syndrome. All of these individual components were used as continuous variables except when found to be non-linear in the model. Whilst developing each of these models, appropriate checks for linearity, and the proportional hazard assumption were carried out using standard statistical methods (207, 208).

Different definitions: To assess and compare the consistency and predictability of the 5 definitions of the metabolic syndrome comparisons of the risks (HRs) associated with all five definitions of the metabolic syndrome and coronary events, stroke events, and total mortality were made for each of these outcomes separately in all three Cox models.

Sensitivity and other analyses: Sensitivity analyses were conducted (using the ATP 6.1 definition) by excluding all subjects with missing values in each of the Cox models. In addition the effect of the presence of diabetes in the definitions of the metabolic syndrome was assessed by excluding all those with diabetes at baseline from the 3 Cox models, for each outcome.

8.6 Results

Of 19,257 hypertensive patients randomised in ASCOT-BPLA, 8434 (43.8%) had the metabolic syndrome based on the ATP 6.1 definition. The prevalence of the metabolic syndrome was slightly higher when using the ATP 5.6 definition (48.8%); however, when using the ASCOT 6.1 and ASCOT 5.6 definitions, the prevalence rates (40.9% and 46.7%, respectively) were similar to the ATP 6.1 and ATP 5.6 definitions, respectively. By contrast, the proportion of patients assigned to having the metabolic syndrome using the IDF definition were considerably lower (28.4%) (Table 8.1). However, almost all patients (98%) that were identified as having the metabolic syndrome using the IDF definitions were also identified using the other definitions (data not shown).

8.6.1 Baseline characteristics

Table 8.2 describes the baseline characteristics of those with and without the metabolic syndrome (ATP 6.1). Compared with those without the metabolic syndrome, patients with the metabolic syndrome had by definition higher mean BMI, serum triglyceride and FPG, and lower mean HDL-cholesterol and included a greater proportion of south Asians, non-smokers, women and those with a previous history of using antihypertensive or lipid-lowering therapy. The metabolic syndrome group also had a lower mean age, systolic and diastolic pressures, and alcohol intake and a smaller proportion of those of African-origin, than those without the metabolic syndrome.

8.6.2 The metabolic syndrome and subsequent rates of coronary and stroke events and death

Table 8.3 describes the event rates (overall and stratified by metabolic status) of coronary and stroke events and death observed among the ASCOT-BPLA patients during a median follow-

up period of 5.6 years, and shows that those with the metabolic syndrome (ATP 6.1) had higher rates for each of the outcomes as compared with those without the syndrome.

Figure 8.1 shows the HRs and 95% CIs associated with the presence of the metabolic syndrome (ATP 6.1) for each of the four pre-specified outcomes (and some additional related outcomes—either their constituents or combinations thereof) in the three Cox models. In Model 1— (unadjusted) — the metabolic syndrome (ATP 6.1) was associated with a significantly increased risk of coronary events (fatal CHD and non-fatal MI: HR 1.24 [95%CI: 1.09 to1.41] and total coronary events: 1.25 [1.14 to 1.35]), but not for total stroke (1.07 [0.93 to 1.24]), nor for all-cause mortality (1.07 [0.97 to 1.19]). In Model 2, after adjusting for age, sex and ethnicity, the relationship between the metabolic syndrome and coronary outcomes became more significant and stronger, and it significantly predicted total stroke (1.18 [1.02 to 1.36]) and all-cause mortality (1.23 [1.11 to 1.35]). However, when Model 2 was further adjusted for the individual components of the metabolic syndrome as continuous variables (Model 3), the association between the metabolic syndrome and total stroke (1.34 [1.07 to 1.68]), and all-cause mortality (1.35 [1.16 to 1.58]) became stronger and remained significant, while the association with coronary outcomes attenuated and became insignificant (fatal CHD and non-fatal MI: 1.16 [0.95 to 1.43] and total coronary events: 1.06 [0.91 to 1.24]) (Table 8.4). These relationships remained unchanged on sensitivity analyses after excluding patients with diabetes at baseline (in fact the association(s) became stronger), or those with missing values at baseline.

The relationship between the metabolic syndrome (ATP 6.1) and the combined end point of stroke and coronary outcomes was also examined, and these results lay consistently between the two contrasting results for coronary outcomes, and total stroke and all-cause mortality in

all the three models (Figure 8.1). Similarly, Table 8.4 shows that the findings related to the cardiovascular mortality outcome were similar to those observed when using the primary outcome of the ASCOT-BPLA, with no significant association apparent between the metabolic syndrome and cardiovascular mortality after adjusting for its individual components (Model 3). .

8.6.3 Different definitions of the metabolic syndrome and rates of coronary events, stroke events and all-cause mortality.

Figures 8.2 to 8.5 describe the relationship between the metabolic syndrome and rates of non-fatal MI plus fatal CHD, total coronary events, strokes and all-cause mortality, using the five definitions of the metabolic syndrome in the three Cox models. The results, for each of the definitions used, showed a consistent trend of the metabolic syndrome significantly predicting the primary outcome of the ASCOT-BPLA trial (fatal CHD and non-fatal MI) and total coronary events in Model 1 and 2, but not in Model 3. By contrast, the association between the metabolic syndrome regardless of the definition used with stroke and all-cause mortality was not apparent in Model 1 but became increasingly apparent in Models 2 and 3 such that in Model 3 the results consistently showed the metabolic syndrome to be an independent predictor of total stroke and all-cause mortality after adjusting for its individual components.

Tables 8.3 to 8.7 describe the HR's and 95% CI associated with the metabolic syndrome for the 4 pre-specified outcomes and cardiovascular mortality, using each of the five definitions separately. The findings are similar in that the metabolic syndrome was associated independently and significantly with an increased risk of stroke and death after adjusting for the impact of its constituent components (Model 3) in each of these five definitions. In model 3, there was no apparent significant association between the metabolic syndrome and

coronary outcomes (non-fatal MI plus fatal CHD, or total coronary events), using any of these five definitions. However, in Model 3 after adjusting for the constituent metabolic components, there were some inconsistencies in the relationship observed between the metabolic syndrome and cardiovascular mortality in the 5 definitions. The metabolic syndrome was not significantly associated with cardiovascular mortality using either the ATP 6.1, ATP 5.6, ASCOT 6.1 or ASCOT 5.6 definitions, but, when using the IDF definition, the metabolic syndrome was associated with a 55% increase (1.55[1.03 to 1.78]) in the risk of cardiovascular mortality.

8.7 Discussion

These analyses of 19,257 hypertensive patients suggest that the metabolic syndrome, independent of its constituent components, is associated with an increased risk of stroke and death but not of coronary outcomes (including two of the pre-specified coronary outcomes in ASCOT-BPLA: non-fatal MI plus fatal CHD, and total coronary events). The pattern of the relationships between the metabolic syndrome and coronary events, stroke events and all-cause mortality, are consistent regardless of the definition of the metabolic syndrome used, and after excluding patients with pre-existing diabetes. Indeed, the findings related to incident stroke, and death, are novel findings, particularly among hypertensive patients. These findings could potentially rekindle the debate about the clinical usefulness of the metabolic syndrome (37), and may have important implications for primary prevention strategies especially for incident stroke among hypertensive patients (408).

8.7.1 Prevalence of the metabolic syndrome among hypertensive patients:

The findings of my analyses are similar to those of previous studies among hypertensive patients (371, 390), where a significant proportion of patients (44%) had the metabolic syndrome at baseline. The prevalence of the metabolic syndrome among hypertensive populations is considerably higher than that seen in community-based observational studies. For example in the ARIC study about a third of patients had the metabolic syndrome at baseline. The apparent difference in the prevalence of the metabolic syndrome seen in these analyses and those in the community could be explained on the basis of following facts. Firstly, patients with hypertension are more likely to have other metabolic risk factors compared with those in the community (226, 409). Secondly, it has been postulated that hypertension and the metabolic syndrome may both share common underlying patho-physiological links, and may have a common central origin (274, 275, 410). For example,

studies have shown that up to 50% of patients with hypertension may have underlying insulin resistance (271), a figure which is not dissimilar to that seen among those with the metabolic syndrome (about 66%) (34, 385, 411). Indeed, similar to the findings of my study, studies among those with diabetes or obesity—i.e. groups with at least one component of the metabolic syndrome—have documented a considerably higher prevalence of the metabolic syndrome than population based survey's (372, 412, 413).

Prevalence of the metabolic syndrome and the role of different definitions: In my analyses, the prevalence of the metabolic syndrome was significantly lower when using the IDF definition, compared with the other 4 definitions. This is likely to be due to the restrictive nature of the IDF definition, with the presence of adiposity (in this case BMI >30 Kg/m^2) as an essential criterion. Another reason for the apparent difference could be that among hypertensive patients, as compared with those in the community, other correlated metabolic risk factors are more likely to be present (because of clustering of metabolic components); hence, the use of the ATP 6.1 definition (or its modifications, ATP 5.6, ASCOT 6.1 and ASCOT 5.6 used in these analyses) is more likely to find a greater prevalence of the metabolic syndrome. This is evident from the fact that, in my analyses, almost all (98%) of those identified as having the metabolic syndrome using the IDF definition, were also assigned to having the metabolic syndrome using the other 4 definitions, but the opposite was not true. Similar inconsistencies in the prevalence rates using different definitions have been reported previously (414, 415), however, the observed differences in my analyses were greater than previously documented.

8.7.2 Coronary outcomes

These findings suggest that among hypertensive patients, the risk of coronary outcomes associated with the metabolic syndrome is mainly conferred by its constituent components, and the diagnosis of the metabolic syndrome does not add further value to the coronary risk prediction. These findings are in keeping with those of some (44, 45) but not all previous reports (40, 43, 416, 417). For example, Irribaren et al reported that the metabolic syndrome (defined using the ATP definition) was not associated with premature coronary artery disease, after accounting for the influence of its individual components (45). In contrast, Bonora et al in their analyses of the data from the Verona Diabetes Complication study showed that, along with sex, age, smoking and glycosylated haemoglobin levels, the presence of the metabolic syndrome was also an independent predictor of incident CVD (373). The conflicting findings in these and other studies may have arisen, because the data in the majority of these studies were inconsistently adjusted for the confounding influence of conventional cardiovascular risk factors (including smoking, age, and gender). Furthermore, only a few studies accounted for the influence of individual components of the metabolic syndrome (416, 417). For example, in the meta-analysis reported by Gami et al (43), the 54% (1.54 [1.32 to 1.79]) the increased risk of cardiovascular events and deaths associated with the metabolic syndrome, after adjusting for the influence of it individual components, is likely to be an overestimate. This is because, two of the three studies included in that meta-analysis (390, 393) have only adjusted for the cumulative risk conferred by some, and not all, of the individual components of the metabolic syndrome. Because of the inconsistencies in the current literature, particularly related to the factors that were considered to confound the relationship between the metabolic syndrome and coronary outcomes, I conducted a sensitivity analysis that further adjusted Model 3 for the influence of other conventional cardiovascular risk factors (including smoking, alcohol intake, number of CV risk factors, and randomised antihypertensive

regimen) that were not previously included in this model. The findings suggested that the association between the metabolic syndrome and both fatal CHD plus non-fatal MI (1.10 [0.90 to 1.35]), and total coronary events (1.01 [0.96 to 1.17]) remained unchanged.

The internal validity of my findings in relation to coronary events is supported by the consistency of these findings in the sensitivity analyses, when using the various different definitions of the metabolic syndrome, and after excluding patients with diabetes. However, despite the consistency of these findings, it is important to remember that in these analyses, all included patients had at-least one metabolic component (i.e. hypertension), which was in addition to at least 3 other cardiovascular risk factors. Therefore all included patients, regardless of the presence or absence of a diagnosis of the metabolic syndrome were at a considerably higher risk of a coronary outcome, compared with those in the community. Therefore, it is likely that in this study, the differences in the associated coronary risk among those with and without the metabolic syndrome may have been attenuated because my comparison included those at a higher cardiovascular risk (because of inclusion criteria of the ASCOT-BPLA), and the presence of at least one metabolic risk component (hypertension) among those classified as having no metabolic syndrome.

8.7.3 Stroke

The finding of an increased risk of incident stroke associated with the metabolic syndrome, independent of its constituent components and regardless of the definition used, extends the findings of previous reports (406, 418, 419). Only one previous study has reported the risk of incident stroke with the metabolic syndrome, adjusted for its components whilst using different definitions of the metabolic syndrome (406). That study found that the risk of stroke was significantly associated with two of the six definitions of the metabolic syndrome. The

inconsistency in the reported findings of Wang et al, in comparison to the findings of my analyses, may reflect a type-II error because of comparatively small sample size in the former. This is more apparent as only 137 strokes were evaluated in the study by Wang et al, compared with the 749 incident strokes in my analyses. In another recent analysis of the ARIC data, those with the metabolic syndrome, compared with those without, were at a significantly higher risk of developing stroke, after adjusting for the influence of age, sex, race, education level, current cigarette smoking, and percentage of saturated fatty acid intake (418). Indeed, in that study, a dose-response relationship between the number of metabolic components and the risk of incident stroke was observed. However, none of the analyses in the ARIC study accounted for the influence of individual metabolic components. In comparison, in my analyses, a significant relationship was apparent even after adjusting for the influence of individual metabolic components. Given the potential implications of these findings, I have further adjusted Model 3 with inclusion of other potential confounders (such as previous history of stroke, number of cardiovascular risk factors, alcohol intake, smoking, history of previous antihypertensive therapy, randomised-treatment allocation), and found no change in association between the metabolic syndrome and incident stroke (1.31[1.04 to 1.64]).

In summary, this analysis is the first to report among a hypertensive population that there is a significant and independent relationship between the metabolic syndrome and incident stroke. However, these findings could also be a function of the characteristics of the study population, in that all included patients were hypertensive. Previous studies have shown a strong independent relationship between high BP and incident stroke (16, 18). Indeed, in a study among those with the metabolic syndrome, including the presence of high BP/hypertension as one of the 3 metabolic components of the syndrome, was found to add

significantly to the strength of the relationship between the metabolic syndrome and cardiovascular outcomes, compared with those without high BP/hypertension (418). Because of these observations, it could be argued that the findings from my analyses are particular to hypertensive populations, and may not be applicable to those in the community. However, this criticism, contrasts with the fact that a similar and a significant relationship between the metabolic syndrome and incident stroke (although not consistently adjusted for all the individual components), has been observed in several studies in the community, and among different ethnic groups (406, 419, 420). It is therefore more likely that similar relationships between the metabolic syndrome and stroke exist in the wider community, and may not be limited to hypertensive patients alone.

8.7.4 All-cause mortality

I have found that among hypertensive patients, the metabolic syndrome, independent of its constituent components, is associated with a significant increase in the risk of all-cause mortality (1.35 [1.16 to 1.58]). These finding are unique, as none of the previously reported studies have adjusted for the influence of the constituent components of the metabolic syndrome (417, 421, 422). One previous study reported an increased risk of all-cause mortality associated with the metabolic syndrome, using ATP 6.1, modified ATP 5.6 and IDF definition, after adjusting for age, sex and smoking (421). In another study, the Kuopio Ischaemic Heart Disease Risk Factor Study, among those with the metabolic syndrome, compared with those without, there was a significantly greater risk of death associated with the metabolic syndrome, after adjusting for age, sex, socio-economic status, smoking, LDL-cholesterol and family history of CHD (417). On the contrary, a report using data from the National Health and Nutrition Examination Survey II Mortality Study, found no significant increase in the risk of death among those with the metabolic syndrome, compared with those

without (423). However, when this study was included in a subsequent meta-analysis, summarizing the findings of published results between July,1998 and February, 2005, the metabolic syndrome was found to be independently associated with a significant increase in the risk of all cause mortality, with 6% to 7% of all deaths attributable to the presence of the metabolic syndrome (422). Given the conflicting reports in the current literature and the fact that none of the previous studies have adjusted for the influence of all components of the metabolic syndrome, the findings of my analyses require further confirmation. However, pending such studies, to compare the results of my finding, with other reported findings, I've further adjusted Model 3 to adjust for the influence of other potential confounders including smoking, treatment allocation, and alcohol intake. The new findings were no different from those reported in these analyses.

If the findings from my analyses are true, they may have important clinical implications. In my analyses, the metabolic syndrome (using the ATP 6.1 definition), independent of its constituent components was not associated with a significantly increased risk of cardiovascular mortality (i.e. mortality due to cardiac, stroke or other vascular causes) (1.19 [0.93 to 1.53]). It may be argued that if the increased risk of all-cause mortality associated with the metabolic syndrome is true, the increase must be due to non-cardiovascular causes. Two thirds of the 953 non-cardiovascular deaths in the ASCOT-BPLA were attributed to cancer, which has previously been found to be associated with the metabolic syndrome in observational studies (424, 425). In a recent study, among 42,336 Korean men and 32,168 Korean women, aged ≥20 years, who were followed up for 5.6 years, there was a 40% (1.41 [1.08 to1.84]) increase in cancer mortality among those with the metabolic syndrome, compared with those without (426). Therefore, it is likely that the observed relationship

between the metabolic syndrome and all cause mortality in these analyses is driven by a greater risk of cancer-associated mortality among those with the metabolic syndrome.

8.7.5 Different definitions of the metabolic syndrome, and coronary and stroke outcomes, and all-cause mortality

These findings have shown that among hypertensive patients, the 3 commonly used definitions of the metabolic syndrome, ATP 6.1, ATP 5.6 and IDF predict the risk of coronary and stroke events, and all-cause mortality similarly. This is particularly surprising, given that the prevalence rates estimated by these definitions differed in these analyses. In particular the prevalence of the metabolic syndrome using the IDF definition, was significantly lower than that estimated by the ATP 6.1 and ATP 5.6 definitions. However, similar findings have been previously reported, where prevalence rates differed but the relationship with the outcomes remained the same when using different definitions (412, 415, 421). In contrast, a few studies have reported inconsistent relationships between the metabolic syndrome and the risk of cardiovascular outcomes, using different definitions (399).

Role of diabetes: In these analyses, the findings using the ASCOT 6.1 and ASCOT 5.6 definitions of the metabolic syndrome, were similar to the findings using ATP 6.1 and ATP 5.6 definitions. This may suggest that exclusion of 'or presence of diabetes' option from the ATP definitions did not affect the relationship between the metabolic syndrome and cardiovascular outcomes, and death. Indeed, this is further confirmed by the findings of a sensitivity analysis, where after exclusion of all those with diabetes, the findings remained unchanged. Therefore, in these analyses, inclusion of diabetes in the definition of the metabolic syndrome did not exert any disproportionate effect on the observed findings.

8.7.6 Limitations & Strengths

The use of BMI instead of waist circumference in my definition of the metabolic syndrome is a possible limitation of this study. However, BMI has been used as part of the metabolic syndrome in previous widely accepted studies (423, 427), and has been shown to have a comparable predictive capability as waist circumference (428). Furthermore, a recent meta-analysis found no evidence of heterogeneity in the association between the metabolic syndrome and cardiovascular risk, when waist circumference, waist-hip ratio or BMI were used in the definition (43). It is possible that our findings are not generalizable beyond a hypertensive population with no history of CHD (47). However, when we adjusted for history of any previous use of antihypertensive agents— a marker for severity and duration of hypertension— we found no appreciable difference in the association between the metabolic syndrome and incident stroke or CHD. Similarly, adjustment for the number of CV risk factors at baseline had no appreciable impact on the associated risks of coronary events and strokes.

The major strength of this study is its power to examine several cardiovascular outcomes and all-cause mortality while using various definitions of the metabolic syndrome in the same population. Our findings on stroke and all-cause mortality, particularly in the absence of an independent association with cardiovascular mortality, are striking, and if confirmed in other populations may have public health significance, particularly given the rapidly increasing prevalence of the metabolic syndrome.

8.8 Conclusions

In summary, our findings suggest that the metabolic syndrome after adjusting for age, sex and ethnicity is a risk factor for coronary outcomes, stroke -and all-cause mortality. However,

when adjusted for its constituent components, the metabolic syndrome remains associated with an increased risk of strokes and all-cause mortality but not of coronary outcomes. Additionally, we have shown that these relationships are unaffected by the presence of diabetes, conventional cardiovascular risk factors and different definitions of the metabolic syndrome. If these findings are replicated in other populations, they may have important implications for the optimal prevention strategies for cardiovascular endpoints, particularly stroke. If confirmed, it is likely that the use of the metabolic syndrome, together with other routine cardiovascular risk estimation tools, would help initiate preventative strategies early, particularly among those who are missed (for example, middle aged individuals with borderline high values of risk factors) using only the traditionally used risk stratification tools.

Chapter 8: Tables

Table 8.1 Prevalence (%) of the metabolic syndrome among hypertensive men and women of the ASCOT-BPLA

Metabolic syndrome* definition used	**Total (n=19,257)**	**Women (n=4,515)**	**Men (n=14,742)**
	N (%)	**N (%)**	**N (%)**
ATP6.1	8434(43.8)	2170(48.1)	6264 (42.5)
ATP 5.6	9389 (48.8)	2318 (51.3)	7071 (48.0)
ASCOT 6.1	8092 (42.0)	2069 (45.8)	6023 (40.9)
ASCOT 5.6	9114 (47.3)	2237 (49.6)	6877 (46.7)
IDF	5470 (28.4)	1410 (31.2)	4060 (27.5)

* using BMI> 30 Kg/m2 instead of waist circumference criterion.

ATP6.1: the original NCEP-ATPIII criteria(170)
ATP 5.6: the modified NCEP-ATPIII definition (33)
IDF: The International Diabetes Federation definition (32)
ASCOT 6.1: A modification of ATP 6.1 by changing the fifth criterion to 'only' FPG ≥ 6.1mmol/l, and removing the option of 'or presence of diabetes' from this criterion
ASCOT 5.6: A modification of ATP 5.6 by changing the fifth criterion to only FPG ≥5.6mmol/l, and removing the option of 'or presence of diabetes' from this criterion [

Table 8.2 Baseline characteristics according to metabolic status at randomisation (defined using ATP 6.1 definition) among 19257 hypertensive patients in ASCOT-BPLA

Baseline characteristics	Metabolic syndrome absent (N=10823)	Metabolic syndrome present (n=8434)	p-value*
	Percent/mean (SD)	Percent/mean (SD)	
Randomisation to atenolol-based (%)	49.9	50.1	0.78
Age (yrs)	63.8(8.4)	62.0(8.5)	<0.001
Male (%)	78.3	74.3	<0.001
Ethnicity			
Europeans (%)	95.3	95.3	<0.001
African origin (%)	2.7	2.0	
South Asians (%)	1.1	1.6	
Current smoker (%)	68.9	66.3	<0.001
Alcohol intake (units/wk)	8.5(11.9)	7.4(11.2)	<0.001
BMI (kg/m2)	26.8(3.5)	31.2(4.6)	<0.001
H/O previous stroke or TIA (%)	12.0	9.6	<0.001
Family history of premature CHD (%)	29.5	24.9	<0.001
H/O previous anti-HT drug (%)	78.3	84.4	<0.001
Diabetes at baseline (%)	11.0	46.8	<0.001
Previous lipid lowering drugs (%)	9.0	12.7	<0.001
Previous aspirin (%)	19.1	19.2	0.832
Number of cardiovascular risk factors at randomisation			
3 risk factors (%)	57.2	40.2	<0.001
4 risk factors (%)	30.4	35.8	
>4 risk factors (%)	12.5	24.0	
LVHE (%)	24.0	18.7	<0.001
FPG (mmol/l)	5.6 (1.4)	7.0(2.5)	<0.001
Total cholesterol (mmol/l)	5.9(1.1)	5.9(1.1)	0.8573
HDL-cholesterol (mmol/l)	1.4 (0.4)	1.1(0.3)	<0.001
Serum triglyceride (mmol/l)	1.4(0.6)	2.4 (1.1)	<0.001
Total Cholesterol /HDL ratio	4.3	5.5	<0.001
SBP (mm Hg)	164.6(18.1)	163.3 (17.8)	<0.001
DBP (mm Hg)	94.9 (10.3)	94.4(10.4)	0.002
HR (beats per minute)	71.1(12.5)	73.0(12.7)	<0.001

*Chi-square or t-test as appropriate.
SD: standard deviation; H/O: History of ; HT: Hypertension ; CHD: Coronary heart disease ; TIA: Transient ischemic attack , LVHE: Left ventricular hypertrophy according to ECG criterion; FPG: Fasting plasma glucose ; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate

Table 8.3 Event rates for pre-specified coronary, stroke and death outcomes associated with those with and without presence of the metabolic syndrome at baseline

Outcomes* observed	Total patients randomised (n=19257)		Without metabolic syndrome† at baseline(n=10823) absent		With metabolic syndrome †at baseline (n=8434)	
	No of events	*Rate‡(95 %CI)*	*No of events*	*Rate‡ (95 %CI)*	*No of events*	*Rate‡ (95 %CI*
NF-MI (both silent and symptomatic)	596	5.7(5.3-6.2)	303	5.1(4.6-5.8)	293	6.4(5.7-7.2)
Fatal CHD	329	3.1(2.8-3.5)	171	2.9(2.5-3.3)	158	3.4(2.9-4.0)
Fatal CHD and MI (NF)	903	8.6(8.1-9.2)	461	7.8(7.1-8.6)	442	9.7(8.8-10.7)
Total coronary endpoints§	1605	15.7(14.9-16.5)	817	14.1(13.2-15.1)	788	17.7(16.5-19.0)
Total stroke (Fatal/NF)	749	7.2(6.7-7.7)	409	7.0(6.3-7.7)	340	7.5(6.7-8.3)
(Fatal/NF) MI plus (Fatal/NF) stroke	1494	14.6(13.8-15.3)	797	13.8(12.8-14.8)	697	15.6(14.5-16.8)
Cardiovascular mortality	605	5.7(5.3-6.2)	331	5.5(5.0-6.2)	274	5.9(5.2-6.7)
Cardiovascular death +MI +stroke	1733	16.9(16.1-17.7)	927	16.0(15.0-17.1)	806	18.0(16.8-19.3)
All-cause mortality	1558	14.7(14.0-15.4)	851	14.2(13.3-15.2)	707	15.2(14.2-16.4)

* Pre-specified coronary, stroke and death outcomes, and some of their constituents or combinations. NB. Time to first event is considered for each of the outcome separately.
†Defined on the basis of ATP 6.1
‡ Event rates are per 1000 person years
§ Includes outcomes such as angina, unstable angina and fatal and non-fatal heart failure in addition to those specified in primary outcome.

NF: Non-fatal; MI: Myocardial infarction, CI: confidence interval

Table 8.4 Hazard ratio (95%CI) associated with the metabolic syndrome (defined using ATP 6.1definition) for coronary, stroke and death outcomes

Outcome	Primary outcome (Fatal CHD* plus NF MI)	Total coronary events†	Total stroke (Fatal and NF)	Cardiovascular mortality	All cause mortality
Model	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**
Model 1	1.24(1.09-1.41)	1.25(1.14-1.38)	1.07(0.93-1.24)	1.07(0.91-1.25)	1.07(0.97-1.19)
Model 2	1.34(1.18-1.53)	1.34(1.21-1.48)	1.18(1.02-1.36)	1.21(1.03-1.42)	1.23(1.11-1.35)
Model-3	1.16(0.95-1.43)	1.06(0.91-1.24)	1.34(1.07-1.68)	1.19 (0.93-1.53)	1.35(1.16-1.58)

Model 1 = Univariate MS ; Model 2= Model 1 plus age, sex & ethnicity ; Model 3= Model 2 plus Fasting plasma glucose, triglyceride, HDLc, SBP & BMI . NF= Non-fatal ; F= Fatal ; CHD= Coronary heart disease

***** Fatal CHD: includes death from MI, acute coronary syndrome or sudden death attributable to ischaemic heart disease **†** Total coronary events include fatal and non-fatal CHD, unstable angina, fatal and non-fatal heart failure

Table 8.5 Hazard ratio (95%CI) associated with ATP 5.6 definition of the metabolic syndrome for coronary, stroke and death outcomes

	Primary outcome (Fatal CHD* plus NF MI)	Total coronary events†	Total stroke (Fatal and NF)	Cardiovascular mortality	All cause mortality
Model	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**
Model 1	1.21(1.06-1.37)	1.24 (1.12-1.36)	1.06 (0.92-1.23)	1.03 (0.88-1.21)	1.04(0.94-1.14)
Model 2	1.30(1.14-1.48)	1.31 (1.19-1.45)	1.17 (1.01-1.35)	1.17(0.99-1.37)	1.18(1.07-1.30)
Model-3	1.10(0.90-1.35)	1.05 (0.90-1.23)	1.37(1.10-1.71)	1.13(0.89-1.45)	1.26(1.08-1.46)

Model 1 = Univariate MS ; Model 2= Model 1 plus age, sex & ethnicity ; Model 3= Model 2 plus Fasting plasma glucose, triglyceride, HDLc, SBP & BMI .
NF= Non-fatal ; F= Fatal ; CHD= Coronary heart disease
***** Fatal CHD: includes death from MI, acute coronary syndrome or sudden death attributable to ischaemic heart disease **†** Total coronary events include fatal and non-fatal CHD, unstable angina, fatal and non-fatal heart failure

Table 8.6 Hazard ratio (95%CI) associated with ASCOT 6.1 definition of the metabolic syndrome for coronary, stroke and death outcomes

	Primary outcome (Fatal CHD* plus NF MI)	Total coronary events†	Total stroke (Fatal and NF)	Cardiovascular mortality	All cause mortality
Model	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**
Model 1	1.17(1.02-1.33)	1.20(1.09-1.32)	1.02(0.88-1.18)	1.02(0.86-1.19)	1.02(0.93-1.13)
Model 2	1.26(1.11-1.44)	1.28(1.16-1.41)	1.12(0.97-1.30)	1.17(0.99-1.38)	1.20(1.08-1.33)
Model-3	1.07 (0.87-1.31)	0.99 (0.85-1.16)	1.26(1.02-1.56)	1.25(0.97-1.62)	1.17 (1.00-1.38)

Model 1 = Univariate MS ; Model 2= Model 1 plus age, sex & ethnicity ; Model 3= Model 2 plus Fasting plasma glucose, triglyceride, HDLc, SBP & BMI . NF= Non-fatal ; F= Fatal ; CHD= Coronary heart disease

***** Fatal CHD: includes death from MI, acute coronary syndrome or sudden death attributable to ischaemic heart disease **†** Total coronary events include fatal and non-fatal CHD, unstable angina, fatal and non-fatal heart failure

Table 8.7 Hazard ratio (95%CI) associated with ASCOT 5.6 definition of the metabolic syndrome for coronary, stroke and death outcomes

	Primary outcome (Fatal CHD* plus NF MI)	Total coronary events†	Total stroke (Fatal and NF)	Cardiovascular mortality	All cause mortality
Model	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**
Model 1	1.13(0.99-1.29)	1.18(1.07-1.30)	1.02(0.88-1.17)	1.00(0.85-1.17)	1.00(0.91-1.10)
Model 2	1.21(1.06-1.38)	1.25(1.14-1.38)	1.12(0.97-1.29)	1.13(0.96-1.32)	1.14(1.03-1.26)
Model-3	1.00(0.82-1.23)	0.99(0.85-1.15)	1.38(1.10-1.72)	1.10(0.86-1.41)	1.25(1.07-1.45)

Model 1 = Univariate MS ; Model 2= Model 1 plus age, sex & ethnicity ; Model 3= Model 2 plus Fasting plasma glucose, triglyceride, HDLc, SBP & BMI . NF= Non-fatal ; F= Fatal ; CHD= Coronary heart disease

***** Fatal CHD: includes death from MI, acute coronary syndrome or sudden death attributable to ischaemic heart disease **†** Total coronary events include fatal and non-fatal CHD, unstable angina, fatal and non-fatal heart failure

Table 8.8 Hazard ratio (95%CI) associated with IDF definition of the metabolic syndrome for coronary, stroke and death outcomes

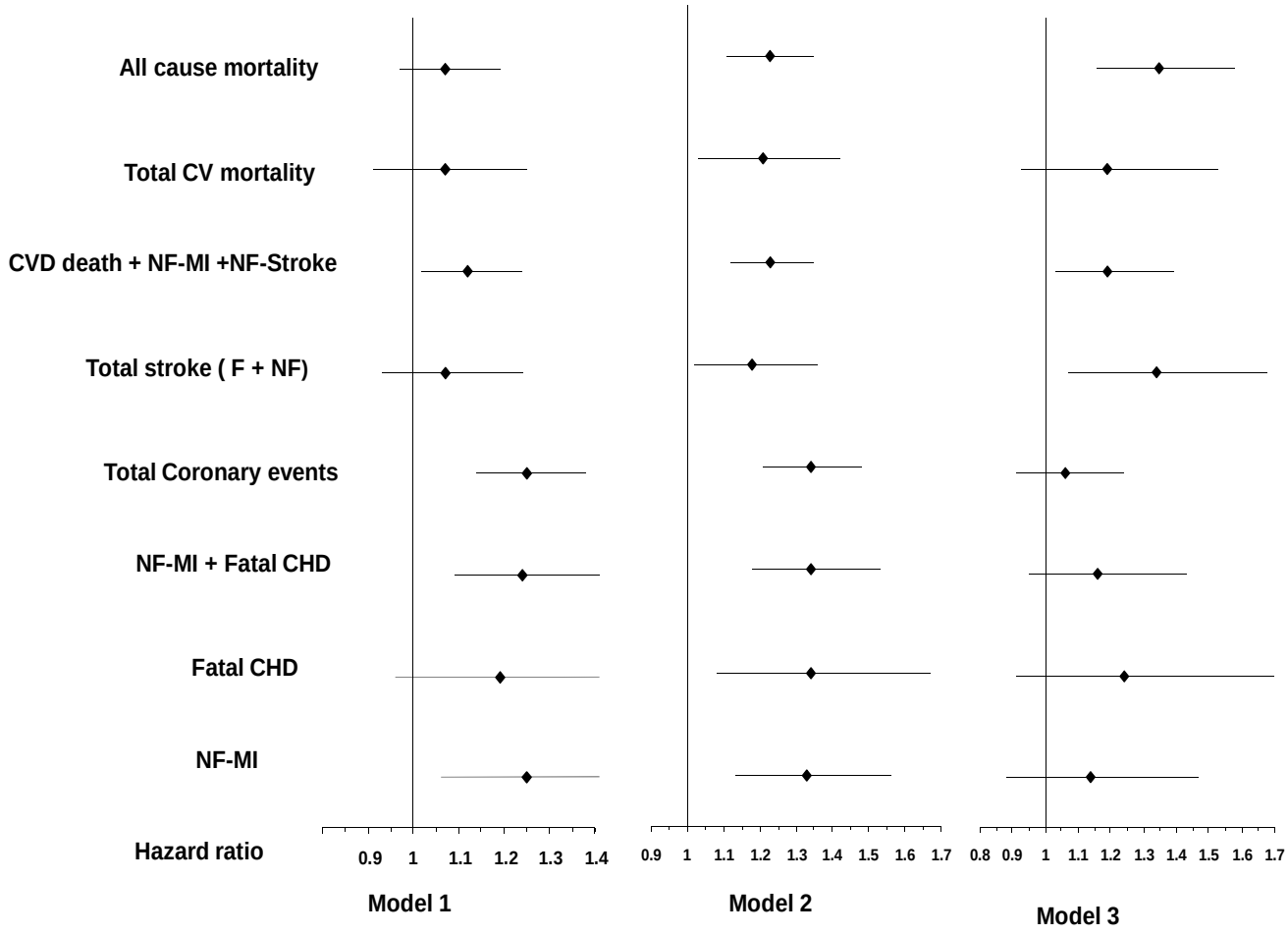
	Primary outcome (Fatal CHD* plus NF MI)	Total coronary events†	Total stroke (Fatal and NF)	Cardiovascular mortality	All cause mortality
Model	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**	**Hazard ratio (95%CI)**
Model 1	1.03(0.89-1.18)	1.07(0.96-1.19)	0.96(0.82-1.12)	1.02(0.86-1.22)	0.99(0.88-1.10)
Model 2	1.14(0.99-1.32)	1.18(1.05-1.31)	1.10(0.93-1.29)	1.23(1.03-1.47)	1.19(1.06-1.33)
Model-3	1.16(0.92-1.46)	1.03(0.87-1.22)	1.50(1.16-1.93)	1.35(1.03-1.78)	1.40(1.18-1.66)

Model 1 = Univariate MS ; Model 2= Model 1 plus age, sex & ethnicity ; Model 3= Model 2 plus Fasting plasma glucose, triglyceride, HDL-c, SBP & BMI . NF= Non-fatal; F= Fatal; CHD= Coronary heart disease

***** Fatal CHD: includes death from MI, acute coronary syndrome or sudden death attributable to ischaemic heart disease **†** Total coronary events include fatal and non-fatal CHD, unstable angina, fatal and non-fatal heart failure

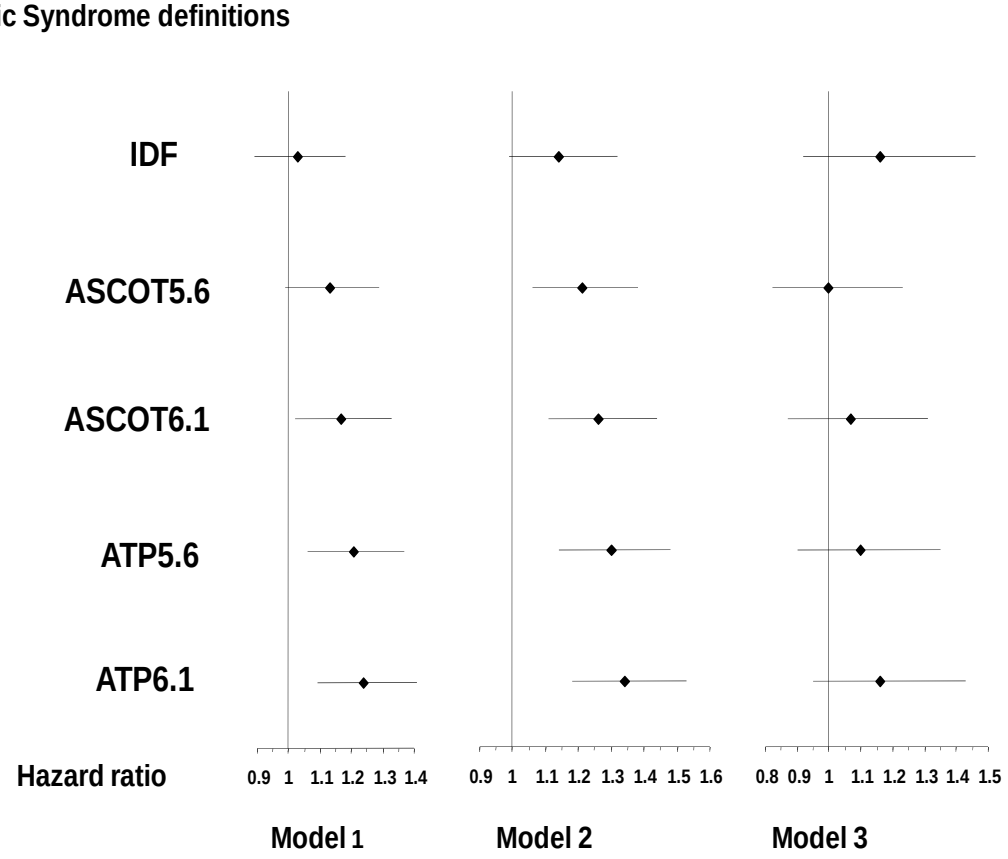
Chapter 8: Figures

Figure 8.1 Risk of coronary, stroke, and death outcomes associated with the metabolic syndrome, defined using ATP 6.1 definition.



Model 1 = Univariate MetS defined using ATP 6.1 ; Model 2= Model 1 plus age, sex & ethnicity ; Model 3= Model 2 plus Fasting plasma glucose, triglyceride, HDLc, SBP & BMI . NF= Non-fatal ; F= Fatal ; CHD= Coronary heart disease

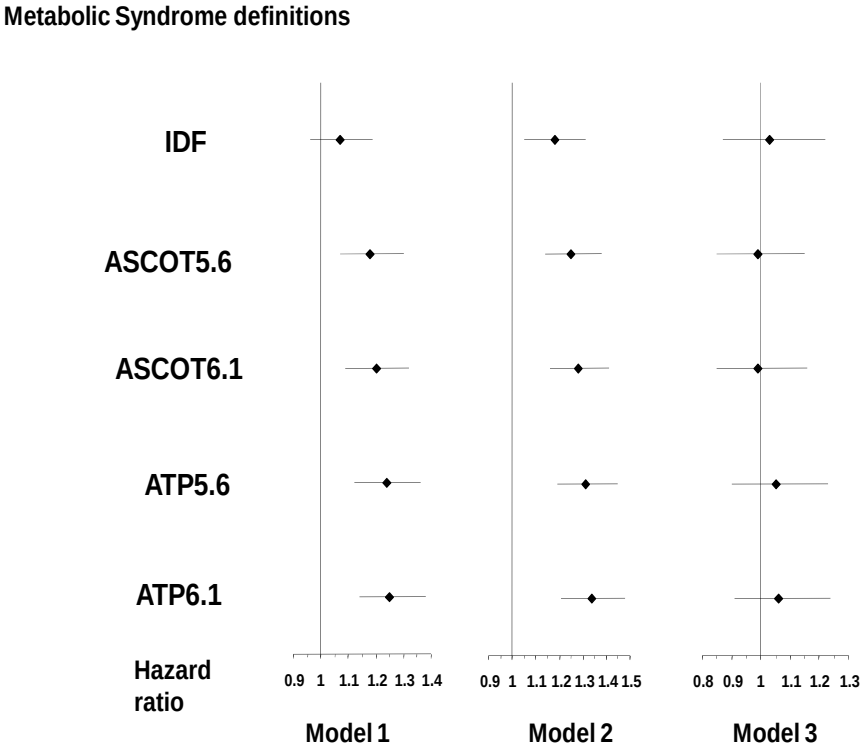
Figure 8.2 Risk of coronary heart disease and non-fatal myocardial infarction associated with the several definitions of the metabolic syndrome.



Model 1 = Univariate metabolic syndrome ; Model 2= Model 1 plus age, sex & ethnicity ; Model 3= Model2 plus Fasting plasma glucose, triglyceride, HDLc, SBP & BMI ; CHD: coronary heart disease; MI: myocardial infarction

*** Fatal CHD: includes death from MI, acute coronary syndrome or sudden death attributable to ischaemic heart disease**

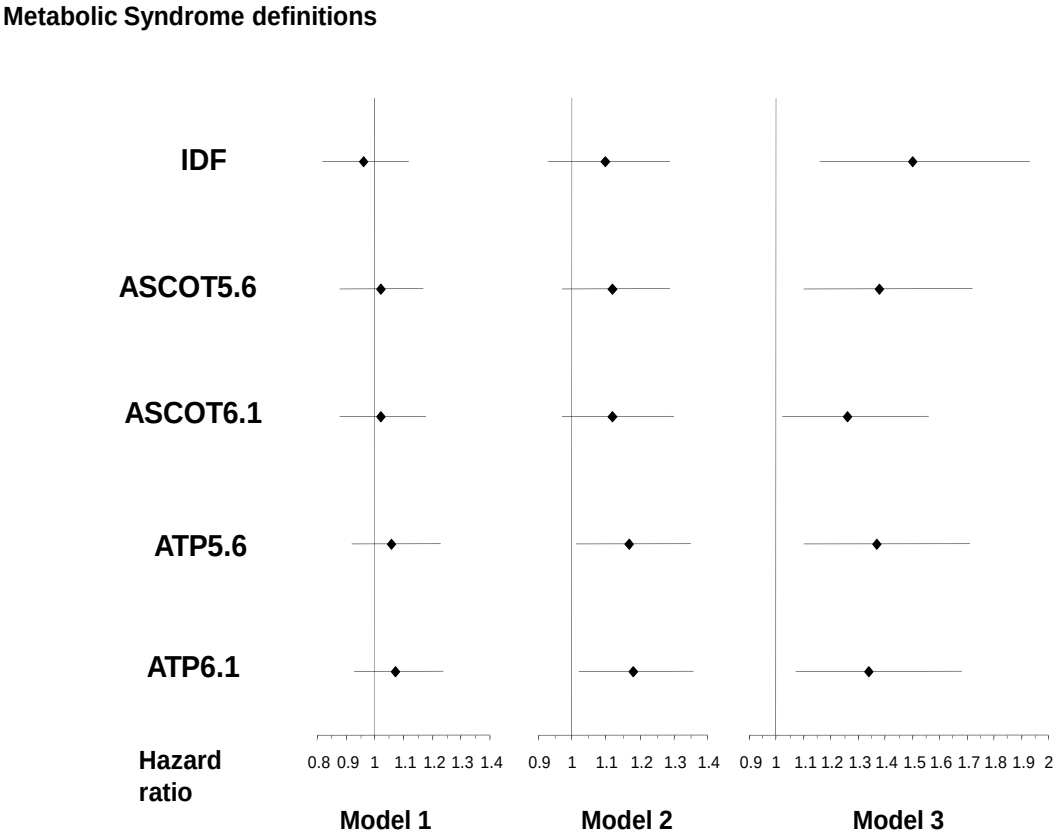
Figure 8.3: Risk of total coronary events† associated with the metabolic syndrome, using all the definitions.



Model 1 = Univariate metabolic syndrome ; Model 2= Model 1 plus age, sex & ethnicity ; Model 3= Model2 plus Fasting plasma glucose, triglyceride, HDLc, SBP & BMI .

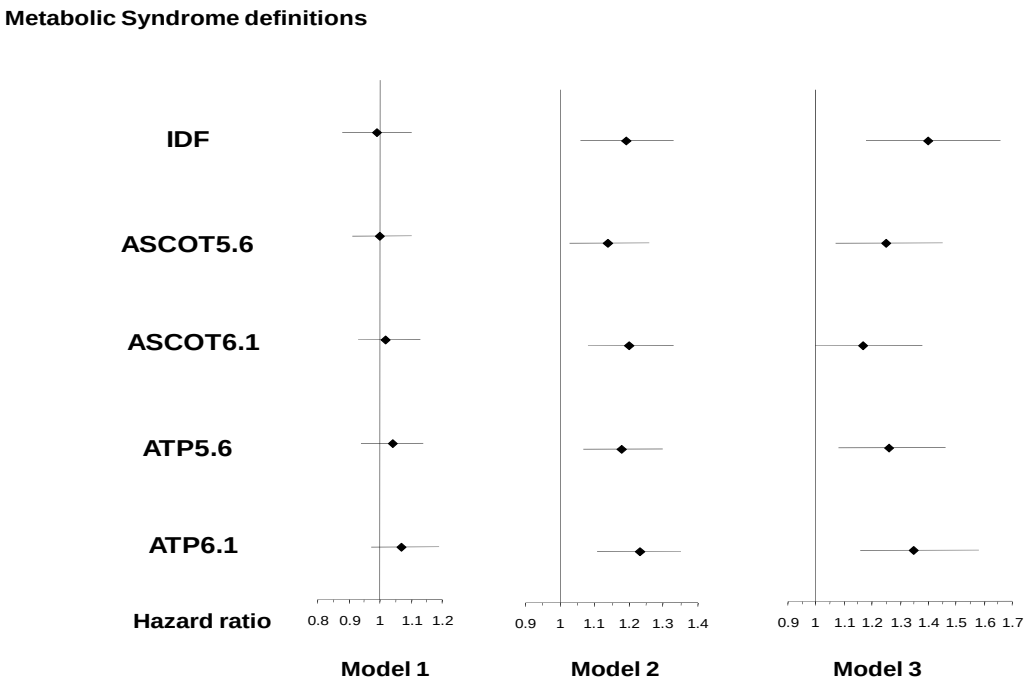
† Total coronary events include fatal and non-fatal CHD, unstable angina, fatal and non-fatal heart failure

Figure 8.4: Risk of fatal and non-fatal stroke associated with the metabolic syndrome



Model 1 = Univariate metabolic syndrome ; Model 2= Model 1 plus age, sex & ethnicity ; Model 3= Model2 plus fasting plasma glucose, triglyceride, HDL-c, SBP & BMI .

Figure 8.5: Risk of all-cause mortality associated with metabolic syndrome



Model 1=Univariate metabolic syndrome; Model 2= Model 1 plus age, sex, ethnicity; Model 3= Model 2 plus fasting plasma glucose, triglyceride, HDLc, SBP and BMI

Chapter 9

THE METABOLIC SYNDROME, AS A PREDICTOR OF INCIDENT DIABETES

Study 4: The Metabolic syndrome, Impaired Fasting Glucose and Obesity, as Predictors of Incident Diabetes in ASCOT-BPLA: Comparison of Their Relative Predictability.

9.1 Summary

The metabolic syndrome and type 2 diabetes share a common pathophysiological pathway, and are strongly correlated. Because of this, several definitions of the metabolic syndrome include the presence of diabetes as one of several components defining the syndrome. Studies have also shown that among those subjects without diabetes, the presence of the metabolic syndrome is associated with a significantly increased risk of new-onset diabetes. The individual components of the metabolic syndrome, such as impaired fasting glucose (IFG) (fasting plasma glucose [FPG] ≥ 5.6 mmol/L) and adiposity, are also independently and significantly related to new-onset diabetes. It is unclear whether the increased risk of new-onset diabetes associated with the metabolic syndrome is independent of its constituent components. This critical question needs further evaluation as it has important clinical implications.

In these analyses, the database of the blood pressure (BP) lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA), was used to evaluate whether the metabolic syndrome was a more accurate predictor of new-onset diabetes compared with IFG, obesity or the other constituent components of the metabolic syndrome alone, or collectively.

For the purpose of these analyses the metabolic syndrome was defined using the updated version of the third report of the National Cholesterol Education Programme (NCEP)-Adult Treatment Panel (ATP) criteria [updated NCEP-ATP], replacing the waist-circumference criterion with body mass index [BMI] >30 kg/m2 (because waist circumference was not recorded in ASCOT-BPLA). Several Cox models were developed to assess the risk of new-onset diabetes associated with the metabolic syndrome after adjusting for a priori

confounders (including age, sex, ethnicity, and concomitant use of non-cardiovascular medications), its individual components, and other determinants of new-onset diabetes. Area under the receiver-operating characteristics curves (aROC) using the metabolic syndrome and IFG models were compared. The ability of these models to correctly identify those who (after 5-years of follow-up) developed and did not develop diabetes was also compared.

In ASCOT-BPLA, among a sub-population of those without pre-existing diabetes, about two-fifths had the metabolic syndrome at baseline. The metabolic syndrome, adjusted for a priori confounders, and independent of its individual components was associated with a significantly increased risk of new-onset diabetes. On further adjustment for the influence of other independent determinants of new-onset diabetes (including treatment allocation, alcohol intake, total cholesterol), the findings remained unchanged, and statistically significant. On further analyses, the metabolic syndrome model was found to be a significantly better predictor of new-onset diabetes than the IFG model. The metabolic syndrome model correctly identified 62.3% of those who developed new-onset diabetes compared with 37.7% identified by the IFG model. The presence of both the metabolic syndrome and IFG were associated with a 9-fold increased risk of new-onset diabetes. Among normoglycaemic patients at baseline, the metabolic syndrome was associated with a significantly increased risk of new-onset diabetes, after adjusting for BMI and a priori confounders. Among those with obesity at baseline, the presence of the metabolic syndrome (compared with its absence) significantly increased the risk of new-onset diabetes, as it did among those without obesity.

In summary, the metabolic syndrome was a more accurate predictor of new-onset diabetes than IFG, particularly among those with normoglycaemia. Furthermore the metabolic syndrome remained a significant predictor of new-onset diabetes, independent of the

collective influence of its constituent components.

Study 4: The Metabolic Syndrome, Impaired Fasting Glucose and Obesity, as Predictors of Incident Diabetes in ASCOT-BPLA: Comparison of Their Relative Predictability.

9.2 Hypothesis

1. Compared with IFG status, the diagnosis of metabolic syndrome is a more accurate predictor of new-onset diabetes among hypertensive patients.

2. The risk of new-onset diabetes associated with the metabolic syndrome is independent of the collective influence of its constituent components.

9.3 Background

Given the rapidly escalating prevalence of diabetes, it is important that preventative strategies are initiated to stem the rising tide of the diabetes epidemic, particularly among high risk populations such as those with hypertension. Previous studies among high risk populations have shown that life-style modifications and/or pharmacological interventions can potentially reduce or delay the incidence of diabetes (106, 195-200). Indeed, several risk scores and clinical algorithms have been developed, specifically with the aim of identifying those individuals at highest risk of developing new-onset diabetes (281, 429, 430). By identifying high risk populations, the intention is to target limited resources in the most efficient way by initiating lifestyle modifications and, if needed, pharmacological measures early in those individuals who are most likely to develop diabetes. However, most of these risk scores are complex, require calculations or web-based support, and are not easily adaptable for use in a routine clinical setting. Moreover, some of these risk scores are designed for (or derived from) specific populations, and hence may not be applicable for use in other settings.

Given the difficulties associated with the use of existing risk scores, and their resultant poor uptake in clinical practice it is likely that only a risk construct that is simple, easy-to-use, efficient and suitable for a wide population settings, will be acceptable for use in routine clinical practice. The metabolic syndrome, defined as a clustering of cardio-metabolic risk factors including dyslipidaemia, dysglycaemia, hypertension and obesity (31-33), is one such concept that meets several of these requirements, and hence offers an attractive option. It is based on readily available measurements in routine clinical practice, and has been shown to be significantly associated with a 3- to 10-fold increased risk of new-onset diabetes, across several population settings (428, 429, 431-433). However, since its constituent components such as IFG and obesity also have significant and independent relationships with the development of diabetes, the clinical utility of the metabolic syndrome, independent of its constituent components, is uncertain.(35, 37, 434). Indeed, a few studies have supported the use of simpler risk constructs, such as IFG to predict the risk of new-onset diabetes (46, 435).

In the sections below, I will briefly review the evidence to date on following issues:

a. The usefulness of the metabolic syndrome and its individual components, as predictors of new-onset diabetes.

b. Whether the metabolic syndrome is a more accurate predictor of new-onset diabetes, compared with the use of simpler risk constructs, such as the determination of IFG status, or the presence of obesity.

c. Whether the metabolic syndrome predicts the risk of new-onset diabetes, beyond the sum of the risk of its individual components.

9.3.1 The metabolic syndrome, its individual components, and the risk of new-onset diabetes

Studies have clearly demonstrated that the metabolic syndrome, IFG, obesity and other constituent components of the syndrome are all independently and significantly associated with an increased risk of new-onset diabetes (428, 429, 431, 432, 434, 436).

9.3.1. A. The metabolic syndrome and the risk of new-onset diabetes.

The metabolic syndrome has been associated with a 3- to 10-fold increased risk of new-onset diabetes in previous reports (394, 427, 428, 431-433, 437-440). In these studies, the reported wide range in the strength of association (i.e. hazard ratio's [HR], odds ratio or relative risks) is likely to be due to differences in the population settings, and the definition of the metabolic syndrome used in these evaluations. For example, in the West of Scotland Coronary Prevention Study (WOSCOPS) (427), among 5,974 hypercholesterolemic men, mean age 55 years, with no previous history of coronary heart disease, the unadjusted metabolic syndrome (defined using the NCEP-ATP definition, but replacing waist circumference criterion with BMI) was associated with a 3.5-fold [95% confidence interval (CI), 2.42 to 4.98] increased risk of new-onset diabetes. In contrast, in the community-based Framingham Offspring Study (FOS) (436), among 2,902 men and women, mean age 53 years, the metabolic syndrome (relative to those without metabolic syndrome) was associated with a 7-fold [4.6 to 10.8] increased risk of new-onset diabetes, even after adjusting for the influence of age, sex, family history and IGT. Indeed, when this analysis was restricted to those with obesity (BMI >30 kg/m^2) (n=638), the metabolic syndrome (compared with those without) was associated with a10-fold [5.4 to 19.5] greater risk of developing new-onset diabetes (436).

Several other studies have reported the association between different definitions of the

metabolic syndrome and new-onset diabetes, among those from non-white ethnic groups (412, 441-443) . In the San Antonio Heart Study (SAHS), among 1,734 Mexican Americans and non-Hispanic white participants, aged 25 to 68 years, 11.3% (n=195) developed diabetes during 7 to 8 years of follow-up. The metabolic syndrome, defined using the NCEP-ATP definition, was associated with a three-fold [2.27 to 4.80] increased risk of new-onset diabetes, after adjustments for age, sex, ethnicity, family history of diabetes, impaired glucose tolerance (IGT) and fasting insulin levels (440). On comparing the area under ROC curves relating to the metabolic syndrome defined using the NCEP-ATP (407) and the World Health Organisation (WHO) definition (169), the NCEP-ATP definition of the metabolic syndrome performed better in predicting the risk of new-onset diabetes. In another study, among 541 Chinese subjects (442), the metabolic syndrome was compared using 5 definitions: the updated NCEP-ATP, WHO, European Group for Study of Insulin resistance (EGIR) (171), American Association of Clinical Endocrinologist (AACE) (173) and International Diabetes Federation (IDF). The findings suggested that regardless of the definition used, the metabolic syndrome was significantly associated with an increased risk of new-onset diabetes, after adjusting for age, sex, education, family history of diabetes and total cholesterol. However, there were some minor differences in the effect size associated with these 5 different definitions of the metabolic syndrome.

In summary, the metabolic syndrome is consistently and significantly associated with an increased risk of new-onset diabetes. However, the magnitude of the effect size (HRs, odds ratio and relative risks) differs in these studies because of the population characteristics and the definition of the metabolic syndrome. The relationship remains significant after accounting for the influence of common confounding variables (including age, sex, and family history of diabetes), and other determinants of diabetes. These findings are echoed in

the results of a recent meta-analysis, comprising 16 cohort studies (433). In that meta-analysis, the metabolic syndrome was found to be uniformly associated with a 4- to 5-fold increased risk of new-onset diabetes, regardless of the definition used.

9.3.1. b Components of the metabolic syndrome and the risk of new-onset diabetes. Studies have also evaluated the relationship between the components of the metabolic syndrome and new-onset diabetes (394, 427, 431, 433). Their findings suggest that each constituent component of the metabolic syndrome has a significant (and independent) association with new-onset diabetes, and that the risk of new-onset diabetes increases linearly with the increase in the number of its components (427, 428, 433, 439, 444).

Metabolic components, the metabolic syndrome and the risk of new-onset diabetes: A few studies have investigated the risk of new-onset diabetes associated with the individual components of the metabolic syndrome, in conjunction with similar evaluations for the metabolic syndrome as a whole (431, 445, 446). In a recent study (431), using the database of 2 cohorts, the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) (n=4,812) and the British Regional Heart Study (BRHS) (n=2,737), the metabolic syndrome and its 5 constituent components were all significantly and independently related to an increased risk of new-onset diabetes. The findings suggest that among the 5 components of the metabolic syndrome, the risk of new-onset diabetes was highest among those with a fasting glucose ≥ 6.1 mmol/l (PROSPER 18.4 [13.9 to 24.5]; BRHS 6.0 [4.1 to 8.8]). Each of the remaining 4 components of the metabolic syndrome was associated with a 2- to 3-fold increase in the risk of new-onset diabetes. In comparison, the corresponding risk of new-onset diabetes associated with the metabolic syndrome was 4.4 [3.3 to 5.8] and 7.5 [4.9 to 11.5]) in the PROSPER and the BRHS respectively (431). In a prospective, community-based study (the

Italian Longitudinal Study in Ageing [ILSA]), including 2,295 subjects aged 65-84 years, among all individual components of the metabolic syndrome, the presence of obesity (BMI >30 kg/m^2) was found to be the strongest predictor of new-onset diabetes (446).

In a post–hoc analysis of the FOS and SAHS studies, among the 5 individual components of the metabolic syndrome, only IFG, waist circumference and increased serum triglyceride levels were found to be significantly associated with the risk of IGT— a surrogate marker for the risk of new-onset diabetes (447). In another study, among 1,918 Pima Indians, insulinaemia (denoting impaired glucose metabolism), increased body size (or similar metrics of obesity) and presence of dyslipidaemia were the three most important components, that accounted for the bulk of the risk of new-onset diabetes associated with the metabolic syndrome (445).

In addition to the reports mentioned above, several other studies in different population settings have established a significant and independent association between each individual component of the metabolic syndrome and the risk of new-onset diabetes (226, 279, 280, 439, 448-450). Some additional information relating to the association between FPG, BMI and the risk of new-onset diabetes is also discussed in sections 6.7.1 and 6.7.2, respectively,

Numbers of metabolic components and the risk of new-onset diabetes: In WOSCOPS, there was a progressive increase in the risk of new-onset diabetes, with each increase in the number of metabolic components at baseline. Compared with those with no components at baseline, those with ≥ 4 metabolic components were at a 24-fold [7.5 to 79.6] increased risk of developing diabetes (427). The findings of a meta-analysis of 16 cohort studies (including WOSCOPS) suggested that those with four or more metabolic components had a 10.9- to

24.4-fold increased risk of new-onset diabetes compared with those with no components at baseline (433).

In summary, each constituent component of the metabolic syndrome is significantly associated with an increased risk of new-onset diabetes. Of them, FPG, BMI and serum triglyceride appear to be more strongly related to the risk of diabetes, as compared with the other 2 components (hypertension and HDL-C). Each increase in the number of constituent components is linearly associated with an increasing risk of new-onset diabetes.

9.3.2 Comparison of the predictive ability of the metabolic syndrome, its individual components and other risk constructs.

A few studies have compared the accuracy of the metabolic syndrome in predicting new-onset diabetes with impaired glycaemia, particularly IFG (46, 435). In addition, several studies have compared the accuracy of the metabolic syndrome in predicting new-onset diabetes, with that of other available risk scores or clinical algorithms (281, 451). The findings of these reports are equivocal, with a few studies suggesting that the risk stratification by the metabolic syndrome was no better than that of IFG alone, or the use of other risk constructs, such as the Diabetes Prediction Model (46).

9.3.2.a. Discriminative ability of the metabolic syndrome and IFG (or IGT), as predictors of new-onset diabetes:

<u>Evidence base for IFG and/or IGT being a more accurate predictor of new-onset diabetes than the metabolic syndrome</u>

In the Australian Diabetes Obesity and Lifestyle (AusDiab) study, the ability of the metabolic syndrome and individual glucose measurements to predict new-onset diabetes was

compared among 5,842 men and women (age ≥25 years) (46). In this analysis, comparing the ROC curves, the metabolic syndrome was found to be a no better predictor of new-onset diabetes than the measurement of blood glucose alone, or the use of a diabetes prediction model. In another study, the clinical usefulness of the metabolic syndrome in identifying those at risk of developing diabetes was compared with that of random plasma glucose ≥ 7 mmol/l (435). The findings suggested that the area under ROC curves was higher among those with a random plasma glucose ≥ 7 mmol/l compared with those with normoglycaemia and the metabolic syndrome. However, in this analysis, compared with random plasma glucose measurements alone, those with the metabolic syndrome and increased FPG had a higher area under the ROC curves (435). This suggests that patients with impaired glycaemia are likely to be at greater risk of diabetes, compared with those with normoglycaemia and the metabolic syndrome. In a few other studies, the predictive ability of the metabolic syndrome was found to be no better than that of IFG alone (394, 431), or that of IGT alone (452). Ford et al, in 2008, in their systematic analyses of the current evidence, reported that there exists "a limited evidence that suggests fasting glucose alone may have comparable diabetes prediction to that with the metabolic syndrome" (433). However, they also reported that the evidence base for this statement is relatively small, and the findings from the majority of the included studies were equivocal.

Evidence base for the metabolic syndrome being superior to IFG or IGT

In contrast to the findings described above, a few studies have reported that the metabolic syndrome predicts new-onset diabetes more accurately than IFG or glucose intolerance alone (378, 453). Lorenzo et al, in 2007, evaluated the risk of new-onset diabetes associated with the metabolic syndrome and 2-hour glucose values, among 2,559 participants of the SAHS study. The findings suggested that the metabolic syndrome provided additional predictive and

discriminative ability, beyond that provided by IGT alone. Similarly, in the Hisayama study, among 1,935 subjects followed for a mean duration of 11.8 years, the metabolic syndrome was found to be significantly associated with an increased risk of new-onset diabetes, independent of the influence of IFG (453). On further analyses, among those with and without IFG at baseline, the risk of new-onset diabetes associated with the metabolic syndrome was 2.98 [1.62 to 5.47]) and 3.71 [1.72 to 8.02], respectively (453).This finding indicates that the excess risk of new-onset diabetes associated with the metabolic syndrome remains significant, and with a similar magnitude, regardless of the baseline glycaemic status of an individual. Similar findings were observed in several other studies, suggesting that the diagnosis of the metabolic syndrome predicts the risk of new-onset diabetes, more accurately and efficiently, compared with IFG or glucose intolerance alone (439).

Critical appraisal of the evidence to date: In my opinion, the conflicting findings in the current literature arise for three reasons. Firstly, studies differ in the emphasis they place on the strength of association between risk predictors (e.g. the metabolic syndrome or FPG) and new-onset diabetes. For example, Sattar et al (431) in their study of two cohorts, found that the effect size associated with the metabolic syndrome was smaller than FPG. This finding was interpreted as indicative of a lesser predictive ability of the metabolic syndrome compared with FPG. However this approach of solely comparing the strength of association (effect size), to comment upon the discriminative (or predictive) ability of a marker is inadequate, as described by Pepe et al (454). I believe that a more robust approach would be to use a combination of tests (and measures) of discrimination, such as the integrated discrimination index, net reclassification index, area under ROC curves, and goodness of fit measures, such as Bayesian information criterion (BIC) (215, 218, 225, 455-457). Secondly, the overlap between those identified using the metabolic syndrome and those identified using

a measure of pre-diabetes (IFG or IGT) is often ignored. (458, 459). Therefore, in the studies where only the associated risks are compared, the findings may favour IFG simply because it is an intermediate step in the natural history of the development of diabetes. Thirdly, studies have shown that those with IFG or IGT may also have other metabolic components (460). This implies that when superficially comparing the predictive ability of those with IFG (or IGT) and the metabolic syndrome, the differences may be attenuated, which may explain the comparable predictive ability reported in some analyses. Taken together, this may partly explain the conflicting findings in the studies to date. In addition to these methodological and analytical issues, I believe some of the observed differences in the findings of the current studies may have been driven by differences in the populations evaluated.

However, given the overlap in those identified by the metabolic syndrome and IFG, it may be simpler to use IFG as a predictor of new-onset diabetes in routine clinical practice. Unfortunately, this argument ignores the fact that the populations identified by the use of IFG and the metabolic syndrome, despite some overlap, are not identical (459, 461). Indeed, by definition the IFG group is more restrictive, whereas, the metabolic syndrome, as a discriminative tool, appears to be applicable to a wider population setting.

9.3.2.b Discriminative ability of the metabolic syndrome and other risk constructs, as predictors of new-onset diabetes:

A few studies have compared the discriminative ability of the metabolic syndrome with commonly used diabetes risk scores (46, 281, 429, 432, 437, 445, 451).

In a post-hoc analysis, using data from the SAHS and the Mexico City Diabetes Study (MCDS), the metabolic syndrome was found to be inferior to the diabetes risk score, in predicting the risk of diabetes (451). In contrast, in a post-hoc analysis of the BRHS,

compared with the Framingham risk score, the metabolic syndrome was found to be a superior predictor of new-onset diabetes (432). Schmidt et al, in 2005, using data from the Atherosclerosis Risk in Communities (ARIC) study, reported that the metabolic syndrome has a comparable predictive ability to that of 'rules' derived from clinical information and laboratory measures (281). Indeed, the authors favoured the use of the metabolic syndrome as a predictor, given the simplicity of its use in comparison with the complex clinical algorithms evaluated in that analysis. The findings of these three studies clearly exemplify the uncertainty related to these comparisons. It is possible, besides the differences in the populations studied, and the methods used, the inconsistent results could also be due to use of different definitions of the metabolic syndrome. For example, in a prospective study, conducted in Mauritius, among 3,198 at risk subjects the metabolic syndrome, defined using the WHO definition, was found to be a better predictor of new-onset diabetes than the diabetes prediction model, with a greater area under the ROC curve. However, the diabetes prediction model was found to be a better predictor of new-onset diabetes when the metabolic syndrome was defined using the NCEP-ATP or IDF definition (437).

In summary, the evidence from these studies points to the metabolic syndrome being a preferable risk construct compared with the complex clinical 'rules' and algorithm given the comparable predictive ability of these two methods in the majority of the studies and inconsistent findings in the others. It is also important to note that, to date, all of these comparisons have used area-under ROC curves to discriminate between those who are more and less likely to develop diabetes (215). This approach has its own limitations, and may be inefficient as compared with the newer (and perhaps more efficient) statistical approaches such as net classification index and integrated discrimination index (218, 455, 457, 462). It is possible, that the use of these newer and efficient discriminative approaches may prove to be

helpful in clarifying these issues further.

9.3.3 The metabolic syndrome and new-onset diabetes: Is the whole greater than the sum of its parts?

A small number of studies have reported on the association between the metabolic syndrome and new-onset diabetes after accounting for the cumulative influence of its constituent components (46, 378, 427, 439, 443). The findings of these studies have been conflicting.

In the WOSCOPS post-hoc analyses (427), unadjusted metabolic syndrome was associated with a 3-fold increased risk of new-onset diabetes. However, on multivariate analyses, including all the individual components, the relationship between the metabolic syndrome and new-onset diabetes attenuated, and became statistically insignificant. Boyko et al in a prospective study, involving 2,605 residents of Mauritius, found that the metabolic syndrome, after adjusting for age, sex, ethnicity and family history of diabetes, was significantly associated with an increased risk of new-onset diabetes. However, the increased risk conferred by the metabolic syndrome was no higher than that expected from the combined risk of its constituent components (443). Consistent with these findings, Cameron at el in the analyses of the AusDiab study, found that the metabolic syndrome did not confer an increased risk of new-onset diabetes, independent of its constituent components, except when using the EGIR definition of the metabolic syndrome (46).

In contrast, in a recent study of 606 aboriginal participants, followed for 10 years, the metabolic syndrome was found to be a more accurate predictor of new-onset diabetes compared with the combined effect of its constituent components (439). In the SAHS, Lorenzo et al found that the metabolic syndrome predicted the risk of new-onset diabetes,

after adjusting for fasting glucose, IGT, and other potential confounders (378). Similar to these findings, Mukai et al in their evaluations of the Hisayama cohort suggested additional importance of the metabolic syndrome in predicting the risk of new-onset diabetes, beyond that of IFG and other potential confounders including family history of diabetes (453). However, despite these suggestive findings, to date no study has unequivocally demonstrated any additional benefits of the metabolic syndrome, in predicting the risk of new-onset diabetes, beyond the sum of its individual components. However, a few studies have shown additional benefits of the diagnosis of the metabolic syndrome, in relation to cardiovascular outcomes (42, 44, 45, 394, 405).

9.3.4 Summary and way forward:

The findings to date suggest that the metabolic syndrome, IFG, obesity and the other components of the metabolic syndrome are all independently and significantly related to an increased risk of new-onset diabetes. However, it is as yet unclear whether the diagnosis of the metabolic syndrome, adds to the risk prediction of type 2 diabetes, beyond the risk predicted by the combination of its individual components, particularly IFG and obesity. Given the rapidly increasing prevalence of diabetes, fuelled by the current obesity epidemic, it is extremely important that the relative importance of risk prediction tools such as IFG (or pre-diabetes), obesity and the metabolic syndrome are evaluated among high-risk populations such as hypertensive patients. Moreover, it is important to ascertain whether the diagnosis of the metabolic syndrome adds value beyond that contributed by the sum of its individual components. In addition it is important to determine the proportion of individuals correctly assigned to the respective risk categories, because this may enable cost-effective targeting of strategies designed to prevent new-onset diabetes.

The database of the blood pressure-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA) (47) provides an excellent opportunity to evaluate these questions among a cohort of hypertensive patients

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9.4 Objectives

1. To determine among hypertensive patients, whether the metabolic syndrome is a more accurate predictor of new-onset diabetes compared with IFG alone.

2. To determine whether the risk of new-onset diabetes associated with the metabolic syndrome is greater than the sum of the risk contributed by its constituent components.

3. To determine the role of metabolic syndrome to predict new-onset diabetes, among normoglycaemic hypertensive patients.

9.5 Materials and Methods

The details of the study design, methods used and the main results of the ASCOT-BPLA trial are described in chapter 4, and have been previously published (47, 48). However, a brief summary of a few details relevant to this study are given below:

9.5.1 Study participants

In ASCOT-BPLA, hypertensive patients were recruited, who were aged between 40 and79 years, arising mainly from family practices in Nordic countries and UK/Ireland, and who had at least three additional cardiovascular risk factors, but, without any active or previous coronary heart disease; and no evidence of heart failure, uncontrolled arrhythmias, haematological or biochemical abnormalities consistent with haematological malignancy or the end-organ damage (such as renal or liver failure), and serum triglyceride levels (fasting) < 4.5 mmol/L (48).

9.5.2 Study population

Of 19,257 randomised patients in the ASCOT-BPLA, all those with pre-existing diabetes (self-reported and receiving drug or dietary therapy) or those who were 'deemed' likely to have diabetes at baseline (based on a single recording of FPG ≥ 7.0 mmol/l or random glucose ≥ 11.1 mmol/l or presence of a combination of FPG≥ 6.1 mmol/l and glycosuria at the randomisation or screening visit) (n=5,137) were excluded to leave a study population of those hypertensive patients 'at risk' of developing diabetes (n=14,120).

9.5.3 Procedures

After an initial run-in period, all eligible patients attended a randomisation visit after an overnight fast, when a detailed clinical examination, medical history, laboratory tests and an

ECG recording were carried out. Eligible subjects were then randomly allocated to receive one of two antihypertensive regimens: atenolol adding a thiazide diuretic as required (atenolol-based regimen) or amlodipine adding perindopril as required (amlodipine-based regimen). Subsequently, fasting blood investigations were routinely carried out at 6 months, 12 months, and thereafter annual visits. At each visit, data were also collected on adverse events and any pre-specified outcome.

9.5.4 Exposure definition

Metabolic syndrome: For the purposes of these analyses, the updated version of the NCEP-ATP-III (33) definition of the metabolic syndrome was used [ATP5.6]; however, the waist circumference criterion was replaced with BMI >30 Kg/m^2, as waist circumference was not measured in ASCOT-BPLA.

Therefore, metabolic syndrome, in these analyses, was considered to be present if any three of the following risk factors were present at baseline.

I. Systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mm Hg or on antihypertensive therapy. Since the presence of hypertension was a necessary inclusion criterion of ASCOT-BPLA every randomised patient had this risk factor.
II. Fasting serum triglyceride ≥ 1.7 mmol/l.
III. HDL-cholesterol ≤ 1.03 mmol/l for males, and ≤ 1.29 mmol/l for females
IV. BMI >30 kg/m2
V. FPG ≥ 5.6 mmol/L.

9.5.5 Outcome

The development of new-onset diabetes was the outcome for these analyses. New-onset diabetes was defined on the basis of the 1999 WHO criteria (169) (i.e. FPG ≥7 mmol/L and/or 2 hour post 75g glucose load [or random glucose] ≥11.1 mmol/l). Since, new-onset diabetes was also a pre-specified tertiary outcome of the ASCOT-BPLA each outcome was adjudicated independently by the members of the ASCOT end-point committee.

9.5.6 Statistical Methods: STATA 10 software was used for all statistical analyses.

Missing values: Only fasting values for plasma glucose and triglyceride were used in these analyses. Approximately 10% (n=1,428) of subjects had non-fasting values of either triglyceride (n=1,392) or glucose (n=1,427) at baseline. These individuals were excluded from the multivariable models where one (or both) of these variables were among the covariates (n=12,692). Patients with missing (or non-fasting) values were nonetheless considered for the allocation of the metabolic status at baseline, based on the available values of other metabolic components.

Analysis population: 14,120 'at risk' hypertensive patients were included in these analyses. Of these 12,692 individuals had no missing values for any metabolic components and were considered for the survival analyses and multivariable Cox models.

Descriptive analyses: All patients at baseline were assigned to a metabolic status (metabolic syndrome or not), based on the updated ATP 5.6 definition. Baseline characteristics of those who subsequently developed diabetes were compared with those who did not develop diabetes. Distribution of the constituent metabolic components at baseline, among those who

did and did not develop diabetes was also evaluated. Similar analyses were done, among those with IFG at baseline. Venn diagrams were developed among those with and without diabetes, to evaluate the distribution and overlap of the constituent metabolic components in the two groups.

Primary analyses: Event rates (per 1000 person years) for new-onset diabetes were determined, according to the baseline metabolic status. Kaplan Meirer curves and Nelson-Aalen cumulative hazard plots according to metabolic status were also examined

Cox models: A Cox regression model (206) was developed to assess the risk of developing new-onset diabetes associated with the metabolic syndrome, after adjusting for a priori confounders, including age, sex, race and concomitant use of non-CV medications (a marker for the presence of non-CV chronic disease) (Model-1). The relative influence of each component of the metabolic syndrome on the risk (HRs) associated with the metabolic syndrome was assessed by entering them separately into Model-1, and hence creating five new models. Harrell's C-statistics, likelihood-ratio chi-square (LR-chi)-statistic and Bayesian information criterion (BIC) were calculated to compare the influence of each metabolic component in these new models, and thereafter, these individual metabolic components were progressively added (in descending order of relative importance) to Model-1 to finally develop a model adjusting for a priori confounders and all individual components of the metabolic syndrome (Model-2). In Model-3, Model-2 was further adjusted for the influence of other determinants of new-onset diabetes (including treatment allocation, alcohol intake, and total cholesterol) (see chapter 6). All components were used as continuous variables, except when found to be non-linear. Proportional hazard assumptions were checked for all models (207, 208).

Model discrimination: The area under the ROC curves (215) obtained from the models, using IFG (defined as FPG <5.6 mmol/l) or the metabolic syndrome, were compared after adjusting for the influence of a priori confounders (Model 1). The ability of the two models to correctly identify those who after 5-years of follow-up did and did not develop diabetes was also assessed using a modification of integrated discrimination improvement (IDI).(455) Accordingly, 5-year-risks (probabilities) of developing diabetes predicted by each of the two models were assigned to an individual, and their respective risk difference (5-year- risk assigned by the IFG model minus that assigned by the metabolic syndrome model) was calculated. The calculated risk differences of subjects were further stratified by their respective observed 5-year outcome status (developed diabetes or not). If the observed status was development of diabetes, the model which assigned a higher predicted risk was deemed to be better (i.e. the predicted risk was closer to the observed outcome), whereas, for a subject with non-diabetic status (after 5-years), the model assigning a lower baseline risk was deemed to be better at predicting the risk of new-onset diabetes. Similar analyses were also done stratified by glycaemic status (normoglycaemic or IFG) at baseline.

Results

At baseline 5,445 of 14,120 'at-risk' patients (38.6%) had the metabolic syndrome. Of these, 16.8% (898) developed new-onset diabetes (incidence rate: 33.3 [31.1 to 35.5] per 1,000 person years) during a median follow-up of 5.5 years (interquartile range: 5.0 to 6.0 years; total follow-up duration of 73,425 person years) as compared with 5.4% (468) of those without metabolic syndrome at baseline (10.1 [9.2-11.0] per 1,000 person years) (Figure 9.1).

9.6.1. Baseline characteristics

Exposure: metabolic syndrome: By definition, those with the metabolic syndrome had a higher mean BMI, serum triglyceride and FPG, and lower mean HDL-cholesterol. However, on comparing other (associated) baseline characteristics among those with and without the metabolic syndrome, there were some apparent differences. Those with the metabolic syndrome (compared with those without) included a greater proportion of non-smokers, women and those with a previous history of using antihypertensive or lipid-lowering therapy. The metabolic syndrome group also had a lower mean age, systolic and diastolic pressures, and alcohol intakes, compared with those without the metabolic syndrome (data not shown, but summary statistics are similar to that reported in table 8.2).

Outcome: new-onset diabetes: Table 9.1 describes the baseline characteristics among those who did and did not develop diabetes during follow-up. Compared with those who did not develop diabetes, those who did were more likely to be male and younger, and have a higher baseline BMI, serum triglyceride, FPG, and systolic and diastolic BPs, and a lower mean HDL-cholesterol. Those who developed diabetes (compared with those who did not) were also more likely to be randomised to the atenolol-based regimen, have the metabolic

syndrome at baseline, and be receiving concomitant non-cardiovascular medications (Table 9.1).

9.6.2 Distribution of the components of metabolic syndrome, among those with and without diabetes.

Figure 9.2 and Table 9.2 describe the distribution and overlap of the metabolic components among those who did and did not develop diabetes. Among 12,692 individuals in the analysis population 6% and 29% of those who did and did not develop diabetes, respectively, had no other metabolic components at baseline (with the exception of the presence of the hypertension – a pre-requisite for all ASCOT-BPLA patients). Figure 9.2 shows that a significantly higher proportion of those who developed diabetes, compared with those who did not, had IFG as one of the 3 components required for defining the metabolic syndrome (73% versus 32%, respectively). Those who developed diabetes were also more likely to have three or more metabolic components at baseline, as compared with those who did not (Table 9.2).

9.6.3 The metabolic syndrome, its individual components and the risk of new-onset diabetes.

Figure 9.3 shows that the unadjusted metabolic syndrome was associated with a 3.7-fold [3.2 to 4.2] increased risk of new-onset diabetes. The risk of new-onset diabetes increased steadily with an increasing number of metabolic components at baseline, with nearly a 12-fold [9.2 to 15] increased risk of developing diabetes among those with all 5 components, compared with those with only 1 component (hypertension) at baseline (Figure9.4).

In Model-1, the risk of new-onset diabetes associated with the metabolic syndrome, adjusted for a priori confounders, remained the same (HR 3.63 [3.20 to 4.11]). However, inclusion of FPG in Model-1 approximately halved the risk of new-onset diabetes associated with the metabolic syndrome (1.87 [1.63 to 2.13]) (Table 9.3). In contrast, the inclusion of triglyceride or HDL-cholesterol or systolic BP in Model-1 had essentially no impact on the risk of new-onset diabetes associated with the metabolic syndrome. Inclusion of BMI to Model-1 reduced the risk of new-onset diabetes associated with the metabolic syndrome to 2.92 [2.13 to 2.72]. When Model-1 was adjusted for both FPG and BMI, the risk of new-onset diabetes associated with the metabolic syndrome was 1.45 [1.25 to 1.68]. In Model-2 (adjusting for a priori confounders and all individual components of the metabolic syndrome), the risk of new-onset diabetes associated with the metabolic syndrome was reduced further but remained significant (1.19 [1.00 to 1.40]). In Model-3, when other independent determinants of new-onset diabetes were added to Model-2, the risk of new-onset diabetes associated with the metabolic syndrome was essentially unchanged (1.22 [1.03 to 1.44]) (Table 9.3). Based on the change in effect size (HRs) and indices of model discrimination and performance (assessed by C-statistics, LR-chi-statistic, and BIC), FPG was the most influential individual component of the metabolic syndrome contributing to the risk of new-onset diabetes. Thereafter, BMI, systolic BP, raised serum triglyceride, and low HDL-cholesterol were decreasingly influential.

9.6.4 Relative impact of Impaired Fasting Glucose and the Metabolic Syndrome on prediction of the risk of new-onset diabetes

Among those with IFG at baseline (n=4,569), two-thirds (62%) had at least one other associated metabolic component (Table 9.4), 51% had increased serum triglyceride levels (≥1.7 mmol/l) and 35% were obese (BMI ≥ 30 kg/m^2) (Figure 9.5). In total, nearly, 20%

(n=889) of those with IFG at baseline developed diabetes during a median follow-up of 5.5 years (Tables 9.4 and 9.5). Among those who developed diabetes, about 80% had 3 or more metabolic components (i.e. the metabolic syndrome by definition). A significantly larger proportion of those with both the metabolic syndrome and IFG at baseline (22.8%) developed diabetes, compared with those with only IFG at baseline (i.e. two metabolic components including hypertension) (12.4%) ($p<0.001$) (Table 9.5).

9.6.4. a. Observed and predicted risk of diabetes associated with IFG and the metabolic syndrome:

Overall, those with IFG at baseline, compared with those without, were at a 5-fold [4.7 to 6.2] greater risk of developing new-onset diabetes. However, among these individuals, the presence of the metabolic syndrome, compared with its absence, was associated with a near doubling of the incidence rate of new-onset diabetes (risk ratio 1.94 [1.65 to 2.29]). The incidence rates of new-onset diabetes among IFG patients with and without associated metabolic syndrome were 14.7 per 1000 person years and 7.3 per 1000 person years, respectively. Figure 9.6 shows the predicted and observed 5-year risk of new-onset diabetes, stratified by the presence of IFG and the metabolic syndrome. The presence of the metabolic syndrome, regardless of an individual's glycaemic status (i.e. IFG or normoglycaemia), was associated with a 2-fold increase in the risk of developing diabetes. There was a 9-fold [7.47 to 10.45] increase in the risk of new-onset diabetes among those with both the metabolic syndrome and IFG, compared with the absence of both these markers. There was no significant interaction between IFG and the metabolic syndrome ($p=0.11$), and no significant differences between predicted and observed 5-year-risks of new-onset diabetes.

9.6.4.b. Discriminative ability of IFG and the metabolic syndrome:

Figure 9.7 compares aROC calculated from the two models using IFG or metabolic syndrome, after adjustment for a priori confounders. Among hypertensive patients, the discriminative ability and predictive performance of the model using the presence of the metabolic syndrome (aROC: 0.764 [0.750 to 0.778]) was significantly better than that using IFG (0.742 [0.727 to 0.757]) ($p<0.001$).

Risk discrimination improvement by the use of IFG and metabolic syndrome:

Figure 9.8 shows the difference between the predicted risks of developing new-onset diabetes using IFG and the metabolic syndrome model, stratified according to observed outcomes (presence or absence of new-onset diabetes) after 5-years of follow-up. The model using IFG status (presence or absence) in comparison with the metabolic syndrome model correctly allocated higher baseline risks among 28.0% of those who subsequently developed new-onset diabetes, and lower risks among 38.6% of those who remained non-diabetic at the end of 5 years of follow-up. Overall the use of IFG status was significantly worse than the use of the metabolic syndrome at predicting new-onset diabetes status. Using IFG status 37.7% of subjects were assigned risks closer to the observed new-onset diabetes status after 5-years of follow-up, compared with 62.3% of subjects using the metabolic syndrome model ($p<0.001$) (Table 9.6).

9.6.5 The Metabolic syndrome, Obesity and the risk of new-onset diabetes among normoglycaemic patients.

Among 8,124 normoglycaemic individuals (FPG <5.6 mmol/l) at baseline, 323 (4.0%) developed new-onset diabetes. Table 9.5 shows the development of diabetes among those with normoglycaemia, stratified by the presence or absence of the metabolic syndrome.

Among those with normoglycaemia, 7% of those with the metabolic syndrome developed diabetes compared with only 2.9% of those without the metabolic syndrome.

On multivariable analysis, among normoglycaemic patients, the presence of the metabolic syndrome at baseline was associated with a 2.4-fold [1.90 to 2.97] increased risk of new-onset diabetes, after adjusting for a priori confounders (Model-1). This increased risk associated with the metabolic syndrome remained significant after adjusting for the influence of obesity (1.66 [1.29 to 2.13]). Furthermore, among those with normoglycaemia, the presence of the metabolic syndrome and obesity together was associated with a three-fold [2.25 to 3.83] increased risk of new-onset diabetes, as compared with the absence of these two factors.

9.6.6 Metabolic syndrome and the risk of new-onset diabetes among those with and without obesity at baseline.

Of the 14,120 patients 'at risk' of diabetes at baseline, 4,058 (28.7%) were obese (BMI $\geq 30 kgm^2$). Among these obese individuals, 3,067 (75.6%) had the metabolic syndrome at baseline. A considerably higher proportion of those with the metabolic syndrome and obesity developed diabetes (18.1%), compared with those obese individuals without the metabolic syndrome (8.5%).

On survival analyses, among all eligible patients (n=12,692), the incidence rate of diabetes among those with obesity (30.8 per 1000 person year) was significantly higher than those without obesity at baseline (13.7 per 1000 person years). On comparison of the risk of new-onset diabetes associated with the metabolic syndrome, stratified by the presence or absence of obesity, those with the metabolic syndrome (compared with those without) were at a three-

fold greater risk of developing diabetes regardless of the presence or absence of obesity. The risk of diabetes associated with the metabolic syndrome among those with and without obesity was 3.38 [2.47 to 4.63]) and 3.27 [2.81 to 3.82], respectively. Figure 9.9 shows the observed and predicted risk of new-onset diabetes, stratified by the presence of obesity and metabolic syndrome at baseline. Compared with those without obesity and the metabolic syndrome, there was a four-fold (4.10 [3.55 to 4.72]) increased risk of new-onset diabetes among those with the presence of both at baseline.

9.7 Discussion

My analyses of 14,120 non-diabetic hypertensive patients suggest that both IFG and the metabolic syndrome are clinically useful predictors of new-onset diabetes. However, whilst the presence of IFG confers a substantial risk of new-onset diabetes among hypertensive patients, the metabolic syndrome correctly identifies the risk of new-onset diabetes in a significantly higher proportion of patients compared with that allocated by the use of IFG status alone. These findings further demonstrate that the metabolic syndrome, independent of its constituent components and other determinants of new-onset diabetes, is associated with an increased risk of new-onset diabetes. Among its individual metabolic components, FPG contributes the most towards the risk of new-onset diabetes, followed by BMI, systolic BP, triglycerides and HDL-cholesterol in that order. Furthermore, these analyses confirm the relative importance of the metabolic syndrome beyond that of obesity, and other metabolic components, in predicting the risk of new-onset diabetes among those with normoglycaemia.

9.7.1 The metabolic syndrome and impaired fasting glucose in prediction of new-onset diabetes.

These findings have clearly established that whilst both IFG and the metabolic syndrome are independent predictors of new-onset diabetes among hypertensive patients, the metabolic syndrome is a more accurate risk marker. These findings conflict with recent studies that have suggested that IFG status may be used instead of the metabolic syndrome to predict the risk of new-onset diabetes (46, 435, 451) . Indeed, the findings of my analyses are, in part, consistent with the reports from these earlier apparently conflicting studies. However, my analyses are more comprehensive and add a new dimension to the earlier knowledge.

In Figure 9.6, I have shown that the risk of new-onset diabetes associated with the metabolic syndrome alone (in the absence of IFG) is substantially less than that associated with the

presence of IFG alone (in the absence of the metabolic syndrome). This finding is, in part, comparable with the findings from previous reports (46, 435, 451). For example, in the AusDiab study, Cameron et al reported that the risk of new-onset diabetes among those with glucose intolerance (IFG or IGT) but no metabolic syndrome, was three times higher than the risk among those with the metabolic syndrome and no IFG or IGT (i.e. normoglycaemia). Indeed, the findings of Cameron et al are superficially similar to those from my analyses. In my analysis, compared with those who did not have either the metabolic syndrome or IFG at baseline, those with the metabolic syndrome alone (and no IFG) or IFG alone (and no metabolic syndrome) were at 2.4 and 4.6-fold increased risk respectively of developing diabetes. Figure 9.6 shows that those with IFG alone (in the absence of the metabolic syndrome) were at nearly two times greater risk of new-onset diabetes compared with those with the metabolic syndrome alone. These findings are comparable with those of Cameron et al. However, my interpretation of these findings differs from those made in the earlier studies in 3 key ways. Firstly, plasma glucose is linearly associated with the risk of incident diabetes. Thus comparing those with normoglycaemia and the metabolic syndrome with those with impaired glycaemia but no metabolic syndrome is an unfair comparison (because impaired glycaemia is an intermediate step in the natural history of diabetes), and may have caused inaccurate interpretation of the earlier studies. Secondly, comparison of the associated effect sizes to expound on a model's discriminative ability is an inefficient, and at times, inaccurate technique, which is now increasingly going out of favour –as reported in several recent studies on statistical methodology (454, 455). Thirdly, and perhaps most importantly, it is often ignored that the individual components of the metabolic syndrome commonly co-exist and overlap. Because of this, the vast majority of those with IFG also have one or more other metabolic components associated with it, and therefore, it is likely that some of the apparent risk of diabetes associated with IFG status is contributed by the other associated metabolic

components. Hence, it is not appropriate to compare IFG (with its associated other metabolic components) and the metabolic syndrome (but without one of its important contributing component, IFG). Notwithstanding these issues, the findings described in Figure 9.6 could potentially be interpreted differently. For example, if the findings are grouped by the glycaemic status of the individuals, there was a 2-fold increased risk of new-onset diabetes associated with the presence of the metabolic syndrome, regardless of the glycaemic status of the patients. In my opinion, this is a more accurate interpretation of the data, and is consistent with the findings from other studies that suggest that the presence of the metabolic syndrome confers an added risk of incident diabetes, that is equal among those with and without IFG (439)

Furthermore, on comparison of the aROC of the two models, comparing their respective sensitivity and specificity curves, the model using the metabolic syndrome was significantly better than that using IFG ($p<0.001$) (Figure 9.7). When the predicted risk allocated by each model (IFG and the metabolic syndrome) was stratified by observed 5-year-outcome, the model using the metabolic syndrome was found to allocate a significantly higher proportion of adults to their correct risk categories (Table 9.6 and Figure 9.8). The IFG model performed less well among those with normoglycaemia at baseline (26.7% of these patients were correctly assigned to the correct risk category using the IFG model, compared with 73.3% correctly assigned using the metabolic syndrome model).

In summary, these analyses highlight the inadequacy of the traditional approach of using odds ratios or hazard ratios alone rather than calculating incremental discrimination or re-classification improvement indexes when evaluating optimal risk prediction (218, 455, 457). Using such techniques, my findings suggest that the metabolic syndrome is superior to IFG in

stratifying the likelihood of developing diabetes, even though the effect sizes associated with the metabolic syndrome were modest.

9.7.2 The metabolic syndrome, its components and the risk of new-onset diabetes:

The findings of my analyses demonstrate that among hypertensive patients, the metabolic syndrome was associated with an excess risk of new-onset diabetes, after adjusting for the influence of all its individual components. These findings are consistent with some, (378, 453) but not all (46, 451) previous reports. These findings are also consistent with the results of recently published studies demonstrating a vastly enhanced risk of new-onset diabetes among those with the presence of both IFG and the metabolic syndrome. (378, 453).

The metabolic syndrome and FPG: Table 9.4 documents the sizeable attenuation in the risk of new-onset diabetes associated with the metabolic syndrome, when adjusted for the FPG component. However, the residual risk of new-onset diabetes associated with the metabolic syndrome remains large and statistically significant. Furthermore, attenuation of the effect size after adjusting for the FPG component of the metabolic syndrome was expected in this analysis, particularly as patients randomised in ASCOT-BPLA were at relatively high risk of developing diabetes (incidence rate: 18.6 per 1,000 person years) as compared with those in the community (for example, in the UK, in 2005, incidence rates of diabetes were estimated to be 4.4 per 1000 person years) (463). This is further evident by a high mean [SD] FPG (5.4 [0.6] mmol/l), and the presence of IFG at baseline among 36% of all those included in these analyses. Once again this is considerably higher than that seen in the community. Moreover, it is important to note that the effect size associated with the metabolic syndrome in these analyses may have been attenuated, because of the presence of at least one metabolic component of this syndrome (i.e. hypertension) among those without the metabolic

syndrome. Therefore, the 87% (1.87 [1.63 to 2.13]) excess risk of new-onset diabetes, associated with the metabolic syndrome after adjusting for FPG and a priori confounders is likely to have been an underestimate of the true effect size.

Metabolic syndrome among those with normoglycaemia: In these analyses, I have also shown that among normoglycaemic individuals, the presence of the metabolic syndrome is associated with a significantly higher risk of developing new-onset diabetes as compared with its individual components, particularly obesity. These findings are consistent with the reports from previous investigations (436). Indeed, the findings of a 3-fold increase in the risk of new-onset diabetes among normoglycaemic patients, with obesity and the metabolic syndrome are important, given the rapidly increasing prevalence of obesity in the community.

Metabolic syndrome, obesity and other constituent components: Among the individual components of the metabolic syndrome, after FPG, BMI contributed the most towards the risk of new-onset diabetes. This is unsurprising as BMI (obesity) is a well established risk factor for diabetes (436) Inclusion of the other components of the metabolic syndrome in the model did not substantially affect the relationship between the metabolic syndrome and new-onset diabetes. Indeed all of the individual components remained independent predictors of new-onset diabetes, as did the metabolic syndrome. The finding of a relatively smaller (though still significant) influence of low-HDL on the risk of new-onset diabetes associated with the metabolic syndrome is consistent with previous studies (453).

Overall, whilst some of these findings are consistent with earlier reports (378, 453), these data are the first to relate specifically to a hypertensive population. The most important finding from these analyses is the clear demonstration that the metabolic syndrome is a more

accurate predictor of new-onset diabetes (particularly among normoglycaemic hypertensive individuals) compared with other markers of risk such as IFG alone, or obesity. Almost all previously established risk scores for diabetes are complex or difficult to use (281, 430, 451, 464). Furthermore there has been no consensus on which diabetes risk score to use in routine clinical practice. The use of the metabolic syndrome or other simpler risk constructs have been proposed,(429, 432, 465) and a recent study suggested that FPG (46) may be preferable. The results of my analyses have highlighted the limitations of earlier analyses that have been based on either comparisons of effect sizes alone, or the additional use of aROC curves (46, 451). In my analyses I have compared the discriminative ability of several risk constructs (including the metabolic syndrome and its individual constituent components) using a combination of newer statistical techniques including net reclassification index and integrated discrimination index (455, 457).

9.7.3 Limitations & Strengths

A possible limitation of this study is the use of BMI instead of waist circumference in the definition of the metabolic syndrome. However, the use of BMI in defining the metabolic syndrome is not new, (431, 433) and has been previously shown to have a comparable predictive capability. (428) Furthermore, a recent meta-analysis found no evidence of heterogeneity in the association between the metabolic syndrome and cardiovascular risk, when waist, waist-hip ratio or BMI were used in the definition (43). Generalizability of these findings is an important limitation, because in ASCOT-BPLA the majority of patients were men of white Caucasian origin. However, the vast majority of randomised patients in ASCOT-BPLA were recruited directly or indirectly from general practices in the Nordic countries and the UK. Moreover, compared with the patients included in several other recent trials (28, 157, 233), the randomised patients in ASCOT-BPLA were fairly typical of the

general hypertensive population (48). However, the presence of hypertension in all included patients in this analysis may have resulted in an underestimation of the associated effect sizes in the comparisons between those with and without the metabolic syndrome, as the latter group also had at least one metabolic component. This is a particularly important consideration when interpreting the results of these findings, and because of that, these findings require further validation among other ethnic groups, and among other high-risk populations and not necessarily hypertensive. The particular strengths of this study include that it is the first such analysis among hypertensive patients, using a large clinical trial database, with accurate exposure and outcome ascertainment. These findings have clearly established the relative predictive performance of the metabolic syndrome, obesity and IFG in relation to the risk of new-onset diabetes among hypertensive patients. Since the estimates in these analyses are conservative, because of the inclusion of at least one metabolic component (hypertension) among comparator group of those without metabolic syndrome, it is also likely that these findings will be applicable to individuals in the community, particularly because the relationships and effect sizes in the community settings are likely to be higher. The use of newer statistical methods, providing better discrimination between the risk models, may help to further extend the current knowledge base, and may result in further research on this important topic.

In summary, these findings suggest that whilst both IFG and the metabolic syndrome may be useful tools for predicting the risk of incident diabetes, the metabolic syndrome is a better predictor than IFG in assigning the risk of diabetes among hypertensive patients, and particularly among those with normoglycaemia. In addition, the metabolic syndrome remains a significant and independent predictor of new-onset diabetes even after adjusting for the sum of its individual components including FPG.

These findings suggest that the use of the metabolic syndrome as a tool for predicting new-onset diabetes is not obsolete. Pending confirmation of these results in other populations, I believe that the metabolic syndrome continues to have a role in routine clinical practice, particularly in the absence of other easy-to-use risk predictors.

9.8 Conclusions

This study has shown that the metabolic syndrome is an independent predictor for the development of new-onset diabetes, even after adjusting for its constituent components, and other determinants of new-onset diabetes. Furthermore, among those with normoglycaemia, the metabolic syndrome was the most important predictor for the development of diabetes. In this study FPG and BMI were the two most important contributors towards the risk of new-onset diabetes associated with the metabolic syndrome. Finally the risk associated with the metabolic syndrome increases incrementally according to the number of its constituent risk factors at baseline.

Chapter 9: Tables

Table 9.1 Baseline characteristics among those who developed diabetes, and those who did not among 'at risk' patients in the ASCOT-BPLA.

Baseline characteristics	At risk population (n=14120)	
	Develop diabetes (n=1366)	Do not develop diabetes (n=12754)
	Percent/mean±SD	Percent/mean±SD
Atenolol-based group (%)	58.5	49
Age (yrs)	61.6 ± 8.3	63.0 ± 8.5
Male (%)	80.7	77.8
BMI (kg/m2)	30.2 ± 4.5	27.9 ± 4.3
Current smoker (%)	72.9	69.5
Total cholesterol (mmol/l)	5.9 ±1.1	6.0 ±1.1
HDL-cholesterol (mmol/l)	1.23 ±0.3	1.34 ±0.4
Serum triglyceride (mmol/l)	2.11 ± 1.1	1.73 ± 0.9
Fasting glucose (mmol/l)	5.9 ± 0.7	5.3 ± 0.6
>4 risk factors (%)	15.5	12.3
H/O previous anti-HT drug (%)	80.1	79.4
Use of non-cardiovascular concomitant medication (%)	60.2	56.4
Previous aspirin (%)	18.4	18.9
Previous lipid lowering drugs (%)	10.1	9
Systolic BP (mm Hg)	165.0 ± 18.3	163.6 ± 17.9
Diastolic BP (mm Hg)	96.4 ± 10.7	95.3 ± 10.2
HR (beats per minute)	72.9 ± 12.9	70.8 ± 12.3
Metabolic syndrome (%)	65.7	35.7

BMI: body mass index; H/O: history of; HT: hypertension; HDL: high density lipoprotein

Table 9.2: Distribution of the metabolic components among those who did and did not develop diabetes among those at risk in the ASCOT-BPLA

Baseline distribution of the metabolic components	Evaluable*at risk population (N=12,692)	Develop diabetes (N=1,212)	Do not develop diabetes N=11,480)
Number of components	**Number (%)**	**Number (%)**	**Number (%)**
Hypertension only: one metabolic component	3388(27)	68(6)	3320(29)
HT plus one another metabolic component: 2 components			
BMI > 30 Kg/m2	741(6)	42(3)	699(6)
HDL-cholesterol <1.03 mmol/L	447(4)	13(1)	434(4)
Triglyceride (≥1.7 mmol/L)	1395(11)	50(4)	1345(12)
FPG ≥ 5.6 mmol/L	1448(11)	179(15)	1269(11)
Metabolic syndrome (any 3 components)	3110(25)	379(31)	2731(24)
Any 4 components	1692(13)	343(28)	1349(12)
All 5 components	471(4)	138(11)	333(3)

* Those with no missing or non-fasting value (n=12,692)
BMI: body mass index; FPG: fasting plasma glucose; HDL: high density lipoprotein

Table 9.3 Risk (Hazards) of the development of new-onset diabetes associated with the MetS* in Cox models after adjusting for a priori confounders, its individual components and other determinants of incident diabetes.

Cox-models[†]	Hazard ratio. [95%Confidence Interval]	P>z	C-statistic	LR chi-statistic	BIC (in thousands)
Univariate: Met Syndrome	3.67 [3.24 to 4.15]	<0.001	0.66	475	22.15
Met syndrome + a priori confounders [‡] ***[Model-1]***	3.63 [3.20 to 4.11]	<0.001	0.67	496	22.18
Model-1 + a component of the MetS					
Model-1 + Glucose	1.87 [1.63 to 2.13]	<0.001	0.78	1,363	21.33
Model-1 + BMI	2.92 [2.54 to 3.35]	<0.001	0.69	549	22.14
Model-1+ SBP	3.65 [3.22 to 4.14]	<0.001	0.68	516	22.17
Model-1+ Triglyceride	3.46 [3.02 to 3.97]	<0.001	0.67	499	22.19
Model-1 + HDL cholesterol	3.65 [3.17 to 4.20]	<0.001	0.67	496	22.19
Met syndrome+ a priori + progressive addition of individual components*					
Model-1 + Glucose	1.87 [1.63 to 2.13]	<0.001	0.78	1,363	21.33
Model-1 + Glucose + BMI	1.45 [1.25 to 1.68]	<0.001	0.79	1,425	21.27
Model-1 + Glucose + BMI + SBP	1.46 [1.26 to 1.70]	<0.001	0.79	1,438	21.27
Model-1 + Glucose + BMI + SBP+ Triglyceride	1.33 [1.13 to 1.55]	<0.001	0.79	1,449	21.27
Model-1 + Glucose + BMI + SBP+ Triglyceride+ HDL Cholesterol [Model-2 [§] ***]***	1.19 [1.00 to 1.40]	0.046	0.79	1,466	21.26
Model-1+ all individual components of the MetS + other determinants of NOD [Model-3 [‖] **]**					
Model-2+ treatment allocation, total cholesterol, & alcohol intake	1.22 [1.03 to 1.44]	0.022	0.80	1,540	21.22

***** using updated NCEP-ATPIII definition
†: After excluding all patients with non-fasting values of glucose and/or serum triglyceride.
Total number of patients in the model =12,692. There was no missing follow-up data.
‡: a priori confounders: Ethnicity, age, sex, & use of non-cardiovascular concomitant medication
§: Adjusted for all its individual components, used as continuous variables except where non-linear
‖: Adjusted in addition for all other independent determinants of the new-onset diabetes found separately in a multivariable component Cox-model: Treatment allocation, total cholesterol, alcohol intake

Table 9.4 Distribution of the metabolic components among hypertensive patients with IFG at baseline, stratified by development of diabetes.

Metabolic components among those with IFG at baseline	Total (4569)	Developed diabetes (n=889)	Did not develop diabetes (n=3,680)
	N (%)	N (%)	N (%)
IFG only (i.e. 2 metabolic components)	1448 (31.7)	179 (20.1)	1269 (34.5)
3 components	1495 (32.7)	275 (30.9)	1220 (33.2)
4 components	1155 (25.3)	297 (33.4)	858 (23.3)
5 components	471 (10.3)	138 (15.5)	333 (9.0)

IFG: impaired fasting glucose

Table 9.5 Baseline glycaemic* and metabolic status and subsequent development of new-onset diabetes among hypertensive patient in the ASCOT-BPLA trial

Glycaemic status (number)	Metabolic syndrome (present/absent)	Total number of patients	Number developing diabetes (%)	p-value
Normoglycaemic (8,124)				
	absent	5,972	173 (2.9%)	<0.001
	present	2,152	150 (7.0%)	
Impaired Glycaemia (4,569)				
	absent	1,448	179 (12.4%)	<0.001
	present	3,121	710 (22.8%)	

* Of 14,120 non-diabetic patients, the baseline fasting status of 1,428 patients was unknown, hence, were excluded from these analyses of 12,692 patients. Of these, 1,212 patients developed diabetes during median follow-up 5.5 years (interquartile range 5.0 to 6.0 years)

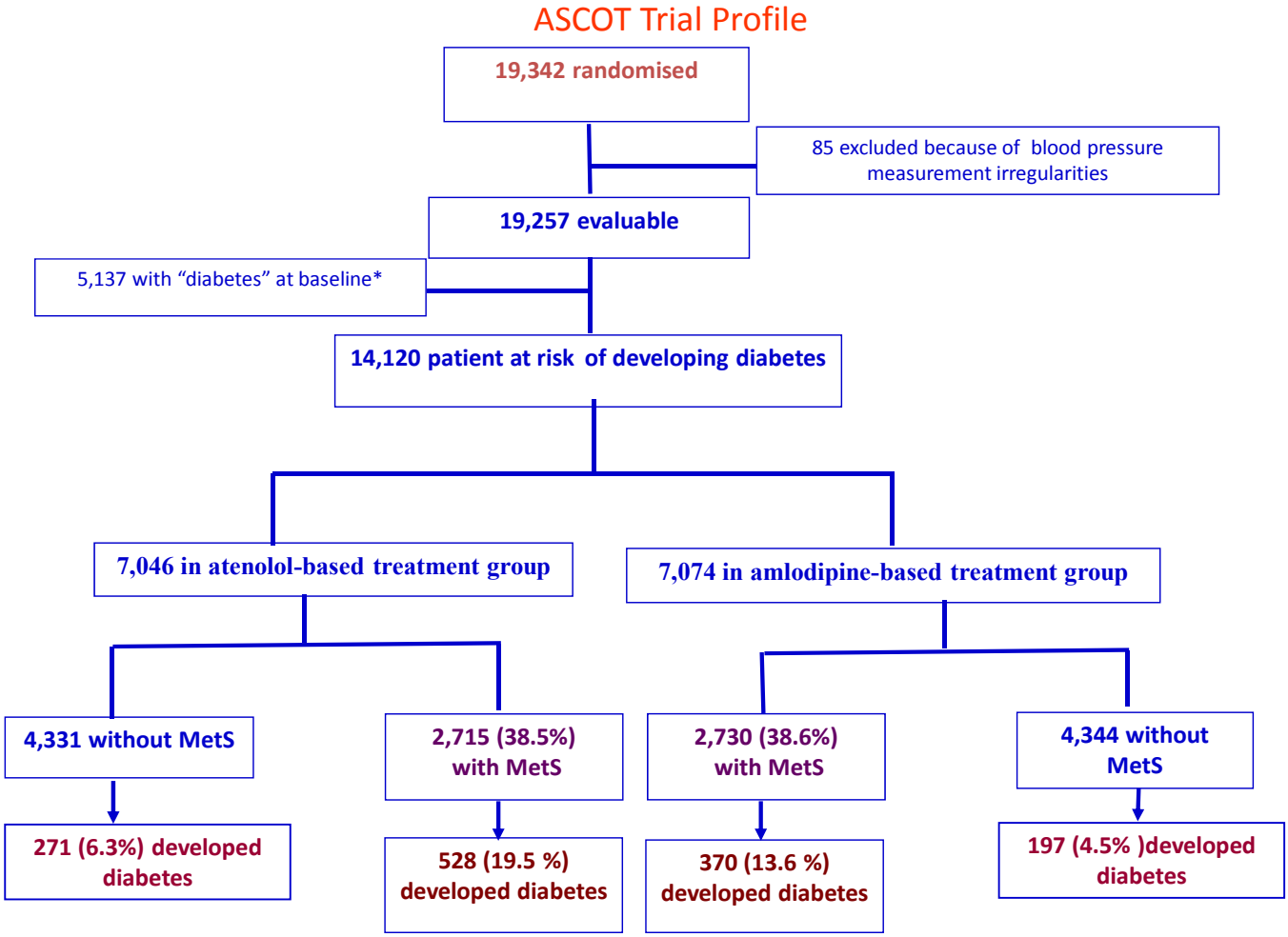
Table 9.6. Net Reclassification Improvement in models using IFG or MetS, after adjusting for a priori confounders.

Risk predictions with models	**Observed Outcome at 5 year**		**In how many hypertensive patients IFG predicts better than the Metabolic syndrome?**		
	Do not develop diabetes	**Develop diabetes**			
	(Numbers)	***(Numbers)***	***IFG model***	***Numbers***	***%***
R_IFG* > *R_MetS	A=7,105	B=314	**Better** (B+C) =	4,781	37.70%
R_IFG* < *R_MetS	C=4,467	D=806	**Worst** (A+D) =	7,911	62.30%
Total	11,572	1,120	A+B+C+D =	12,692	100%
Test Prop=50%			P < 0.001		

R_IFG: Risk predicted with IFG model; R_MetS: Risk predicted with MetS model. The model which predicted higher risk was better for those who subsequently developed diabetes. In contrast, the model which predicted lower risk was better among those who did not develop diabetes during the 5 year follow-up period.

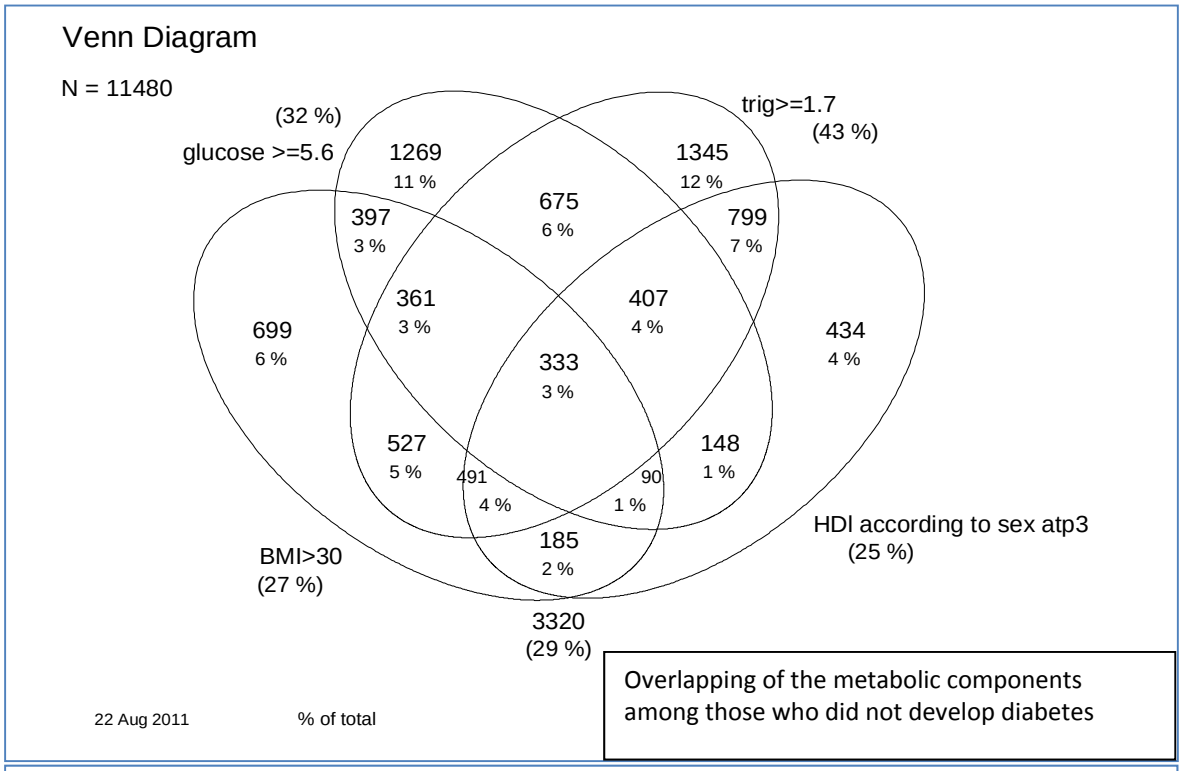
Chapter 9: Figures

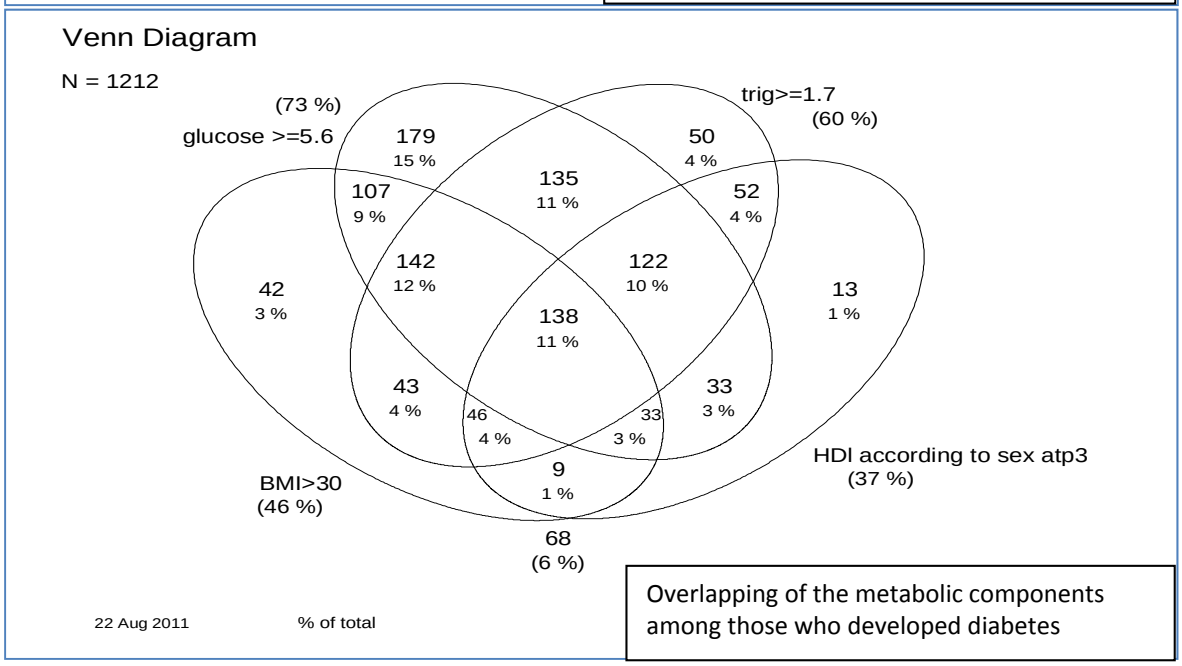
Figure 9.1: Baseline treatment allocation, metabolic syndrome, and development of diabetes among those randomized in the ASCOT-BPLA.



MetS: Metabolic syndrome

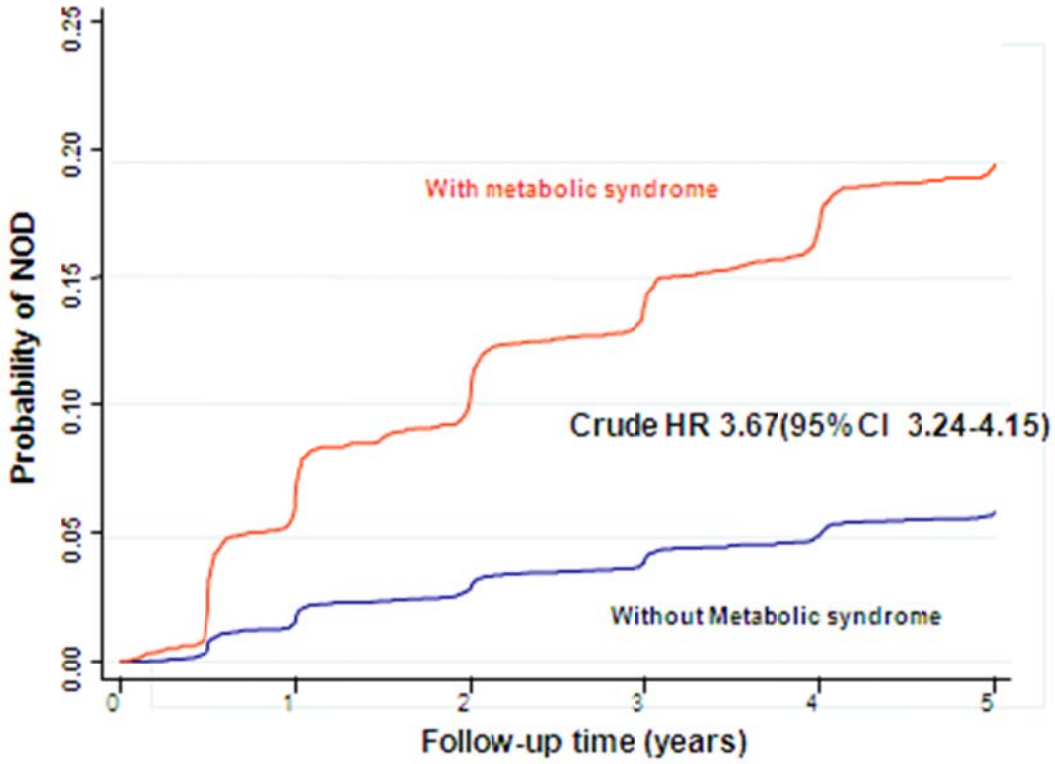
Figure 9.2 Distribution of the components of the metabolic syndrome, and their overlapping, among 12,692* included patients in Cox models, stratified by the development of diabetes





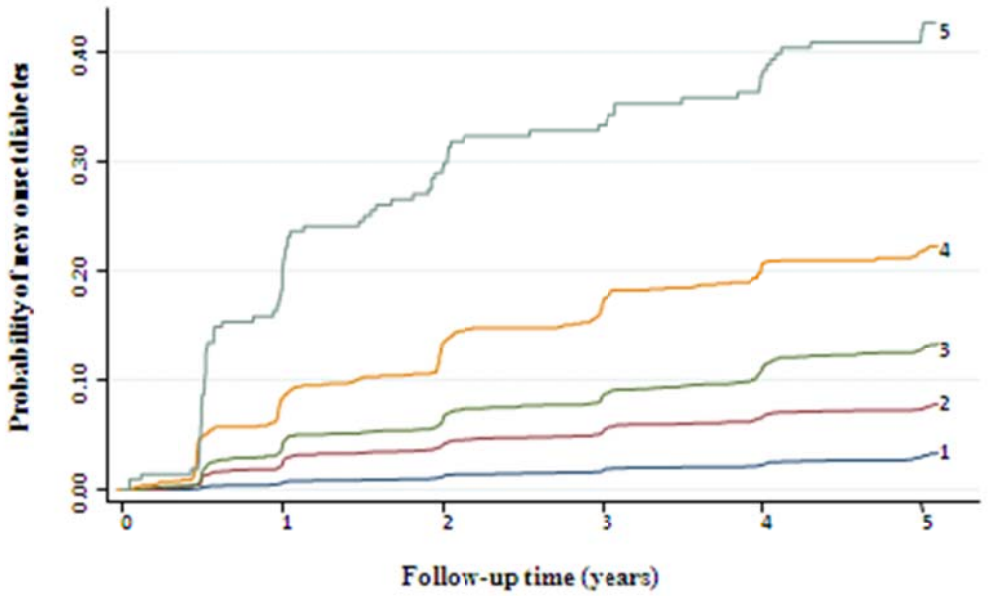
* Only those included at risk patients, who had no missing (or non-fasting) value of any metabolic components variable.
trig: triglyceride≥ 1.7 mmol/L; BMI> 30 kg/m^2; HDL-cholesterol ≤ 1.03 mmol/l for males, and ≤ 1.29 mmol/l for females; fasting plasma glucose(FPG)≥5.6 mmol/L.29% and 6%, respectively, among those who did not and those who did develop diabetes, had no other metabolic component except the presence of hypertension

Figure 9.3 Cumulative hazards (hazard ratio and 95% confidence intervals) of developing new-onset diabetes according to presence of metabolic syndrome at baseline



- NOD: new-onset diabetes; HR: hazard ratio.
- HRs are estimated among 12,692 patients with no missing value of any component variable.
- Among 14,120 at risk patients, the HR for the risk of diabetes associated with the metabolic syndrome were 3.25[2.91 to 3.64])

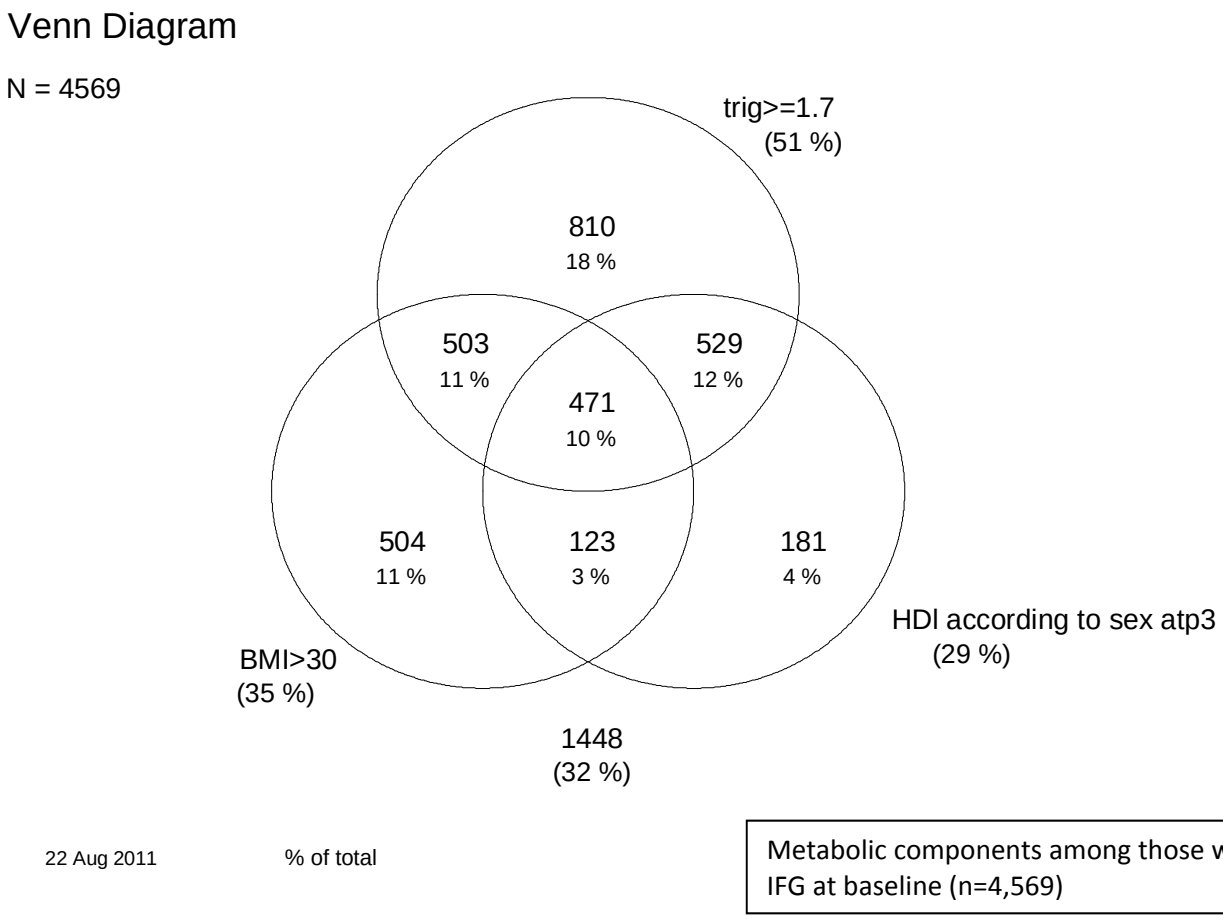
Figure 9.4 The risk of new-onset diabetes among 'at risk' hypertensive patients of the ASCOT-BPLA, according to the number of components of metabolic syndrome at baseline.



Number of metabolic components	1 MC:HT	2 MC.	3 MC.	4 MC.	5 MC
Hazard Ratio (95% CI)	1 referent	2.7 (2.2-3.3)	4.6 (3.7-5.6)	7.6 (6.1-9.3)	11.8 (9.2-15.0)

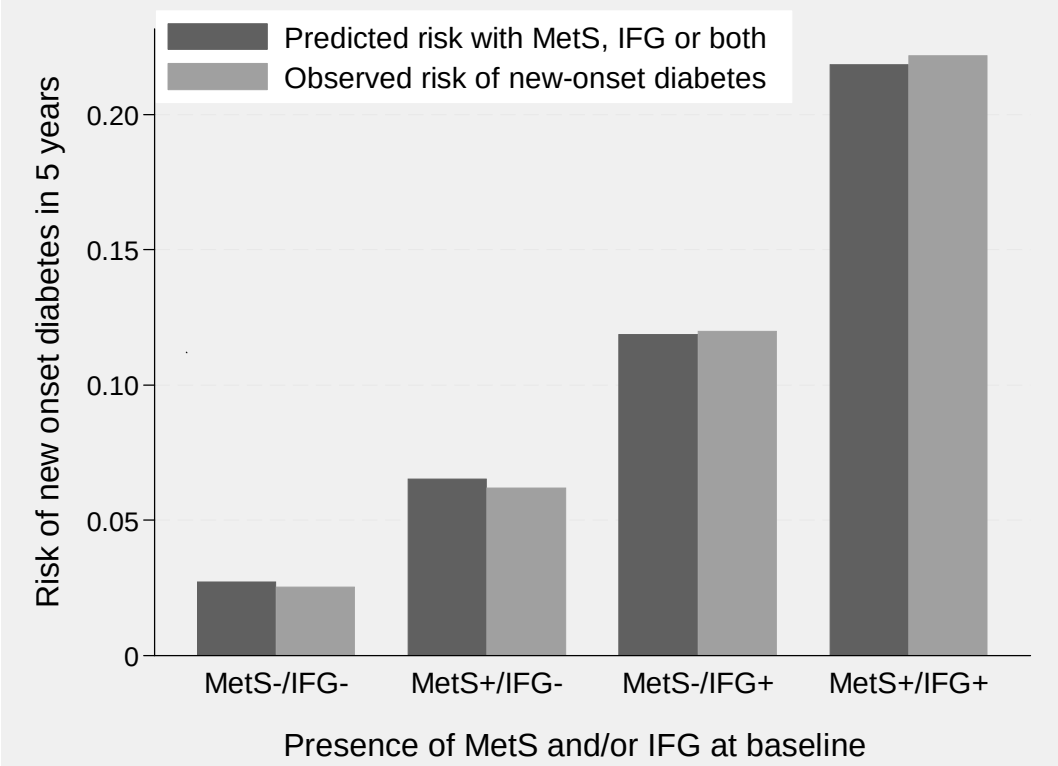
MC: metabolic components; HT: hypertension

Figure 9.5.Overlapping and distribution of other metabolic components among 4569 of those hypertensive patients with impaired fasting glucose at a baseline.



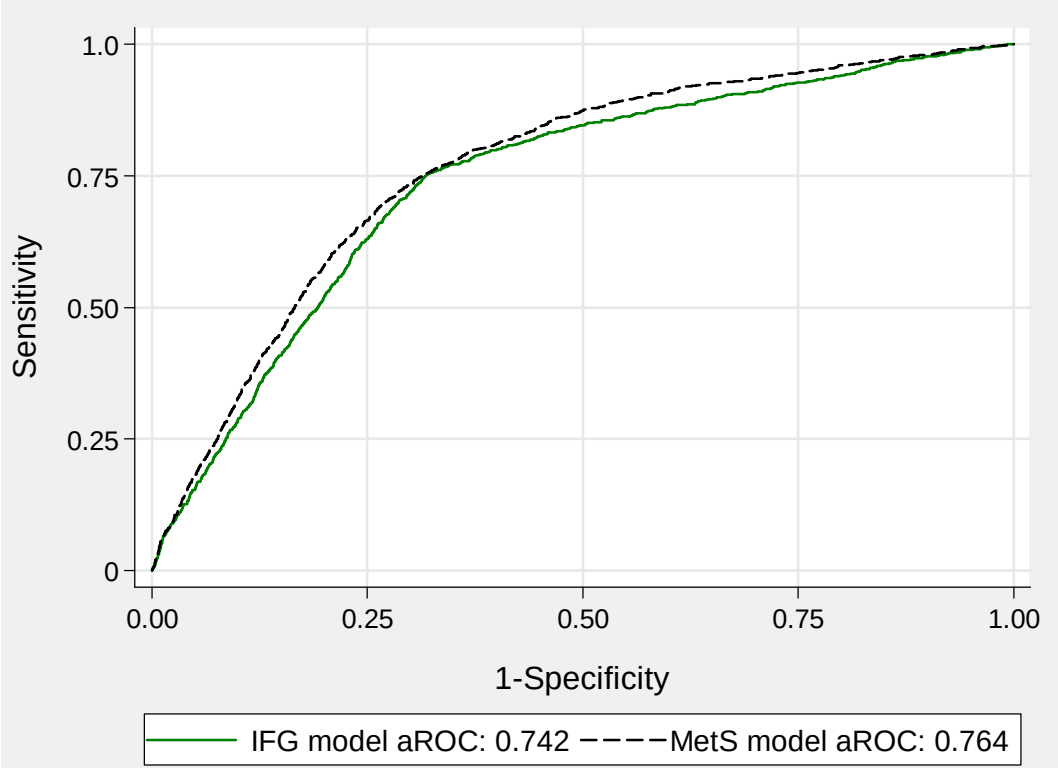
IFG: impaired fasting glucose. trig: triglyceride≥ 1.7 mmol/L; BMI> 30 kg/m^2; HDL-cholesterol according to sex ≤ 1.03 mmol/l for males, and ≤ 1.29 mmol/l for females
*4569 of those at risk patients, who had no missing value of any metabolic components variable, and had IFG at baseline. 32% of those IFG patients did not have any other associated component.

Figure 9.6: **Predicted and observed risk of new-onset diabetes by baseline presence of the metabolic syndrome or impaired fasting glucose alone and together**



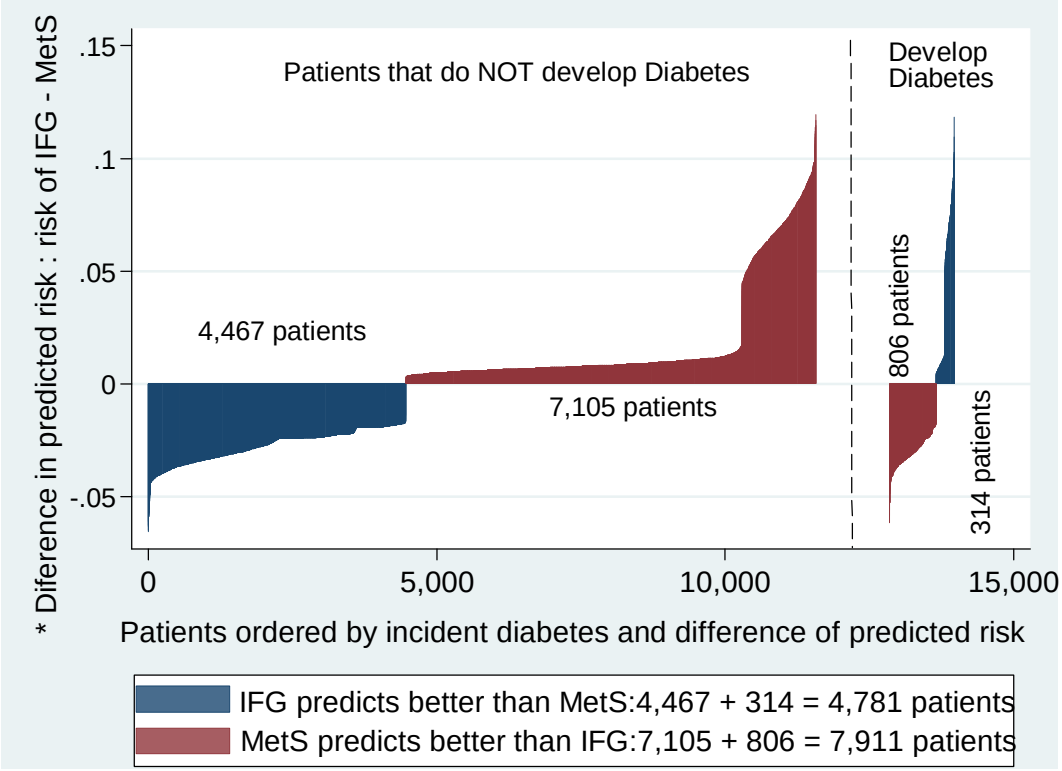
MetS: metabolic syndrome
IFG: impaired fasting glucose (i.e. FPG ≥ 5.6 mmol/l)

Figure 9.7 Area under Receiver-Operating Characteristics Curves for the models using IFG or metabolic syndrome, and adjusting for a priori confounders.



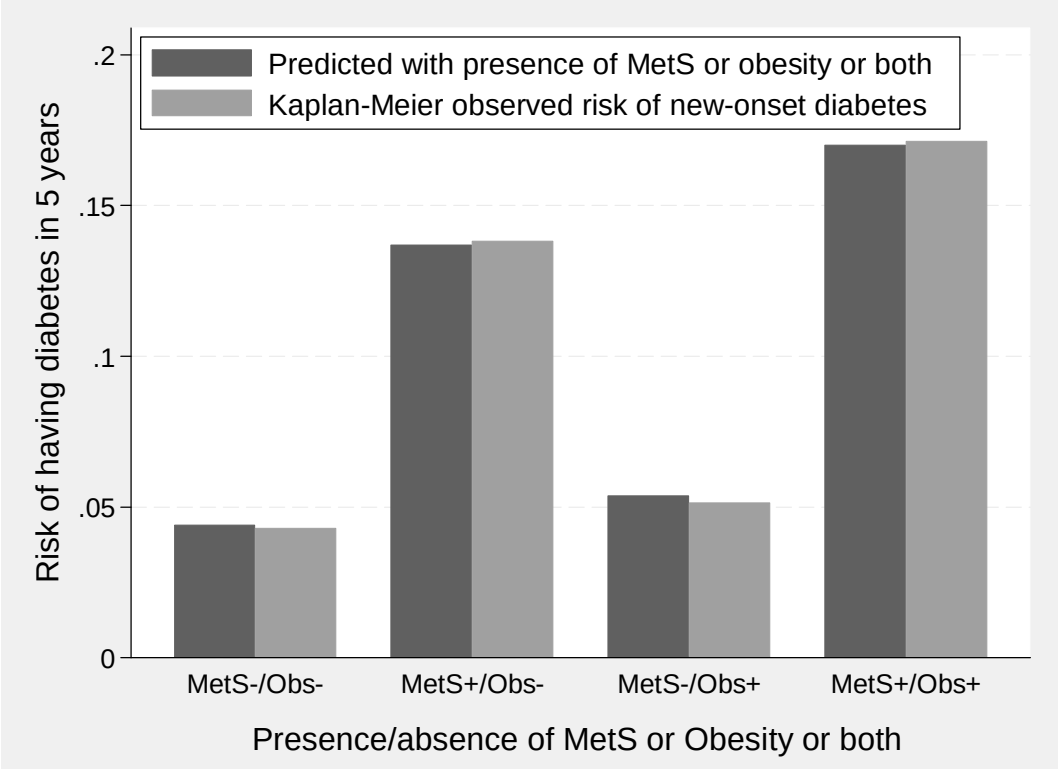
aROC: area under receiver-operating characteristics curves
MetS: metabolic syndrome
IFG: impaired fasting glucose (i.e. FPG ≥ 5.6 mmol/l)
a priori confounders include age, sex, ethnicity, use of concomitant non-cardiovascular medication

Figure 9.8:Differences in predicted risks between the risk predicted by the model using impaired fasting glucose and that using the metabolic syndrome, stratified by the outcome status (presence or absence of diabetes) after 5 year of follow-up.



MetS: metabolic syndrome
IFG: impaired fasting glucose (i.e. FPG ≥ 5.6 mmol/l)
Risk difference= 5 year risk of developing diabetes using IFG model minus the risk estimated using the metabolic syndrome model. Among those who do not develop diabetes during follow-up, the model predicting the lesser 5 years risk is better among the two models. Similarly, among those who develop diabetes during the 5 year of follow-up, the model predicting the higher 5 year risk is better among the two models.

Figure 9.9: Risk of development of new-onset diabetes among normoglycaemic patients on basis of presence/absence of obesity, metabolic syndrome or both.



MetS: metabolic syndrome
Obs: obesity (i.e. BMI $\geq$ 30 kg/m^2)

Chapter 10

CONCLUSIONS

&

IMPLICATIONS FOR FUTURE RESEARCH

Determinants of, and Outcomes Associated with Antihypertensive-associated Incident Diabetes and the Metabolic Syndrome in Hypertensive Patients in the ASCOT-Trial

10.1 Conclusions

Based on the findings from 4 studies (Chapter 6 to 9), the following conclusions can be drawn:

1. Treating hypertensive patients with a regimen based on amlodipine ± perindopril compared with a regimen based on atenolol ± thiazide diuretic significantly reduces the risk of new-onset diabetes.
2. In addition to the blood pressure (BP)-treatment allocation, among hypertensive patients, baseline fasting plasma glucose (FPG), body mass index (BMI), systolic BP, serum triglycerides and high density lipoprotein (HDL)-cholesterol are the other independent predictors of the new-onset diabetes. Whilst, allocation to the amlodipine-based therapy was the most protective factor in ASCOT-BPLA, the increase in baseline FPG was the most significant risk factor, followed by the increase in baseline BMI and serum triglyceride levels.
3. The risk score developed from the model has an excellent internal validity and good discriminative ability, and can potentially be an important tool to identify those hypertensives at high risk of developing new-onset diabetes.
4. Both baseline FPG and cumulative mean glucose (CMG) are independent and significant risk factors for major cardiovascular outcomes and death.
5. Among hypertensive patients, in-trial worsening of the glycaemic status is progressively and significantly associated with the increasing risk of cardiovascular morbidity and mortality; suggesting that the antihypertensive induced glycaemic changes are no different in their relationship with the cardiovascular outcomes, than those observed between impaired glycaemia, diabetes and cardiovascular outcomes in the community (so called ‘naturally occurring’ glycaemic changes).
6. BP-treatment allocation significantly influences CMG levels and glycaemic status, which could partly explain the difference in death and cardiovascular event rates

observed between the two treatment groups in ASCOT-BPLA.

7. CMG may be a more sensitive and accurate predictor of cardiovascular events and death compared with the crude clinical categorizations of glycaemic status.
8. Among hypertensive patients, the metabolic syndrome remains an independent risk factor for coronary outcomes, stroke -and all-cause mortality, after adjusting for the influence of conventional cardiovascular risk factors.
9. The metabolic syndrome, independently of its constituent metabolic components, is also an independent and significant risk factor for stroke and death, but not for coronary outcomes. This implies that the presence of the metabolic syndrome confers added risk for stroke and death among hypertensive patients, and it is likely that the use of the metabolic syndrome, together with other routine cardiovascular risk estimation tools, would help initiate preventive strategies early, particularly among those who are missed (for example, middle aged individuals with borderline high values of risk factors) using only standard risk stratification tools.
10. Both impaired fasting glucose (IFG) and the metabolic syndrome are independent and significant predictors of the new-onset diabetes and both can be used as tools for predicting the risk of new-onset diabetes among hypertensive patients.
11. Metabolic syndrome is a better predictor than IFG in assigning the risk of new-onset diabetes among hypertensive patients.
12. Metabolic syndrome is an independent predictor for the development of new-onset diabetes, even after adjusting for its constituent components, and other determinants of new-onset diabetes. This finding supports the clinical utility of the metabolic syndrome in the prediction of new-onset diabetes.
13. Among those with normoglycaemia, the metabolic syndrome is the most significant predictor of the development of new-onset diabetes, independent of the influence of

other metabolic components including the presence of obesity.

14. Amongst the individual metabolic components of the metabolic syndrome, FPG contributes the most towards the risk of new-onset diabetes, followed by BMI, systolic BP, triglycerides and HDL-cholesterol in that order. In addition, these findings confirm that the risk of new-onset diabetes increases incrementally with progressively increasing numbers of the metabolic components at the baseline.

10.2 Implications for clinical practice and understanding

The findings of these studies have incrementally improved understanding relating to several issues surrounding the cardiovascular impact of the antihypertensive-associated glycaemic changes, and the clinical utility of the metabolic syndrome.

My findings—particularly those relating to the predictors of the new-onset diabetes amongst hypertensive patients and the development of a new 'user-friendly' risk score— are likely to be helpful to physicians, allowing them to choose appropriate antihypertensive medications, and effectively target preventative strategies against the development of new-onset diabetes. For example, these findings will encourage the choice of an angiotensin-converting enzyme inhibitors/angiotensinogen-receptor blockers or a calcium-channel blocker instead of a beta-blocker or a thiazide-diuretic amongst high-risk hypertensive patients, for example, those with either obesity, impaired fasting glucose, low HDL-cholesterol, high triglycerides or their combinations. Indeed, my findings have contributed in the development of several (136, 238) (but not all (23, 239)) important practice guidelines.

My other findings on the outcomes associated with antihypertensive-induced glycaemic changes will help clarify prevailing controversy relating to this issue, and may have an

impact on the practice standards. Previous studies have raised a possibility that the (in-trial) antihypertensive-associated glycaemic worsening (25, 26) is harmless, and is not associated with a similar adverse cardiovascular toll, as that observed among those with diabetes in the community (85-88). These controversial findings have encouraged (and often promoted) the use of beta-blockers and thiazide diuretics in routine practice i.e. despite the increased risk of new-onset diabetes associated with them. However, finding of my analyses have found that the basis of this view-point is incorrect, and that the antihypertensive-induced (in-trial) glycaemic changes are significantly associated with an increasing risk of cardiovascular morbidity and mortality. Moreover, in contrast to the previous such analyses (25, 26, 157, 311), my analyses are likely to be more robust, and have methodological and analytical strengths. For example, unlike other studies, I have evaluated follow-up recording of blood sugar available for > 99% of patients in the populations, and have used standard definition for new-onset diabetes and pre-specified end-points. My finding of a significant linear trend for increasing risk of cardiovascular morbidity and mortality with worsening glycaemic status is also consistent with observations in other settings (104, 269, 331, 340, 359). Furthermore, my findings relating to the use of CMG to assess the association between antihypertensive-associated glycaemic changes and cardiovascular risk, have added considerable strength to the findings on glycaemic categorisations. These findings clearly illustrates that, compared with crude clinical categorizations, CMG is a more sensitive and accurate predictor of cardiovascular events and death. In summary, my findings clearly suggest that antihypertensive-associated glycaemic and\or glucose changes are associated with adverse cardiovascular outcomes, and this in-turn may have important clinical implications on the choice of appropriate antihypertensive agents in the routine practice, particularly among those with a high-risk.

My findings of significant association of the metabolic syndrome (independently of its constituent component) with new-onset diabetes, cardiovascular outcomes and death, have added to the current knowledge (37, 38). I have shown that, when adjusted for its constituent components, the metabolic syndrome remains associated with an increased risk of strokes and all-cause mortality but not of coronary outcomes. These findings are new, and have important implications for cardiovascular risk estimation, particularly for those who are missed using only the traditionally used risk stratification tools (for example, middle aged individuals with borderline high values of the risk factors). These relationships of the metabolic syndrome with cardiovascular outcomes and death, may potentially reveal (and are likely to be as a consequence of) the important underlying pathogenetic relationships (34, 192)— particularly those between the insulin resistance and cardiovascular outcomes(398, 466-469).

My findings could potentially rekindle the debate about the clinical usefulness of the metabolic syndrome (37), and may have important implications for primary prevention strategies, especially for incident stroke among hypertensive patients (408). My other findings, relating to the ability of the metabolic syndrome to identify correctly the risk of new-onset diabetes would be helpful in routine clinical setting, mainly among those with normoglycaemia. These findings (again) are unsurprising, given the fact that insulin resistance may initially manifest (clinically) without overt glycaemic changes (469). Altogether, these findings suggest that, despite recent controversies, the metabolic syndrome continues to have an important role in routine clinical practice, particularly as an easy-to-use risk predictor for incident diabetes and in conjunction with other cardiovascular risk scores, for the risk of cardiovascular disease.

10.3 Implications for future research:

The findings of the 4 studies in this thesis have extended the current knowledge on several important issues. However, they have also created scope for several other exciting projects. Whilst, I have briefly discussed the clinical implications of the findings of each one of the 4 studies in their respective chapters (chapter 6 to 9), a summary of further research implications for each one of them follows.

10. 3.1 Study-1: Determinants of new-onset diabetes

There are several exciting possibilities for further extension of this work. Firstly, whilst we have shown that our simple, easy-to-use integer-based risk model has an excellent internal validity, the external validation of this risk model is a natural extension of this project, not only among hypertensive populations, but also among other high-risk groups. Secondly, little is known about to what extent beneficial changes in determinants of new-onset diabetes (such as BMI, SBP, HDL-cholesterol and triglyceride) while on treatment would reduce the risk of the development of new-onset diabetes among hypertensive patients. The evaluation of this research question would be helpful in incrementally improving the preventive strategies against the development of diabetes among hypertensive patients.

Other projects that may also add to the findings of this study include the evaluation of the association of the baseline levels of vitamin-D with the development of new-onset diabetes among hypertensive patients. More importantly, it would be useful to compare the predictive and discriminative ability of the risk prediction models with and without vitamin-D (and other biomarkers). This would allow us to establish whether the use of these novel biomarkers adds significantly to the information provided by the models using only routinely measured variables. Furthermore, it would be useful to establish whether the protection

afforded by amlodipine ± perindopril regimen, compared with atenolol± thiazide regimen, remains the same regardless of the baseline levels of Vitamin D.

Vitamin D is an exciting new biomarker, implicated in a variety of chronic diseases (470-473). Observational studies have shown an increased association of hypovitaminosis-D with obesity, diabetes, hypertension, and the metabolic syndrome (470-472, 474-478). These multiple and wide-spread associations (involving variety of etiological pathways) are unsurprising—particularly, given that vitamin-D receptor (VDR) in humans is present in more than thirty different tissues (such as islet cells of pancreas, aortic endothelial cells, distal renal cells, activated T-cells) (479), and was one of the earliest receptor in evolutionary term. Amongst these associations, the relationship of vitamin D and diabetes has evoked recent interest. Experimental studies have shown important role of vitamin D in insulin secretion and synthesis, and these findings are well supported by the findings of recent observational studies, showing a consistent association of vitamin-D deficiency with reduced insulin synthesis and secretion (478, 480). VDR gene polymorphism has also been shown in some, but not all, studies to be associated with development of type 2 diabetes (481-483). Other studies have shown vitamin-D analogues – particularly low calcaemic analogues— have a capacity to regulate renin-angiotensin system, and thereby suggest a role of vitamin-D in regulation of volume and electrolyte homeostasis, and blood pressure control (484, 485). Indeed, this accumulating evidence has prompted a few studies to explore the effects of vitamin-D supplementation in patients with diabetes, chronic kidney disease, and impaired glucose tolerance (486-488); but with mixed and often conflicting results (480, 486, 487, 489). Whilst in person with diabetes, supplementation of vitamin D has a little effect on glycaemic control and insulin resistance; amongst those with chronic kidney disease on haemodialysis, the supplementation of calcium and vitamin-D is associated with significantly

reduced risk of cardiovascular morbidity and mortality (473, 479, 490, 491). This conflicting data notwithstanding, presently there are a very few studies in hypertensive or high cardiovascular risk populations-- that have prospectively or otherwise evaluated the role of vitamin-D level as a predictor of type 2 diabetes and cardiovascular disease, and it's inter-relationship vis-à-vis antihypertensive medications. Furthermore, in these populations, there are no available data whether the use of vitamin D (as a biomarker) will add value to existing cardiovascular risk prediction models.

Similarly, another interesting (and clinically relevant) project would be an evaluation of the biomarkers, lipid levels and other risk markers that may explain the relationship between statin therapy and the risk of new-onset diabetes. It is known that statin reduces in-trial high sensitivity C - reactive protein (CRP) and lipid levels (including apolipoprotein A-1 and B levels). It would be useful to evaluate whether the relationship between statin therapy and new-onset diabetes is mediated via these changes in lipids, or CRP or other biomarkers, and whether the relationship between statin therapy and new-onset diabetes is independent of other risk determinants.

10.3.2 Study-2: Outcomes associated with glucose changes and incident diabetes

In this study, I have shown that antihypertensive-induced glycaemic (and glucose) changes are associated with a progressively increasing risk of the cardiovascular events and death. However, critics can still argue that those who developed in-trial diabetes in ASCOT-BPLA did not have a significant association with the adverse cardiovascular outcomes evaluated. I have previously discussed this issue (see section 7.7.3), and have argued that the lack of such a significant relationship, for each stratum of the glycaemic category (except pre-existing diabetes), is because of the lack of power for such comparisons. We now have access to 11-

year mortality follow-up data on all 8,999 UK patients randomised in the ASCOT-BPLA trial. It is therefore possible for us to use the long-term mortality data to re-evaluate the relationship between the in-trial glycaemic category and all-cause mortality. This new additional analysis will add substantially to the findings of the study to date.

10.3.3 Study-3: The metabolic syndrome and the cardiovascular outcomes

I have discussed in section 8.7.4 that it is likely (based on the findings of this study) that the observed relationship between the metabolic syndrome and all-cause mortality in my analyses is driven by a greater risk of cancer-associated mortality among those with the metabolic syndrome. To extend this hypothesis further, we have developed two new projects. First, we have now cleaned and developed the ASCOT-BPLA database to list all cancer-related mortality, and incident cancer among randomized patients in ASCOT-BPLA. It will now be possible for us to explore whether the metabolic syndrome is an independent predictor for cancer mortality. Second, we have compiled all reported findings to date on the association of the metabolic syndrome and incident cancer. We plan to do a systematic review/meta-analyses to conclusively support (or refute) our hypothesis developed on the basis of the findings of this study.

10.3.4 Study-4: The metabolic syndrome and new-onset diabetes

In this analysis, I have used a relatively novel statistical technique to evaluate an on-going controversy, regarding the usefulness of the metabolic syndrome as compared with IFG in predicting the risk of new-onset diabetes. This technique can be used in other cohorts, to confirm or refute these findings, not only among hypertensive populations, but also in other risk groups. More importantly, I have found that the metabolic syndrome is an independent predictor of the development of new-onset diabetes, even after adjusting for its constituent

components, and other determinants of new-onset diabetes. Whilst this finding is important to establish the clinical utility of the metabolic syndrome, it also brings up a basic question about what is driving this finding. It is possible that this apparent relationship could be explained on the basis of other confounding relationships that patients with metabolic syndrome may have, such as an association of the metabolic syndrome with the non-alcoholic steatohepatitis; or there may be some other basic mechanistic issues involved. We have planned a series of studies on biomarkers (including Vitamin D, apolipoprotein-A and B, CRP levels) that may further improve our understanding on the latter issue, whilst, the evaluation of the relationship between the levels of liver enzymes among patients with and without metabolic syndrome, and the risk of new onset diabetes is planned and will provide more information regarding the former.

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Appendix

Publications

Determinants of New-Onset Diabetes Among 19,257 Hypertensive Patients Randomized in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm and the Relative Influence of Antihypertensive Medication

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ON BEHALF OF THE ANGLO-SCANDINAVIAN CARDIAC OUTCOMES TRIAL (ASCOT) INVESTIGATORS

OBJECTIVE — The purpose of this study was to determine the baseline predictors of new-onset diabetes (NOD) in hypertensive patients and to develop a risk score to identify those at high risk of NOD.

RESEARCH DESIGN AND METHODS — Among 19,257 hypertensive patients in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA) who were randomly assigned to receive one of two antihypertensive regimens (atenolol ± thiazide or amlodipine ± perindopril), 14,120 were at risk of developing diabetes at baseline. Of these, 1,366 (9.7%) subsequently developed NOD during median follow-up of 5.5 years. A multivariate Cox model was developed to identify the independent predictors of NOD and individual risk scores.

RESULTS — NOD was significantly associated with an increase in baseline fasting plasma glucose (FPG), BMI, serum triglycerides, and systolic blood pressure. In contrast, amlodipine ± perindopril in comparison with atenolol ± thiazide treatment (hazard ratio 0.66 [95% CI 0.59–0.74]), high HDL cholesterol, alcohol use, and age >55 years were found to be significantly protective factors. FPG was the most powerful predictor with risk increasing by 5.8 times (95% CI 5.23–6.43) for each millimole per liter rise >5 mmol/l. The risk of NOD increased steadily with increasing quartile of risk score, with a 19-fold increase (95% CI 14.3–25.4) among those in the highest compared with those in the lowest quartile. The model showed excellent internal validity and discriminative ability.

CONCLUSIONS — Baseline FPG >5 mmol/l, BMI, and use of an atenolol ± diuretic regimen were among the major determinants of NOD in hypertensive patients. The model developed from these data allows accurate prediction of NOD among hypertensive subjects.

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Abbreviations: ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; BPLA, Blood Pressure Lowering Arm; FPG, fasting plasma glucose; NOD, new-onset diabetes; SBP, systolic blood pressure.

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Observational data suggest that hypertension is a risk factor for type 2 diabetes (1); hence, the two conditions frequently coexist. The increased propensity of the hypertensive population to develop diabetes is variably affected by different classes of antihypertensive medication. Recently, results of a network meta-analysis, using data from 22 clinical trials comprising 143,153 participants who did not have diabetes at randomization, suggested that the association between antihypertensive agents and incident diabetes is lowest for angiotensinogen receptor blockers and ACE inhibitors followed by calcium channel blockers and placebo, with β-blockers and diuretics increasing risk (2). The diabetogenicity of β-blockers and diuretics is consistent with their adverse impact on blood glucose levels, which has been reported for several decades (3–5). In contrast with the adverse effects of diuretics (3,6,7) and β-blockers (8) on the incidence of new-onset diabetes (NOD) in randomized trials, the bulk of trial evidence suggests that drugs that block the renin-angiotensin system exert a protective role against the development of NOD (2,9,10). These differential effects have influenced recommendations for antihypertensive drug sequencing contained in British guidelines (11 12), whereas the extensive use of β-blockers and diuretics, often in combination, continues worldwide, in part because of controversy regarding whether there is any cardiovascular toll associated with antihypertensive agent–associated incident diabetes (13–16).This controversy notwithstanding, little is known about the other baseline predictors of NOD in hypertensive populations and the importance of antihypertensive therapy relative to these variables.

Because NOD was a predefined tertiary end point of the Blood Pressure-Lowering Arm of the Anglo-Scandinavian

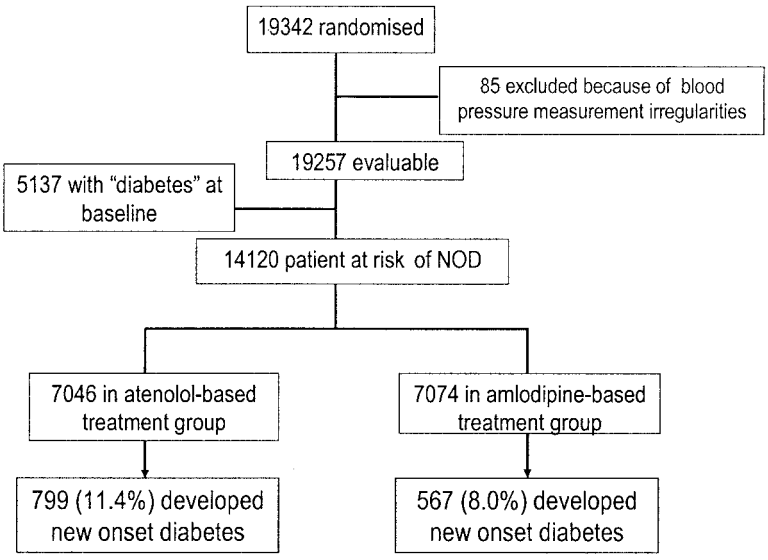


Figure 1—*NOD development according to the randomized treatment group in ASCOT-BPLA Trial.*

Cardiac Outcomes Trial (ASCOT-BPLA) (17,18), its database provides an excellent opportunity to evaluate baseline predictors for development of NOD among a large hypertensive population.

RESEARCH DESIGN AND METHODS

— Details of the methods used and the main results of the ASCOT-BPLA trial have been described previously (17,18). In brief, 19,257 hypertensive patients, aged 40–79 years, with ≥3 cardiovascular risk factors but without any previous coronary heart disease were randomly assigned using a prospective randomized open blinded end points design to receive one of two antihypertensive regimens: atenolol with the addition of a thiazide diuretic as required (atenolol-based regimen) or amlodipine with the addition of perindopril as required (amlodipine-based regimen) to reach blood pressure targets. Subsequently, these patients were followed up with fasting blood samples obtained at 6 months, 12 months, and annually thereafter.

Definitions

For the purposes of these analyses, patients were considered to potentially have "diabetes at baseline" if they satisfied any one of the following three sets of criteria:

1. Fasting plasma glucose (FPG) ≥7mmol/l or random glucose ≥11.1 mmol/l at randomization or screening visits.
2. Self-reported history of diabetes and receiving drug or dietary therapy for diabetes.
3. Presence of both impaired fasting glucose (>6 and <7 mmol/l) and glycosuria at randomization or screening visits. This criterion was chosen to avoid misclassification of such people as nondiabetic at baseline when full investigation with an oral glucose tolerance test may have revealed diabetes.

Individuals included in one or more of these three groups were therefore excluded from the population considered to be at risk of developing NOD in these analyses. Development of diabetes (NOD) during follow-up was determined on the basis of the 1999 World Health Organization criteria (19).

Statistical methods

STATA 9 software was used for all statistical analyses. The impact on the development of NOD of demographic, clinical, and laboratory data at baseline was assessed using the Cox proportional hazards model. Approximately 10% of subjects at baseline had nonfasting values of either triglycerides or glucose or both and were excluded for the purpose of our main analysis.

Baseline characteristics among those who developed NOD were compared with characteristics of those who did not. For each of the baseline characteristics, a univariate Cox model was used to estimate the hazard (risk) ratio (HR) and 95% CI for development of NOD.

Multivariate Cox regression models were developed using forward stepwise selection ($P < 0.05$ for inclusion) with age, sex, and randomized blood pressure treatment group as prespecified covariates in all models. All baseline variables were considered for inclusion in the multivariate model. Three continuous variables, viz., age, FPG, and BMI showed some evidence of nonlinearity at extreme values. However, these were retained as continuous variables in the model with appropriate cutoff values to account for nonlinearity. Three multivariate Cox models were built: model 1 including all 12,692 patients with known values (1,212 cases of NOD); model 2 including patients with known values who were randomly assigned to the atenolol-based treatment group (n = 6,321, cases = 705); and model 3 including patients with known values who were randomly assigned to the amlodipine-based group (n = 6,371, cases = 507) .

Model 1 was taken forward as the primary model to develop a risk score and to test any prespecified interactions between the treatment groups and other variables. The risk score for each patient was calculated from the primary model by summing the products of the coefficients derived from the primary model and the actual values of the variables in the model. The distribution of risk scores was then divided into quartiles of increasing risk, and calibration of the model was evaluated by comparison of the plots of the actual and predicted outcomes. Bootstrap resampling (100 repetitions) was used to assess the internal validity of the primary model.

RESULTS

— Of 19,257 hypertensive patients randomly assigned to ASCOT-BPLA, 14,120 were considered to be at risk of developing NOD at baseline (Fig. 1). Of these, 1,366 subsequently developed NOD during an accumulated follow-up of 73,425 years (median follow-up 5.5 years; incidence rate 18.6 per 1,000 patient-years).

Baseline characteristics

Baseline characteristics in the at-risk population were well matched among those randomly assigned to the two blood pressure–lowering regimens (Table 1). In each of the two treatment groups those who developed diabetes were also much more likely to be younger with higher BMI, FPG, pulse rate, diastolic blood pressure, and serum triglyceride levels

Table 1—*Baseline characteristics in the at-risk population by treatment group and development of NOD*

Baseline characteristics	Atenolol-based regimen			Amlodipine-based regimen		
	Total	Developed diabetes	*P* value*	Total	Developed diabetes	*P* value
n	7,046	799		7,074	567	
Age (years)	62.8 ± 8.6	61.5 ± 8.3	<0.001	62.9 ± 8.5	61.9 ± 8.2	0.006
Male sex (%)	77.9	79.9	0.156	78.2	81.8	0.028
European (%)	96.6	97.1	0.589	96.6	95.9	0.569
BMI (kg/m^2)	28.2 ± 4.3	30.3 ± 4.5	<0.001	28.2 ± 4.4	30.1 ± 4.6	<0.001
Current smoker (%)†	69.7	71.1	0.354	70.1	75.5	0.003
Alcohol intake (units/week)	8.3 ± 11.9	8.2 ± 11.3	0.72	8.4 ± 11.8	8.1 ± 10.7	0.445
Family history of early CAD (%)	30.8	33.2	0.123	30.7	28.9	0.338
History of previous stroke or TIA (%)	11.8	8.9	0.006	11.6	11.5	0.904
History of previous PVD (%)	6.3	6.4	0.962	6.2	6.0	0.841
Presence of LVH (%)	22.8	20.4	0.083	22.7	22.1	0.697
Presence of microalbuminuria (%)	61.8	66.7	0.002	61.2	64.6	0.084
Triglyceride-to-HDL ratio ≥6 (%)	24.3	31.2	<0.001	24.6	28.8	0.017
Total cholesterol (mmol/l)	6.0 ± 1.1	5.9 ± 1.1	0.06	6.0 ± 1.1	5.9 ± 1.1	0.03
HDL (mmol/l)	1.3 ± 0.4	1.2 ± 0.3	<0.001	1.3 ± 0.4	1.2 ± 0.3	<0.001
Triglycerides (mmol/l)‡	1.8 ± 0.9	2.2 ± 1.1	<0.001	1.8 ± 1.0	2.1 ± 1.1	<0.001
FPG (mmol/l)‡	5.4 ± 0.7	5.9 ± 0.6	<0.001	5.4 ± 0.7	5.9 ± 0.7	<0.001
Number of cardiovascular risk factors (cf. 3 risk factors)						
4 risk factors (%)	31.2	32.8	0.008	31.1	33.5	0.016
>4 risk factors (%)	12.8	15.6		12.5	15.3	
History of previous antihypertension drug (%)	79.8	80.4	0.66	79.2	79.7	0.754
Non-CAD concomitant medication (%)	57.7	61.8	0.012	55.8	57.9	0.295
SBP (mmHg)	163.6 ± 18.0	164.6 ± 18.3	0.107	163.8 ± 18.0	165.5 ± 18.3	0.017
DBP (mmHg)	95.4 ± 10.3	96.2 ± 10.8	0.019	95.5 ± 10.3	96.7 ± 10.6	0.007
Heart rate (beats/min)	70.9 ± 12.3	72.5 ± 12.5	<0.001	71.1 ± 12.5	73.5 ± 13.4	<0.001

Data are % or mean ± SD. n = 14,120. *Comparison between those who developed diabetes and those who remained nondiabetic for each of the antihypertensive treatment groups at the end of follow-up: χ^2 or t test, whichever was applicable. †Including those who smoked within 1 year. ‡Of 14,210 at-risk patients, 1,428 (10.1%) patients in all had nonfasting values of either triglycerides (n = 1,392: atenolol-based treatment n = 705 and amlodipine-based treatment n = 687) or FPG (n = 1,427: atenolol-based treatment n = 725 and amlodipine-based treatment n = 702) or both. CAD, coronary artery disease; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; PVD, peripheral vascular disease; TIA, transient ischemic attack.

and lower HDL cholesterol levels compared with those who remained nondiabetic. However, some differences were apparent between those who did and did not develop diabetes in each of the two blood pressure–lowering treatment groups, e.g., prevalence of current smoking.

Risk factors for the development of diabetes

On univariate analysis (online appendix Table A [available at http://dx.doi.org/10.2337/dc07-1768]), patients assigned to the amlodipine-based regimen were 31% less likely to develop NOD than those assigned to the atenolol-based regimen (HR 0.69 [95% CI 0.62–0.77]), and for each unit rise in HDL cholesterol or total cholesterol the risk of NOD fell by 61 and 8%, respectively. In contrast, for each 5-unit rise in BMI or 10 mmHg rise in baseline systolic blood pressure (SBP) the risk of NOD increased by 42 and 6%, respectively. The presence of microalbuminuria, >3 cardiovascular risk factors, and higher serum triglyceride levels, diastolic blood pressure, and heart rate at baseline were among other notable and significant risk factors for NOD. However, the largest impact on risk of NOD was that induced by FPG level, which was associated with a >5-fold increase in risk for each 1 mmol/l increase.

On multivariable analysis (model 1; n = 12,692), higher levels of FPG, BMI, serum triglyceride, SBP, and concomitant use of noncardiovascular medications were found to be significant risk factors for NOD at baseline. In contrast, amlodipine-based treatment (HR 0.66 [95% CI 0.59–0.74]), higher total and HDL cholesterol levels, alcohol use, and age >55 were found to be significantly protective factors. FPG was again the most powerful predictor with risk increasing by 5.8 times (95% CI 5.23–6.43) for each 1 mmol/l rise >5 mmol/l. Risk increased by 49 and 12% for each 5-unit increase in BMI (up to 35 kg/m^2) and 1 mmol/l increase in serum triglyceride levels, respectively, whereas randomization to amlodipine-based treatment and an increase in baseline HDL by 1 mmol/l reduced the risk by 34 and 28%, respectively (Table 2).

On multivariable analysis based on treatment allocation, the predictors for NOD among those randomly assigned to atenolol-based (model 2) and amlodipine-based (model 3) treatment groups were essentially similar to those of the primary model; however, some differences were apparent (online appendix Table B). For example, although FPG, BMI, total cholesterol, SBP, and age were significant predictors in both blood pressure treatment groups, a raised serum triglyceride

Table 2—*Primary multivariate Cox proportional hazard regression model for the development of NOD (model 1)*

Baseline characteristics	HR (95% CI)	β-Coefficient	*z* score*	*P* value	Contribution to risk score
FPG (per mmol/l >5 mmol/l)†	5.8 (5.24–6.43)	1.758	33.55	<0.001	If FPG ≤5 mmol/l add 8.79 to the score, for FPG >5 mmol/l multiply the value with coefficient, and add
BMI (per 5 units)‡	1.49 (1.38–1.62)	0.399	9.73	<0.001	If BMI <35 kg/m^2 multiply the β-coefficient with BMI/5 and add, and for those with BMI ≥35 m/kg^2 add 2.814
Amlodipine-based regimen§	0.66 (0.59–0.74)	−0.412	−7.05	<0.001	Subtract β-coefficient if yes
Triglycerides (per mmol/l)	1.12 (1.07–1.17)	0.109	4.70	<0.001	Multiply β-coefficient with the value of triglyceride, and add
SBP (per 10 mmHg)‖	1.07 (1.04–1.1)	0.067	4.19	<0.001	Multiply the coefficient with SBP/10, and add
Total cholesterol (per mmol/l)	0.89 (0.84–0.94)	−0.118	−3.97	<0.001	Multiply the coefficient with total cholesterol value and subtract
Use of non-CAD medication (yes/no)	1.25 (1.11–1.40)	0.22	3.69	<0.001	Add β-coefficient if yes
HDL cholesterol (per mmol/l)	0.72 (0.58–0.89)	−0.329	−3.07	0.002	Multiply the β-coefficient with HDL value and subtract
Age >55 (per 5 years)¶	0.94 (0.90–0.98)	−0.061	−2.77	0.006	If age ≤55 subtract 0.671 from score, and if age >55 multiply β-coefficient by age/11, and subtract
Alcohol intake (units/week)	0.99 (0.99–1.00)	−0.006	−2.38	0.017	Multiply β-coefficient with units/week, and subtract
Male sex	0.98 (0.84–1.14)	−0.025	−0.31	0.75	Subtract β-coefficient if yes

*Irrespective of sign, it indicates strength of association and relative influence. Those with negative signs indicates protective influence in this model. †All those with FPG ≤5 mmol/l were given the same risk; HR is from every subsequent 1 mmol/l rise. ‡All those with BMI ≥35 kg/m^2 were given the same risk as those with BMI = 35 kg/m^2; HR is for every 5 kg/m^2 rise in those with BMI ≤35 at baseline. §Compared with those receiving the atenolol-based regimen. ‖HR for every 10 mmHg rise in SBP. ¶All those aged ≤55 were given the same risk; HR is for every subsequent 5-year increase. CAD, coronary artery disease.

level was a major predictor only among those randomly assigned to the atenolol-based regimen (HR 1.24 [95% CI 1.17–1.32]). Conversely, raised HDL cholesterol (0.55 [0.51–0.75]), alcohol intake, baseline heart rate, and smoking were significant predictors only among those randomly assigned to the amlodipine-based regimen. However, when these differences between the two treatment groups were evaluated in the primary Cox model, there was no strong evidence of a significant interaction between allocated drug treatment and baseline triglyceride ($P = 0.09$, after excluding an outlier), smoking ($P = 0.09$), HDL cholesterol ($P = 0.75$), alcohol intake ($P = 0.25$), and baseline heart rate ($P = 0.13$). Of note, among these potential interactions only that between treatment allocation and serum triglyceride was prespecified in the statistical analysis plan.

Risk scores

The β-coefficients, *z* scores, and *P* values of each of the baseline variables used in the risk score are shown in Table 2. Larger values of the *z* score (irrespective of the sign) indicate the strength of the variables as a predictor. Figure 2*A* illustrates the increasing risk of NOD with an increase in risk quartile using Kaplan-Meier plots. Compared with the lowest risk quartile, patients in the highest quartile had a 19-fold increase in risk of NOD (HR 19.04 [95% CI 14.27–25.41]). There was no evidence of an interaction between risk quartile and antihypertensive treatment group when the risk score was calculated without allocated treatment. Figure 2*B* shows that allocation to the amlodipine-based regimen reduced the risk to the same extent in each risk quartile. The model had excellent internal validity and reasonably strong discriminative ability (Harrell's c index of 0.80) (appendix Figure A).

CONCLUSIONS — These analyses of baseline measures among >14,000 hypertensive patients considered to be free of diabetes at the start of the ASCOT-BPLA trial (17) indicate that randomization to antihypertensive treatment, low HDL cholesterol, and raised BMI, serum triglycerides, SBP, and particularly FPG are important determinants of NOD. The relative importance of each of the determinants of incident diabetes is implied by an increase in *z* score regardless of its sign (Table 2). The risk model thus developed allows the accurate prediction of NOD over a 5-year period for an individual.

The >5-fold increase in risk of NOD for each 1 mmol/l rise in FPG reported in this article is larger than that observed in most (8–10) but not all (20) earlier reports. In contrast with some earlier studies (8), the exclusive use of fasting glucose and unambiguous, robust definitions may have contributed to the large effect size observed. The putative effects of FPG were linear and apparent from 5 mmol/l onward, a threshold for incremental risk that has previously been identified (21). The risk attenuated progressively through the trial with the effect reducing from a HR of 9.72 (95% CI 8.06–11.72) during the first year to 1.88 (95% CI 1.25–2.83) after ≥5 years of follow-up. This trend may reflect the attrition of subjects susceptible to development of NOD.

These results are consistent with most other analyses of trials using antihypertensive agents in finding that a regimen based on a calcium channel blocker to which an ACE inhibitor was added was associated with significantly less NOD than a regimen based on a β-blocker to which a diuretic was usually added (3–9). Indeed, the randomization to amlodip-

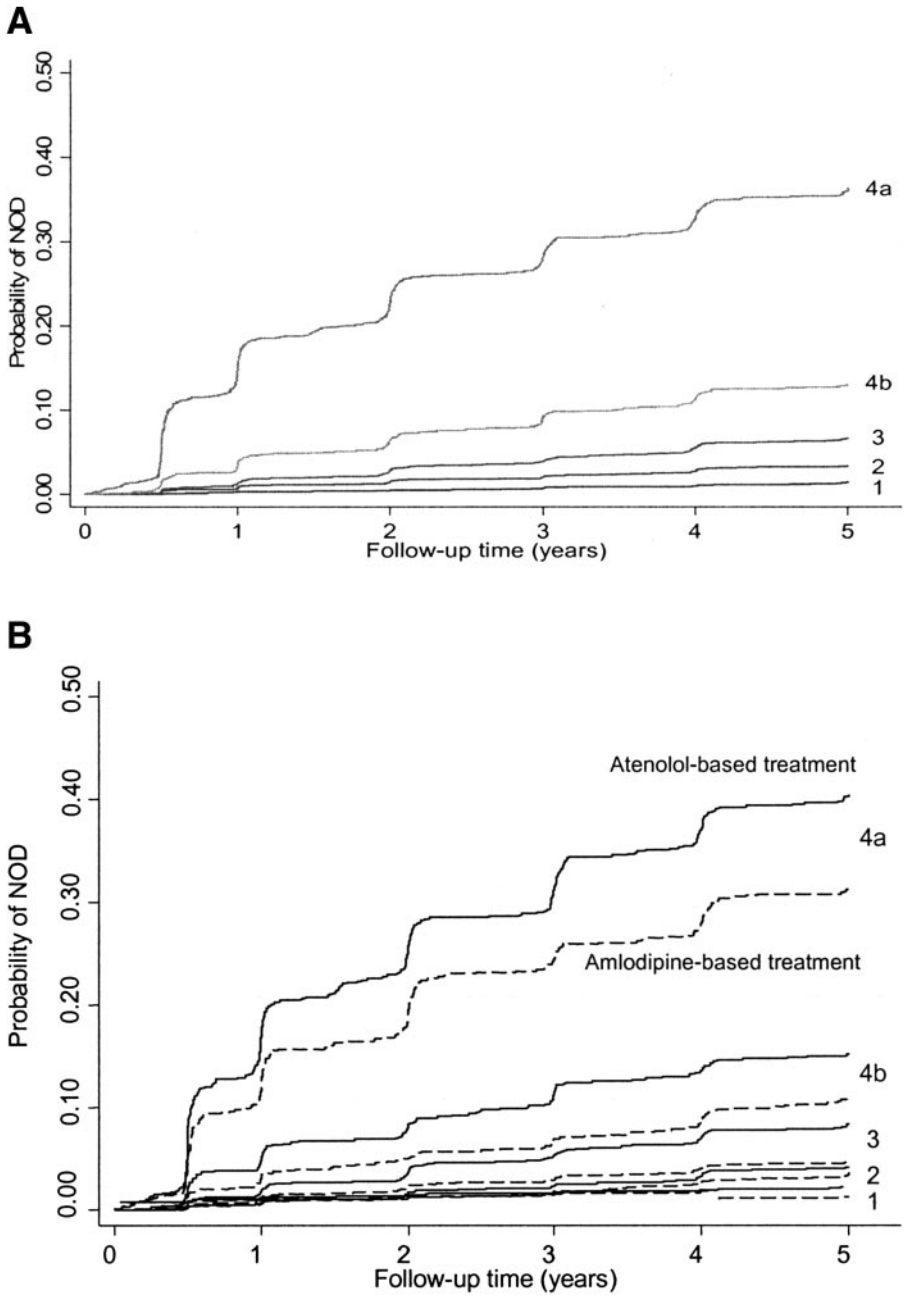


Figure 2—A: *Kaplan-Meier graphs of incidence of NOD stratified by quartiles of risk score (*) with the uppermost quartile divided equally into two as 4a and 4b (cutoff at 5-year follow-up). *HRs (95% CI) for each of the risk quartile with the first quartile as the reference group: second quartile 2.5 (1.8–3.5); third quartile 5.0 (3.7–6.9); and fourth quartile 19.0 (14.3–25.4) [4b quartile 9.72 (7.14–13.25) and 4a quartile 30.31 (22.64–40.57)]. Corresponding risk scores for each of the quartile groups are as follows: first quartile <10.26; second quartile 10.26–10.85; third quartile 10.86–11.62; and fourth quartile ≥11.63 (4b quartile 11.63–12.29 and 4a quartile ≥12.30).* B: *Kaplan-Meier graph of incidence of NOD stratified by quartile of risk score and the blood pressure–lowering treatment (cutoff at 5-year follow-up).* ——, *atenolol-based treatment;* – – –, *amlodipine-based treatment.*

ine-based regimen emerged as the strongest protective factor of the variables evaluated. The finding that the differential risk of NOD between the two antihypertensive regimens remained the same irrespective of baseline risk (Fig. 2*B*), contrasts with results in the Captopril Prevention Project (CAPPP) Trial (10) but is in keeping with findings in the Losartan Intervention For Endpoint (LIFE) trial (8).

Increasing age was an independent protective factor for the development of diabetes that contrasts with some (10) but not all trial results (22) and is consistent with several observational studies (23,24). These studies have shown that although the prevalence continues to increase with age, the incidence of diabetes plateaus in elderly individuals.

Our study is consistent with several other observational studies in finding alcohol intake to be protective (25,26) and increased triglycerides to be a putative risk factor for NOD (27,28). Somewhat counterintuitively, raised total cholesterol appeared to be protective in these analyses, although this finding too has been reported in other trials (8–10). The increased risk associated with concomitant use of ≥1 noncardiovascular medications, including some that are known to be diabetogenic, may reflect or be a marker of chronic ill health.

The performance of several previous analyses relating to NOD has been subject to methodological criticism (9,29), such as being post hoc analyses, using different definitions of NOD, and using nonfasting and/or whole blood glucose values, but most of these criticisms do not apply to the current study design and analyses. This study demonstrates the relative importance of antihypertensive medications, after FPG and BMI, and suggests that their judicious use will benefit all regardless of risk category. These analyses allowed the development of a relatively simple risk score for predicting NOD. This score appears to have excellent internal validity and pending further external validation, could be potentially useful in routine clinical practice to guide not just prescribing of antihypertensive medication but other interventions aimed to prevent NOD.

Given evidence from previous trials (2,9,30), it seems likely that the differential effect of the two antihypertensive regimens used in ASCOT-BPLA on NOD is a composite of the adverse effects on risk produced by atenolol and thiazide, plus the protective effects of perindopril, with amlodipine probably playing a neutral role. However, recent analyses of the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial (31) in contrast to the Heart Outcomes Prevention Evaluation (HOPE) trial (32) did not show a significant protective effect of ramipril against NOD. Nevertheless, 2-h glucose levels were significantly improved among those taking ramipril in the DREAM trial,

which, allied with the 9% nonsignificant reduction in NOD, suggests that the apparently "negative" findings in the DREAM trial may reflect inadequate power to detect an effect in too short a time.

Although individuals studied in the ASCOT trial were more representative of the general hypertensive population than those in several other recent trials (6–8,20,30,32), the population was largely Caucasian and male and from the U.K., Ireland, and Nordic countries. Whether and to what extent the findings relate to other ethnic groups requires evaluation in other studies. Furthermore, given the large sample size and hence power of these analyses, the clinical relevance of some of the less significant relationships needs to be considered when the results are interpreted.

Further analyses evaluating the effects of changes in baseline variables (e.g., body weight, blood pressure, and others) throughout the trial are in progress, as are analyses evaluating whether worsening dysglycemia and NOD are associated with worsening cardiovascular outcomes. Although these analyses may inform policy decisions on prescribing for hypertensive patients, the limited power of such analyses with relatively limited follow-up hampers appropriate interpretation of such data and possibly explains earlier conflicting results (14–16).

In summary, the present analyses provide robust evidence that treating hypertensive patients with a regimen based on amlodipine and perindopril compared with a regimen based on atenolol and a thiazide diuretic significantly reduces the risk of NOD such that the number needed to treat 30 patients for just >5 years is required to prevent 1 case of NOD (95% CI 23–42). They further describe a robust, discriminative model, which helps to determine accurately the risk of NOD in hypertensive patients and highlights the relative importance of various other independent predictors such as FPG, BMI, SBP, serum HDL cholesterol, and triglycerides in the development of NOD. Pending further definitive evidence related to cardiovascular morbidity and mortality with antihypertensive-associated incident diabetes, it seems at best unwise, except where compelling indications apply, to use β-blockers and diuretics in combination in preference to other combinations such as a calcium channel blocker plus an ACE inhibitor, particularly because the latter agents have been shown to be more cost-effective (11).

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Metabolic Syndrome, Independent of Its Components, Is a Risk Factor for Stroke and Death But Not for Coronary Heart Disease Among Hypertensive Patients in the ASCOT-BPLA

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OBJECTIVE — To evaluate whether in hypertensive patients the risk of cardiovascular disease is greater in association with the metabolic syndrome (MetS) or the sum of its individual components.

RESEARCH DESIGN AND METHODS — Cox regression analysis models were developed to assess the influence of age, sex, ethnicity, and the individual components of MetS on risk associated with the MetS (using several definitions) of coronary outcomes, stroke, and all-cause mortality.

RESULTS — MetS was significantly associated with coronary outcomes, stroke, and all-cause mortality after adjusting for age, sex, and ethnicity. However, when the model was further adjusted for the individual components, MetS was associated with significantly increased risk of stroke (hazard ratio 1.34 [95% CI 1.07–1.68]) and all-cause mortality (1.35 [1.16–1.58]) but not coronary outcomes (fatal coronary heart disease plus nonfatal myocardial infarction 1.16 [0.95–1.43] and total coronary events 1.06 [0.91–1.24]).

CONCLUSIONS — MetS, independent of its individual components, is associated with increased risk of stroke and all-cause mortality but not coronary outcomes.

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Studies in the recent past evaluating the usefulness of the metabolic syndrome (MetS) have provided equivocal results (1–4). The database from the blood pressure–lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) (5) provides an excellent opportunity to evaluate whether in hypertensive patients the risk of cardiovascular (CV) disease and death is greater in association with the MetS or the sum of its individual components.

RESEARCH DESIGN AND METHODS

— Details of the study design and methods of the ASCOT-BPLA have been described previously (5).

Definitions

BMI >30 kg/m^2 was used instead of waist circumference in defining MetS because waist circumference was not measured in ASCOT-BPLA. The original National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) definition (6) of MetS (ATP 6.1) was considered as the primary definition in these analyses. In addition, the updated NCEP-ATP III (ATP 5.6) (7), International Diabetes Federation (IDF) (8), and two other definitions, ASCOT 6.1 and ASCOT 5.6 (modified from ATP 6.1 and ATP 5.6, respectively, by excluding the "or presence of diabetes" component from the fifth criterion), were also considered. The latter two were included to reduce some of the increased CV risk conferred by the presence of diabetes at baseline.

Outcomes

Fatal coronary heart disease (CHD) plus nonfatal myocardial infarction (MI), total coronary events, stroke, and all-cause mortality were prespecified outcomes.

Statistical analyses

Three separate Cox regression analysis models were developed for each of the prespecified outcomes using the ATP 6.1 definition of MetS: model 1, unadjusted MetS; model 2, adjusted for age, sex, and ethnicity; and model 3, included model 2 plus all the individual components (used as continuous variables where linear) of the MetS. Risk (hazard ratios) associated with all five definitions of the MetS for each of the four prespecified outcomes was compared. Sensitivity assessments, which excluded all subjects with the presence of diabetes (or missing values) at baseline, were done in Cox regression analysis models using the ATP 6.1 definition.

RESULTS

— Of 19,257 hypertensive patients randomized in ASCOT-BPLA, 8,434 (43.8%) had the MetS based on the ATP 6.1 definition.

MetS and rates of coronary and stroke events and death using the ATP 6.1 definition

In model 1, MetS was associated with a significantly increased risk of coronary

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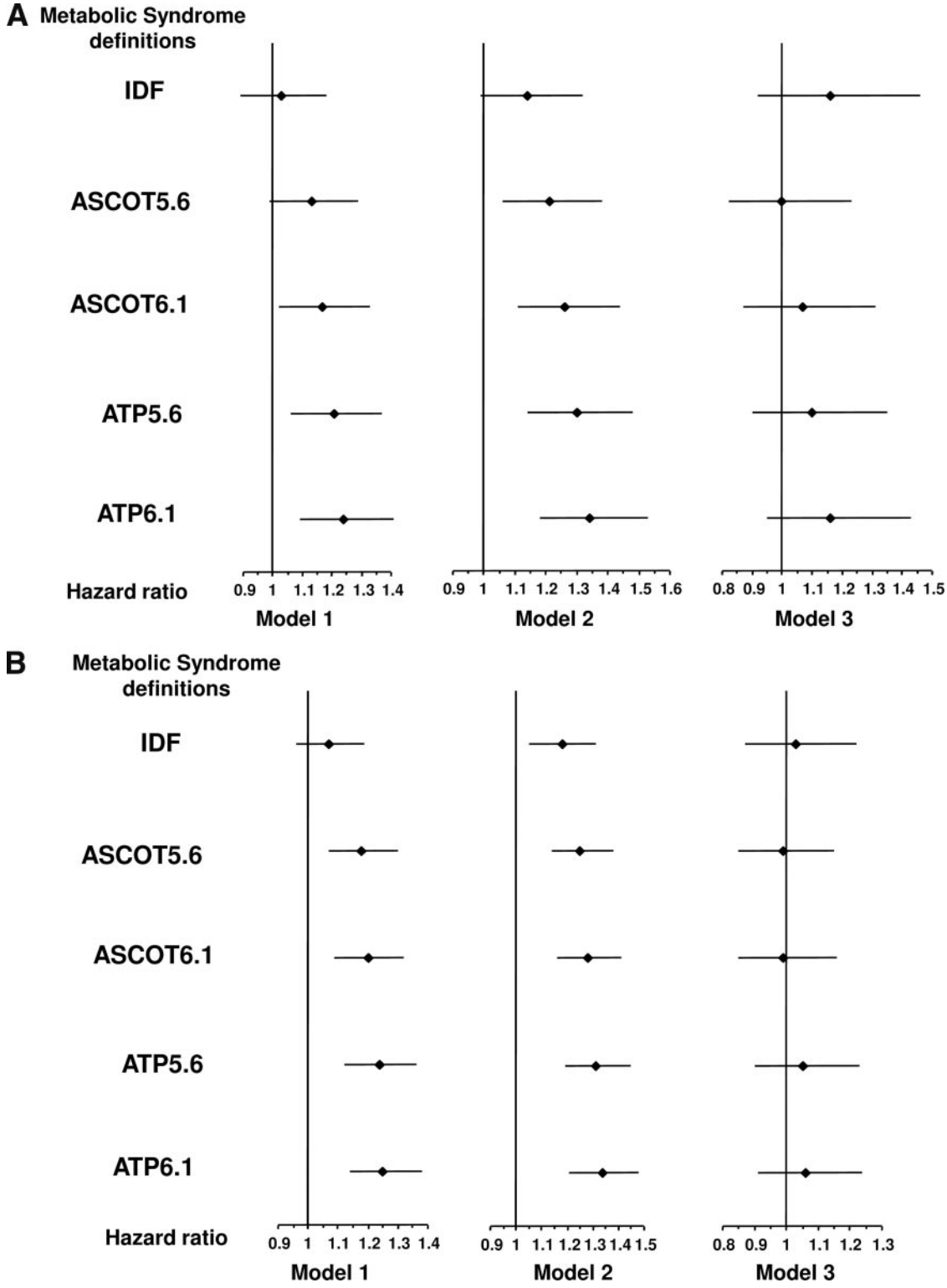
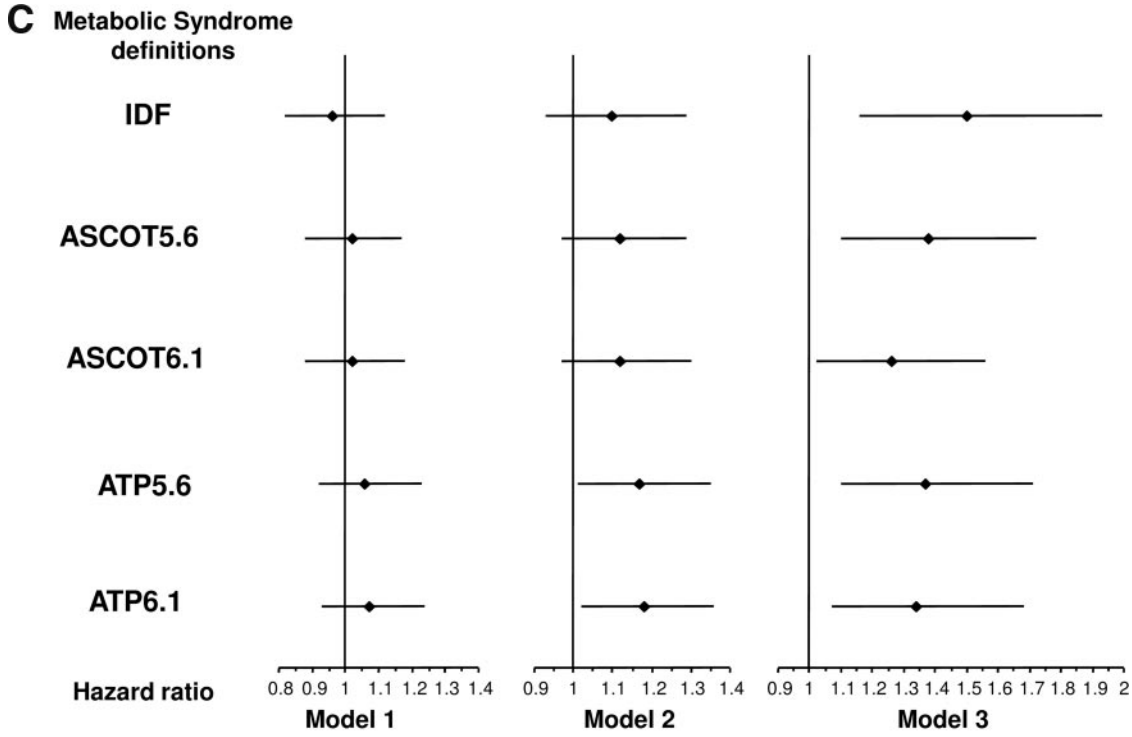


Figure 1—*Different definitions of the MetS and risk of coronary, stroke, and death outcomes.* A*: Risk of fatal CHD (includes death from MI, acute coronary syndrome, or sudden death attributable to ischemic heart disease) and nonfatal MI associated with MetS.* B*: Risk of total coronary events (includes fatal and nonfatal CHD, unstable angina, fatal and nonfatal heart failure) associated with MetS.* C*: Risk of stroke associated with MetS.* D*: Risk of all-cause mortality associated with MetS. Model 1: Univariate MetS. Model 2: Model 1 plus age, sex, and ethnicity. Model 3: Model 2 plus fasting plasma glucose, triglycerides, HDL cholesterol, systolic blood pressure, and BMI.*

events (fatal CHD plus nonfatal MI, hazard ratio [HR] 1.24 [95% CI 1.09–1.41], and total coronary events 1.25 [1.14–1.35]), but was not associated with total stroke (1.07 [0.93–1.24]), or all-cause mortality (1.07 [0.97–1.19]). In model 2, the relationship of the MetS with coronary outcomes became more significant and stronger, and it signifi-



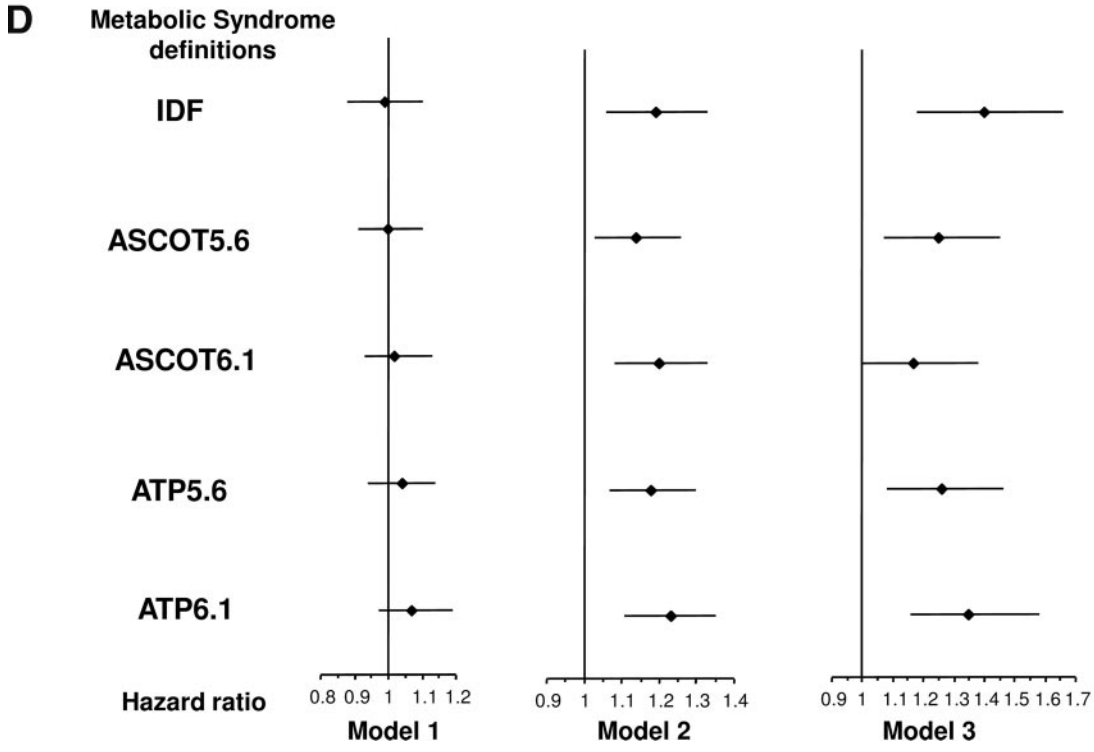


Figure 1—*Continued.*

cantly predicted total stroke (1.18 [1.02–1.36]) and all-cause mortality (1.23 [1.11–1.35]). However, when model 2 was further adjusted for the individual components of the MetS (model 3), the association between MetS and total stroke (1.34 [1.07–1.68]) and all-cause mortality (1.35 [1.16–1.58]) became stronger and remained significant, while the association with coronary outcomes attenuated and became insignificant (fatal CHD plus nonfatal MI 1.16 [0.95–1.43] and total coronary events 1.06 [0.91–1.24]) (see the online appendix available at http://care.diabetesjournals.org/cgi/content/full/dc09-2208/DC1). These relationships remained unchanged on sen-

sitivity analyses after excluding patients with diabetes at baseline.

Different definitions of MetS and coronary and stroke events, and death

The results, for each of the definitions used, showed a consistent trend of the MetS to significantly predict fatal CHD plus nonfatal MI and total coronary events in models 1 and 2 but not in model 3 (Fig. 1*A* and *B*). By contrast, the association between the MetS, regardless of the definition used, with stroke and all-cause mortality was not apparent in model 1 but became increasingly apparent in models 2 and 3 such that in model 3 the results consistently showed the MetS to be an independent predictor of total stroke and all-cause mortality after adjusting for its individual components (Fig. 1*C* and *D*).

CONCLUSIONS — These analyses of 19,257 hypertensive patients suggest that the MetS, independently of its components, is associated with increased risk of stroke and death but not of coronary outcomes.

The lack of any synergy among the individual components of the MetS on the risk of coronary outcomes seen in our analyses is in keeping with findings of some (3,4) but not all previous reports (1,2). To compare our findings with the studies that adjusted for classical confounders, we further adjusted our model 3 for confounders such as smoking, alcohol intake, number of CV risk factors, and randomized antihypertensive regimen, but this did not change the association of the MetS with either fatal CHD plus nonfatal MI (HR 1.10 [95% CI 0.90–1.35]) or total coronary events (1.01 [0.96–1.17]).

The finding of an increased risk of incident stroke associated with the MetS, independent of its constituent components and regardless of the definition used, extends the findings of previous reports (9,10). Given the potential implications of these findings, we further adjusted model 3 to include confounders such as previous history of stroke or transient ischemic attack, number of CV risk factors, alcohol intake, smoking, history of previous antihypertensive therapy, and randomized treatment allocation and found no change in association of the MetS and incident stroke (HR 1.31[95% CI 1.04–1.64]).

None of the previous studies (11,12) have reported on the risk of death associated with the MetS adjusted for all its constituent components. Because in our analyses, the MetS independently of its components was not associated with a significantly increased risk of CV mortality (HR 1.19 [95% CI 0.93–1.53]), this suggests that if the increased risk of all-cause mortality associated with the MetS is true, the increase must be due to non-CV causes. Two-thirds of the 953 non-CV deaths in the ASCOT population were due to cancer, which has previously been found to be associated with the MetS in observational studies (13).

The use of BMI instead of waist circumference in our definition of the MetS is a possible limitation of this study. However, BMI has been used as part of previous widely accepted studies of MetS (11,14) and has been shown to have a comparable predictive capability (15). The major strength of this study is its power to examine several CV outcomes and all-cause mortality while using different definitions of the MetS in the same population.

In summary, our findings suggest that, after adjusting for its individual components, the MetS is associated with increased risk of strokes and all-cause mortality but not coronary outcomes in the hypertensive population.

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A.K.G. researched and analyzed data and wrote the manuscript. N.R.P. contributed to the discussion and reviewed the manuscript. P.S.S. and B.D. reviewed the manuscript.

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Article: Epidemiology

Metabolic syndrome, impaired fasting glucose and obesity, as predictors of incident diabetes in 14 120 hypertensive patients of ASCOT-BPLA: comparison of their relative predictability using a novel approach

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Abstract

Aims To evaluate, in hypertensive patients, whether the metabolic syndrome is a better predictor of new-onset diabetes compared with impaired fasting glucose, obesity or its other individual components alone, or collectively.

Methods Cox models were developed to assess the risk of new-onset diabetes associated with the metabolic syndrome after adjusting for a priori confounders (age, sex, ethnicity and concomitant use of non-cardiovascular medications), its individual components and other determinants of new-onset diabetes. Area under receiver operator curves using the metabolic syndrome or models of impaired fasting glucose were compared, and the ability of these models to correctly identify those who (after 5-years of follow-up) would or would not develop diabetes was assessed.

Results The metabolic syndrome adjusted for *a priori* confounders and its individual components, and further adjusted for other determinants, was associated with significantly increased risk of new-onset diabetes [1.19 (1.00–1.40), $P = 0.05$ and 1.22 (1.03–1.44), $P = 0.02$, respectively]. The discriminative ability of the metabolic syndrome model [area under receiver operating curve: 0.764 (0.750–0.778)] was significantly better than the model of impaired fasting glucose [0.742 (0.727–0.757)] ($P < 0.001$). The metabolic syndrome correctly allocates the risk of new-onset diabetes in a significantly higher proportion of patients (62.3%) than impaired fasting glucose status (37.7%) ($P < 0.001$). The presence of both the metabolic syndrome and impaired fasting glucose were associated with an approximately 9-fold (7.47–10.45) increased risk of new-onset diabetes. Among normoglycaemic patients, the metabolic syndrome was also associated with significantly increased risk of new-onset diabetes, after adjusting for BMI and a priori confounders [1.66 (1.29–2.13)].

Conclusions Both impaired fasting glucose and the metabolic syndrome predict the risk of new-onset diabetes; however, the metabolic syndrome is a better predictor than impaired fasting glucose in assigning the risk of new-onset diabetes in hypertensive patients, and among those with normoglycaemia.

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Keywords diabetes, hypertension, impaired fasting glucose, metabolic syndrome, obesity

Abbreviation ASCOT-BPLA, Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure-Lowering Arm

Introduction

Previous studies have shown that the metabolic syndrome, impaired fasting glucose and obesity are all independently associated with an increased risk of the development of new-onset diabetes [1–6]. As both impaired fasting glucose and obesity are included amongst the clustering of metabolic components that define the metabolic syndrome, the clinical utility of the metabolic syndrome, independently of its constituent components, is uncertain [3,7–9]. A recent study has shown that a single fasting glucose measurement alone can be at least as effective (and efficient) as the risk construct of the metabolic syndrome in predicting future risk of new-onset

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diabetes [10]. This finding is in contrast to the data from other studies which have shown that the metabolic syndrome predicts new-onset diabetes more effectively than impaired fasting glucose or glucose intolerance alone [11,12].

Given a rapidly increasing prevalence of diabetes, fuelled by the obesity epidemic, it is vital that the relative importance of risk prediction tools such as impaired fasting glucose (or pre-diabetes), obesity and the metabolic syndrome are evaluated in different high-risk populations, such as hypertensive patients. Moreover, it is important to ascertain whether the diagnosis of the metabolic syndrome adds value beyond that contributed by the sum of its individual components; not only in terms of associated excess risk, but more importantly, the numbers (or proportions) of individuals correctly assigned to respective risk categories, because the latter enables cost-effective targeting of strategies designed to prevent new-onset diabetes.

The database of the blood pressure-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA) [13] provides an excellent opportunity to evaluate these questions in hypertensive patients.

Patients and methods

Details of the design and methods of ASCOT-BPLA have been published previously [13]. Briefly, 19 257 hypertensive patients, aged 40–79 years, with three cardiovascular risk factors, but without any active or previous coronary heart disease, were randomized to receive one of two blood pressure-treatment regimens: atenolol ± thiazide or amlodipine ± perindopril.

Definitions

For the purpose of this analysis, all those with pre-existing diabetes (self-reported and receiving drug or dietary therapy) or those who were 'deemed' likely to have diabetes at baseline (based on a single recording of fasting plasma glucose ≥ 7.0 mmol/l or random glucose ≥ 11.1 mmol/l or the presence of a combination of fasting plasma glucose ≥ 6.1 mmol/l and glycosuria at the randomization or screening visit) (n = 5137) were excluded to leave a residual population 'at risk' of diabetes. The updated National Cholesterol Education Program–Adult Treatment Panel III (NCEP-ATP III) [14] criteria were used to identify the presence of the metabolic syndrome at baseline; however, BMI > 30 kg/m^2 was used instead of waist circumference, as waist circumference was not measured in ASCOT-BPLA. Development of diabetes during follow-up (the primary outcome of this analysis and a pre-specified outcome of the ASCOT trial) was diagnosed on the basis of the 1999 World Health Organization (WHO) criteria [15].

Statistical analyses

A Cox regression model was developed to assess the risk of development of new-onset diabetes associated with the metabolic syndrome, after adjusting for a priori confounders: age, sex, race and concomitant use of non-cardiovascular medications (a marker of the presence of non-cardiovascular chronic diseases) (model 1). The relative influence of each component of the metabolic syndrome on the risk (hazard ratio) associated with the metabolic syndrome was assessed by entering them separately to model 1, and hence creating five new models. Harrell's C-statistics, likelihood-ratio χ^2 (LR-χ)-statistic and Bayesian information criterion (BIC) were calculated to compare the influence of each metabolic component in these new models and, thereafter, these individual metabolic components were progressively added (in descending order of relative importance) to model 1 to finally develop a model adjusting for a priori confounders and all individual components of the metabolic syndrome (model 2). In model 3, we further adjusted model 2 for other determinants of new-onset diabetes (treatment allocation, alcohol intake and total cholesterol) [16]. All components were used as continuous variables, except when found to be non-linear. Proportional hazard assumptions were checked for all models.

The area under receiver operator curves obtained from the models, adjusting for a priori confounders and using impaired fasting glucose (defined as fasting plasma glucose < 5.6 mmol/l) or the metabolic syndrome, were compared. The ability of the two models to identify correctly those who, after 5-years of follow-up, would develop diabetes or not was also assessed by using a modification of integrated discrimination improvement (IDI) [17]. Accordingly, we assigned 5-year-risks (probabilities) of developing diabetes predicted by each of the two models to an individual and calculated their respective risk difference (5-year risk assigned by the impaired fasting glucose model minus that assigned by the metabolic syndrome model). We further stratified the calculated risk differences of subjects with their observed 5-year outcome status (developed diabetes or not). If the observed status was development of diabetes, the model which assigned (predicted) more risk was better (i.e. predicting risks closer to the observed outcome), whereas, for a subject with non-diabetic status (after 5 years), the model assigning a lower baseline risk would be better at predicting the risk of new-onset diabetes. Similar analyses were also performed, stratified by glycaemic status (normoglycaemic or impaired fasting glucose) at baseline.

Results

Approximately 38.6% (5445) of 14 120 'at-risk' patients had the metabolic syndrome at baseline. Of these, 16.8% (898) developed new-onset diabetes [incidence rate: 33.3 (95% confidence interval 31.1–35.5) per 1000 person-years] during a median follow-up of 5.5 years (interquartile range 5.0–6.0 years; total follow-up duration of 73 425 person-years) as compared with 5.4% (468) of those without the metabolic syndrome at baseline [10.1 (9.2–11.0) per 1000 person-years] (see also Supporting Information, Fig. S1).

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The metabolic syndrome, its individual components and the risk of new-onset diabetes

The unadjusted metabolic syndrome was associated with 3.6-fold increased risk of new-onset diabetes. In model 1, the risk of new-onset diabetes associated with the metabolic syndrome, adjusted for a priori confounders, remained the same [hazard ratio 3.63 (3.20–4.11)]. However, inclusion of fasting plasma glucose in model 1 approximately halved the risk of new-onset diabetes associated with the metabolic syndrome [1.87 (1.63–2.13)]. In contrast, the inclusion of triglyceride or HDL cholesterol or systolic blood pressure in model 1 had essentially no impact on the risk of new-onset diabetes associated with the metabolic syndrome. Inclusion of BMI to model 1 reduced the risk of new-onset diabetes associated with the metabolic syndrome to 2.92 (2.13–2.72). When model 1 was adjusted for both fasting plasma glucose and BMI, the risk of new-onset diabetes associated with the metabolic syndrome was 1.45 (1.25–1.68). In model 2 (adjusting for a priori confounders and all individual components of the metabolic syndrome), the risk of new-onset diabetes associated with the metabolic syndrome was reduced further but remained significant [1.19 (1.00–1.40), $P = 0.05$]. In model 3, when other independent determinants of new-onset diabetes were added to model 2, the risk of new-onset diabetes associated with the metabolic syndrome was essentially unchanged [1.22 (1.03–1.44), $P = 0.02$] (Table 1). Based on change in the effect size (hazard ratios) and indices of model discrimination and performance (assessed by C-statistics, likelihood ratio χ-statistic and Bayesian information criterion), fasting plasma glucose was the most influential individual component of the metabolic syndrome contributing to the risk of new-onset diabetes. Thereafter, BMI, systolic blood pressure, serum triglyceride and HDL cholesterol were decreasingly influential.

Relative impact of impaired fasting glucose and the metabolic syndrome on prediction of the risk of new-onset diabetes

Figure 1a shows the predicted and observed 5-year risk of new-onset diabetes, stratified by the presence of impaired

Table 1 Risk (hazards) of the development of new onset diabetes associated with the metabolic syndrome* in Cox models after adjusting for a priori confounders, its individual components and other determinants of incident diabetes

Cox-models†	Hazard ratio (95% CI)	$P > z$	C-statistic**	LR χ-statistic	BIC (in thousands)
Univariate: metabolic syndrome	3.67 (3.24–4.15)	< 0.001	0.66	475	22.15
Metabolic syndrome + a priori confounders‡ (model 1)	3.63 (3.20–4.11)	< 0.001	0.67	496	22.18
Model 1 + a component of the metabolic syndrome					
Model 1 + glucose	1.87 (1.63–2.13)	< 0.001	0.78	1363	21.33
Model 1 + BMI	2.92 (2.54–3.35)	< 0.001	0.69	549	22.14
Model 1 + SBP	3.65 (3.22–4.14)	< 0.001	0.68	516	22.17
Model 1 + triglyceride	3.46 (3.02–3.97)	< 0.001	0.67	499	22.19
Model 1 + HDL cholesterol	3.65 (3.17–4.20)	< 0.001	0.67	496	22.19
Metabolic syndrome + a priori + progressive addition of individual components*					
Model 1 + glucose	1.87 (1.63–2.13)	< 0.001	0.78	1363	21.33
Model 1 + glucose + BMI	1.45 (1.25–1.68)	< 0.001	0.79	1425	21.27
Model 1 + glucose + BMI + SBP	1.46 (1.26–1.70)	< 0.001	0.79	1438	21.27
Model 1 + glucose + BMI + SBP + triglyceride	1.33 (1.13–1.55)	< 0.001	0.79	1449	21.27
Model 1 + glucose + BMI + SBP + triglyceride + HDL-c (model 2§)	1.19 (1.00–1.40)	0.046	0.79	1466	21.26
Model 1 + all individual components of the metabolic syndrome + other determinants of new-onset diabetes (model 3¶)					
Model 2 + treatment allocation, total cholesterol and alcohol intake (model 3)	1.22(1.03–1.44)	0.022	0.80	1540	21.22

*Using updated National Cholesterol Education Treatment Panel III definition.
†After excluding all patients with non-fasting values of glucose and/or serum triglyceride. Total number of patients in the model was 12 692. There were no missing follow-up data.
‡A priori confounders: ethnicity, age, sex and use of non-cardiovascular concomitant medication.
§Adjusted for all its individual components, used as continuous variables except where non-linear.
¶Adjusted in addition for all other independent determinants of the new onset diabetes found separately in a multivariable component Cox-model: treatment allocation; total cholesterol; alcohol intake.
**Harrell's C-statistic.
BIC, Bayesian information criterion; HDL-c, high density lipoprotein cholesterol; LR, likelihood ratio; SBP, systolic blood pressure.

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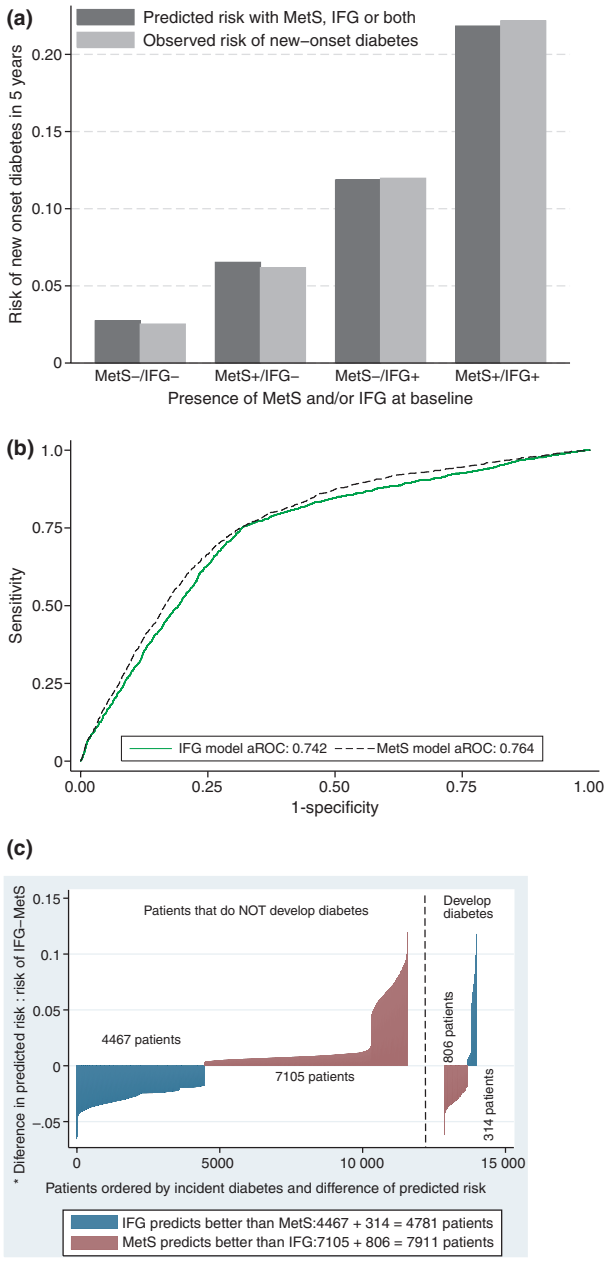


FIGURE 1 Relative impact of impaired fasting glucose (IFG) and the metabolic syndrome (MetS) on prediction of the risk of new-onset diabetes. (a) Predicted and observed risk of new-onset diabetes by baseline presence of the metabolic syndrome or impaired fasting glucose alone and together. (b) Area receiver operator curves (ROC) for models using impaired fasting glucose or the metabolic syndrome, after adjusting for a priori confounders. (c) Differences in predicted risks between the risk predicted by the model using impaired fasting glucose and that using the metabolic syndrome, stratified by the outcome status (presence or absence of diabetes) after 5 years of follow-up. *The risk difference is the 5-year risk of developing diabetes using impaired fasting glucose model minus the risk estimated using the metabolic syndrome model. **Among those who do not develop diabetes during follow-up, the model predicting the lesser 5 years' risk is better among the two models. Similarly, among those who develop diabetes during the 5 years of follow-up, the model predicting the higher 5-year risk is better among the two models.

fasting glucose and the metabolic syndrome. Among those with normoglycaemia or impaired fasting glucose at baseline, the presence of the metabolic syndrome was uniformly associated with a 2-fold increased risk of developing new-onset diabetes. The presence of both the metabolic syndrome and impaired fasting glucose was associated with approximately a 9-fold (7.47–10.45) increased risk of new-onset diabetes. There was no significant interaction between impaired fasting glucose and the metabolic syndrome ($P = 0.11$) and no significant differences between predicted and observed 5-year risks of new-onset diabetes. Figure 1b compares area under receiver operator curves calculated from the two models using impaired fasting glucose or the metabolic syndrome, and after adjusting for a priori confounders. Accordingly, among hypertensive patients, the discriminative ability and performance of the model using the presence of the metabolic syndrome [area under receiver operator curves 0.764 (0.750–0.778)] was significantly better than that using impaired fasting glucose [0.742 (0.727–0.757)] ($P < 0.001$). Figure 1c shows the difference between the predicted risks of developing new-onset diabetes using impaired fasting glucose and the metabolic syndrome model, stratified according to observed outcomes (presence or absence of new-onset diabetes) at 5 years of follow-up. The model using impaired fasting glucose status (presence or absence) in comparison with the metabolic syndrome model correctly allocates higher baseline risks among 28.0% of those who subsequently develop new-onset diabetes within 5 years, and lower risks among 38.6% of those who remained without diabetes at the end of 5 years of follow-up. However, overall, the use of impaired fasting glucose status was significantly worse than the use of the metabolic syndrome at predicting new-onset diabetes status (presence or absence of new-onset diabetes), with 37.7% of subjects accurately assigned the risk (i.e. assigning the risks closer to the observed new-onset diabetes status after 5 years of follow-up) by use of impaired fasting glucose, compared with 62.3% of subjects correctly identified by use of the metabolic syndrome model ($P < 0.001$) (Table 2).

The metabolic syndrome, obesity and risk of new-onset diabetes among normoglycaemic patients

Four per cent (323) of 8124 normoglycaemic patients (fasting plasma glucose < 5.6 mmol/l) at baseline developed new-onset diabetes. Among normoglycaemic patients, the presence of the metabolic syndrome at baseline was associated with a 2.4-fold (1.90 to 2.97) increased risk of new-onset diabetes, after adjusting for a priori confounders (model 1). When model 1 was further adjusted for BMI, the metabolic syndrome was still a significant predictor of risk [1.66 (1.29–2.13)]. There was a threefold (2.25–3.83) increased risk of new-onset diabetes among those with the presence of both the metabolic syndrome and obesity (BMI > 30 kg/m^2) as compared with those without the two factors (Fig. 2).

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Table 2 Net reclassification improvement in models using impaired fasting glucose or the metabolic syndrome after adjusting for a priori confounders

	Observed outcome at 5 years		In how many hypertensive patients does IFG predict better than the metabolic syndrome?†		
Risk predictions with models*	Do not develop diabetes (*n*)	Develop diabetes (*n*)	IFG model	*n*	%
R_IFG > R_MetS	A = 7105	B = 314	Better (B + C)†	4781	37.7
R_IFG < R_MetS	C = 4467	D = 806	Worse (A + D)	7911	62.3
Total	11 572	1120	A + B + C + D	12 692	100
Test for proportions (better and worse) = 50%				$P < 0.001$	

*R_IFG, risk predicted with IFG model; R_MetS, risk predicted with MetS model.
† The model which predicted higher risk was better for those who subsequently developed diabetes. In contrast, the model which predicted lower risk was better among those who did not develop diabetes during the 5-year follow-up period.

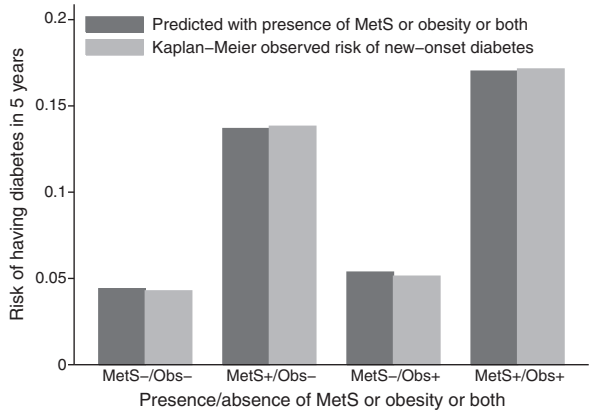


FIGURE 2 Risk of development of new-onset diabetes among normoglycaemic patients on basis of presence/absence of obesity, the metabolic syndrome (MetS) or both.

Discussion

These analyses of 14 120 hypertensive patients without diabetes suggest that the metabolic syndrome, independently of its components and other determinants of new-onset diabetes, is associated with increased risk of new-onset diabetes. Among its individual metabolic components, fasting plasma glucose contributes the most towards risk of new-onset diabetes, followed by BMI, systolic blood pressure, triglycerides and HDL cholesterol, in that order. Both impaired fasting glucose and the metabolic syndrome may be used as predictors of new-onset diabetes: whilst the presence of impaired fasting glucose confers substantial risk of incident diabetes, among hypertensive patients, the metabolic syndrome correctly allocates the risk of new-onset diabetes in a significantly higher proportion of patients compared with that allocated by the use of impaired fasting glucose status alone, more so for normoglycaemic hypertensive patients.

Recent studies have suggested that impaired fasting glucose status may be used instead of the metabolic syndrome to predict the risk of new-onset diabetes [10,18,19]. Our results partially agree with these analyses, whilst adding a new dimension to them. For example, the data shown in Fig. 1 are comparable with previous studies [10,18,19], which have noted that the hazards (risks) associated with the metabolic syndrome alone (in the absence of impaired fasting glucose) are substantially less than those associated with the presence of impaired fasting glucose alone (in the absence of the metabolic syndrome). However, given the fact that the increase in plasma glucose is linearly associated with the increased risk of incident diabetes, comparison of those with normoglycaemia (metabolic syndrome present) with those with impaired glycaemia (metabolic syndrome absent) is probably not fair. In contrast, Fig. 1a also shows a consistent 2-fold increased risk of new-onset diabetes associated with the presence of the metabolic syndrome, among those who were normoglycaemic or with impaired fasting glucose at baseline. This perhaps suggests that, in addition to the knowledge of glycaemic status, the presence of the metabolic syndrome confers added risk of incident diabetes. Furthermore, on comparison of the area under receiver operator curves of the two models, comparing their respective sensitivity and specificity curves, the model using the metabolic syndrome was significantly better than that using impaired fasting glucose ($P < 0.001$). When the predicted risk allocated by each model (impaired fasting glucose and metabolic syndrome) was stratified by observed 5-year-outcome, the model using the metabolic syndrome was found to allocate a significantly higher proportion of adults into their correct risk categories (Table 2). The impaired fasting glucose model performed particularly less well among those with normoglycaemia at baseline (26.7% of these patients were correctly assigned the risk of incident diabetes with the use of the impaired fasting glucose model, compared with 73.3% correctly assigned the risk with the metabolic syndrome model). Our analysis highlights the inadequacy of the traditional approach of using odds or hazard ratios alone rather than additionally calculating incremental discrimination or reclassification improvement when evaluating optimal risk prediction [17,20,21]. Using such techniques, our findings

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suggest that the metabolic syndrome supersedes impaired fasting glucose in stratifying likelihood of developing diabetes, even although the effect sizes associated with the metabolic syndrome are modest.

We have also shown that, among hypertensive patients, the metabolic syndrome was associated with an excess risk of new-onset diabetes after adjusting for all its individual components. These findings are consistent with some [11,12], but not all [10,19] previous reports. Table 1 clearly documents a sizeable attenuation in the risk of new-onset diabetes associated with the metabolic syndrome, when adjusted for the fasting plasma glucose component; however, the excess residual risk of new-onset diabetes associated with the metabolic syndrome remains significant and considerable. Furthermore, attenuation of the effect size after adjusting for the fasting plasma glucose component was expected in this analysis, particularly as patients randomized in this study were at relatively high risk (compared with those in the community) of developing diabetes (incidence rate: 18.6 per 1000 person-years), as evidenced by a high mean (SD) fasting plasma glucose [5.4 (0.6) mmol/l], with more than one third of patients with impaired fasting glucose at baseline. Moreover, these analyses may have underestimated the effect sizes associated with the metabolic syndrome, as those without the metabolic syndrome also had the presence of at least one metabolic component of this syndrome (i.e. hypertension). Either way, we have also shown that, among normoglycaemic individuals, the presence of the metabolic syndrome is associated with a significantly higher risk of developing new-onset diabetes as compared with that associated with its individual components, especially obesity (Fig. 2), in keeping with previous observations [2]. Our findings are also consistent with the results of recently published studies demonstrating vastly enhanced risk of new-onset diabetes among those with the presence of both impaired fasting glucose and the metabolic syndrome [11,12].

Among the individual components of the metabolic syndrome, after fasting plasma glucose, BMI contributed the most towards the risk of new-onset diabetes associated with the metabolic syndrome. This is unsurprising as BMI (obesity) is a well-established risk factor for diabetes [2]. Inclusion of the other components of the metabolic syndrome in the model did not affect the relationship of the metabolic syndrome substantially, although all of these individual components remained independent predictors of new-onset diabetes, as did the metabolic syndrome. Our finding of a relatively smaller (although still significant) influence of low HDL on the risk of new-onset diabetes associated with the metabolic syndrome has been shown previously [12].

Some of our findings are consistent with earlier reports [11,12], but our data are the first to relate specifically to a hypertensive population. Our most important finding is the clear demonstration of the importance of the metabolic syndrome (particularly among hypertensive and normoglycaemic individuals) over the other simpler variables, such as impaired fasting glucose or obesity, in predicting the risk of the new-onset diabetes. Almost all previously established risk scores for diabetes are complex or difficult to use [19,22–24], with no consensus regarding which score to use. Hence, the use of the metabolic syndrome or simpler risk constructs was proposed [4,6,25], with a recent study suggesting that fasting plasma glucose [10] may be preferable. We have shown shortcomings of earlier analyses [10,19] and have highlighted the need to compare the discriminative ability of a risk construct to correctly classify the risk of individuals [17,21].

A possible limitation of this study is the use of BMI instead of waist circumference. However, the use of BMI in defining the metabolic syndrome is not new [1,26] and has been previously shown to have a comparable predictive capability [5]. It is also possible that our findings are not generalizable beyond hypertensive populations with no history of coronary heart disease [13]. It is therefore important that these findings are confirmed in other similar studies and among other high-risk populations.

In summary, our findings suggest that, whilst both impaired fasting glucose and the metabolic syndrome may be useful for predicting the risk of incident diabetes, the metabolic syndrome is a better predictor than impaired fasting glucose in assigning the risk of diabetes in hypertensive patients and among those with normoglycaemia. In addition, the metabolic syndrome remains a significant and independent predictor even after adjusting for the sum of its individual components, including fasting plasma glucose.

These findings suggest that the use of the metabolic syndrome, as a tool for predicting new-onset diabetes, is not obsolete and, pending further investigations (using newer techniques to differentiate risk), its use for diabetes prevention strategies should continue, particularly in the absence of other easy-to-use risk predictors of new-onset diabetes.

Competing interests

AKG, BD, DP-M, PSS and NRP do not have any conflicts of interests related to this publication. The ASCOT Study was an investigator-led study supported mainly by Pfizer Inc., New York, with funding also provided by the Servier Research Group, Paris, France.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Baseline treatment allocation, metabolic syndrome and development of diabetes among those randomized in the ASCOT-BPLA trial.

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COMMENTS & OPINIONS

Antihypertensive-Associated Incident Diabetes: Controversy Persists

The study by Barzilay et al[1] reconfirms that thiazide-like diuretics are associated with an increased risk of new-onset diabetes compared with other antihypertensive agents and that incident diabetes is associated with increased risk of all cardiovascular events and significantly so for coronary heart disease. However the authors of these analyses suggest that diuretic-associated incident diabetes may be "innocent." If true, this would be a surprising observation with important clinical implications and therefore merits careful examination.

As the authors point out, this is a post hoc analysis of nonrandomized data with only 53% of the eligible "nondiabetic" patients having 1 or more measurement of fasting glucose. Those excluded were biased toward blacks and women who are more prone to diabetes and/or risk of diabetes-related cardiovascular outcomes, respectively. The definition of incident diabetes used (a single measurement of fasting glucose >125 mg/dL [to convert to millimoles per liter, multiply by 0.0555]), especially in this group of elderly patients, is likely to lead to diabetic subjects being misclassified as nondiabetic. In addition, while building the Cox model for evaluating cardiovascular risk among the 590 incident diabetes cases at the end of 2 years, the authors included—as part of their "nondiabetic" comparator group—588 patients who subsequently became diabetic.

These methodological shortcomings are likely to result in reducing the ability to detect differences in cardiovascular outcomes between so-called "diabetic" and "nondiabetic" subgroups. Despite these shortcomings, the authors report that incident diabetes (compared with no diabetes—at least at 2 years) is "only" associated with the increase in coronary heart disease (the primary end point of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [ALLHAT]), while failing to mention the limited power of these data to explain the large albeit nonsignificant increases in stroke (61%), total mortality (31%), and end-stage renal disease (186%) among so few in a such a short time.

Diminishing their power yet further, the authors try to differentiate effects of incident diabetes by randomized drug class, comparing only 329, 150, and 111 cases among those randomized to chlorthalidone, amlodipine, and lisinopril, respectively. Their own interaction analyses suggest that "the effect of incident DM [diabetes mellitus] on end points was similar in all 3 treatment groups,"[1(p2196)] and yet elsewhere they suggest that the diuretic-induced diabetes was "innocent" compared with that from the other 2 groups.

Evaluation of the cardiovascular toll associated with antihypertensive-associated incident diabetes is fraught with methodological problems—critically, power and short-term follow-up. Post hoc studies in a nonrandomized, biased subgroup of 53% of the potential population under investigation are unlikely to help clarify this difficult area.

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The Putative Link Between Glycemic Control and Cardiac Arrhythmias

Barzilay et al[1] demonstrate that mean fasting glucose (FG) levels increased during follow-up in all treatment groups within the ALLHAT substudy observed over a mean duration of 4.9 years. At year 2, those randomized to the chlorthalidone group had the greatest increase in FG level (+8.5 mg/dL vs +5.5 mg/dL in the amlodipine subgroup and +3.5 mg/dL in the lisinopril subgroup). They conclude that for those taking chlorthalidone vs other medications, the risk of developing FG levels higher than 125 mg/dL is modestly

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The validity of the observation that dronedarone reduces cardiovascular hospitalization would have been strengthened if the trial had documented systematically the underlying reasons for hospitalizations (typically hemodynamic instability, exacerbation of heart failure, anticoagulation, or cardioversion) and the expected attendant improvement in symptom status and quality of life. Coupled with the lack of external adjudication (that minimizes the vulnerability to cardiovascular versus noncardiovascular misclassification errors, particularly in trials that span geographic regions and clinical practice settings) (3,4) and the exploratory nature of the analysis (given the pre-specified hierarchical sequential plan), these limitations serve not only to undermine the clinical relevance of this finding, but also to raise questions about the overall quality of the data, and ultimately the reliability of the findings.

The original report mentions 1 amendment dated March 8, 2006, to alter the enrollment criterion to include older subjects (2). No further protocol changes are mentioned, including the amendment dated August 25, 2006, to increase the sample size from 3,700 to 4,300, nor is any reason given for the extension of the sample size from 4,300 to 4,628. We do not doubt these protocol changes were done blindly, without knowledge of any emerging treatment effects. However, we are intrigued that investigators stopped at 255 deaths, 5 short of achieving the protocol-specified goal of 260 deaths. Nonetheless, these protocol changes should have been reported in a transparent manner and appropriate caution should have been urged in interpreting cardiovascular death results as being exploratory, given the rules of engagement of a hierarchical sequential analysis plan. Instead, the published conclusion that the drug reduced cardiovascular deaths is highly misleading, when in reality that benefit was not significant under the original plan (1). Although no malfeasance is implied, we nonetheless feel strongly that changing rules in the middle of the trial is antithetical to the principles of good clinical trial practice. Moreover, the mechanisms that underlie dronedarone's reduction of cardiovascular death remain unclear. Death resulting from stroke, ventricular arrhythmia, or heart failure was not impacted favorably by dronedarone (2). Did the associated reductions in acute coronary syndromes—a post-hoc observation—account for this finding, or was this merely the play of chance? In the end, the ATHENA trial was not designed to answer these questions, and the observed reduction in cardiovascular death is at best exploratory and hypothesis generating, requiring confirmation in subsequent studies.

The authors have raised issues with our meta-analysis. The objective was not solely to estimate an overall measure of effect (a synthesis-centric goal), where it is appropriate to question whether certain studies should be combined, but rather to explore the reasons for differences between the studies (an analysis-centric goal) to place the evidence in its proper context. The results are insightful because they provide reassurance about dronedarone's safety in the target population (1). The weighting is described in the figure legend (1), and adjusting for patient-years of exposure did not materially change the summary relative risk estimate. Finally, we acknowledge the typographical error regarding the mean follow-up in the ANDROMEDA (ANti-arrhythmic trial with DROnedarone in Moderate to severe congestive heart failure Evaluating morbidity DecreAse) trial, which had no impact on our analysis.

Rather than missing the forest for the trees, we present the evidence in an objective and unembellished manner. Although the truth can be determined by each reader, the plain fact, in our opinion, is that dronedarone has very modest efficacy as an antiarrhythmic agent, and based on the current evidence, its use for the treatment of nonpermanent atrial fibrillation or atrial flutter can be supported only as a second- or third-line agent in individuals who are not able to tolerate amiodarone or other first-line agents recommended by the guidelines.

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The Concept of the Metabolic Syndrome

Is It Dead Yet?

The main finding of the case-control study by Mente et al. (1) is that the risk of myocardial infarction associated with the diagnosis of metabolic syndrome (MS) is no greater than that of the sum of its individual components. However, this interpretation is solely based on a finding of similar effect sizes (odds ratio) associated with MS and previously diagnosed (and/or treated) diabetes mellitus or hypertension. The authors note that, in this study (as in many other studies), both hypertension and diabetes frequently coexisted. Moreover, they suggest that the patients with hypertension or diabetes were more likely to have at least 1 additional component of MS present (most commonly, central obesity: 71%). Therefore, it is not surprising that the odds ratio associated with each of them in separate regression models was found to be similar to that obtained by the use of MS, as patients with both diabetes and hypertension also had clustering of other individual components. We believe it would be more informative to describe the effect sizes associated with those with only diabetes or only hypertension, when comparing them with those associated with the presence of MS. However, to assess whether the sum of the risk associated with individual components is greater than that associated with the presence of MS, it may be better to estimate the risk of myocardial infarction associated with MS, after adjusting for all its individual components (when used as continuous variables) in a regression model.

Furthermore, a review of current literature suggests that the approach of using only effect sizes when comparing the utility of risk factors may be obsolete—particularly in light of more efficient statistical approaches such as net reclassification index and incremental discrimination index (2,3)—the techniques that enable comparisons based on number of subjects correctly allocated with the enhanced risk or not.

However, we agree that despite these further analyses, the eventual interpretation may remain unchanged, as evidenced by findings of a recent study (4) among >19,000 hypertensive patients, where there was an absence of any synergy among the individual components of MS on the risk of coronary outcomes associated with MS. However, in that study, the risk of stroke and all-cause mortality associated with MS, independent of its components, was found to be significant. We believe these apparent contradictions in the current literature are likely to be minimized by interrogating prospective data, to evaluate whether the risk of myocardial infarction (both in terms of magnitude and the number of patients correctly identified) is more closely associated with MS or with the presence of each of the individual risk factors, separately and in combination.

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Reply

Drs. Gupta and Poulter raise an interesting point about our study (1) and about estimating the risk of myocardial infarction (MI) associated with metabolic syndrome (MS), after adjusting for all its individual components (as continuous variables). The idea of controlling for all components and MS simultaneously to assess each of the effects comparatively seems intuitive. However, there are statistical assumptions in constructing such a model. Controlling for component factors that were used to define MS would likely substantially alter the association between MS and MI risk. Indeed, when adjusting for all of the individual MS components, the odds of MS on MI risk is <1 (odds ratio: 0.79; 95% confidence interval: 0.68 to 0.91); however, the effects of diabetes mellitus (odds ratio: 2.52; 95% confidence interval: 2.24 to 2.83) and hypertension (odds ratio: 2.22; 95% confidence interval: 2.05 to 2.39) remain robust after simultaneous adjustment. Prior investigations have used a similar approach to that of our study in assessing the effects of MS and component factors (2,3).

We agree that alternative analytical approaches may be used to determine the agreement between MS and component factors classification versus MI (e.g., net reclassification). However, this approach is usually applied to prospective cohort data, and not to retrospective case-control data. Nonetheless, as the investigators recognize, the general pattern of results and eventual interpretation is unlikely to change. Moreover, an important advantage of estimating the effect size is that it may be used to estimate population attributable risk (PAR), an approach used previously in the first INTERHEART study (a global case-control study of risk factors for acute myocardial infarction) paper, which showed that 90% of risk of MI is explained by 9 modifiable risk factors (4). An assessment of the PAR of MS on MI is particularly important in the current study, since the use of a dichotomous definition of MS based on ≥3 risk factors leads to a substantially lower prevalence of MS than its component factors (e.g., 10% for MS compared with 19.6% for diabetes and 23.4% for hypertension). This finding partly explains our observation that the PAR of MS is substantially lower than the PAR of several component factors considered separately, including diabetes and hypertension, and indicates that MS accounts for a smaller number of MI cases in a population compared with several of its constituent components. Thus, our findings highlight an important limitation of MS diagnosis.

We also agree that a cohort study might provide more rigorous data. However, an important strength of the INTERHEART study is that it is a large international study of 52 countries using a standardized protocol, and it is the first large study to show that the risk of MI associated with MS is qualitatively similar across sex, global regions, and ethnic groups. A cohort study with similar objectives would require an enormous sample size and 2 decades of follow-up. Although not impossible, such a study would be extremely costly to conduct.

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