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Pharmacologic treatment in patients with established coronary artery disease and diabetes needs improvement: a report from the EUROASPIRE III cross-sectional study

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Abstract:	Purpose: Diabetes is common in patients with coronary artery disease and this combination is accompanied by a serious prognosis, which may be improved by a target driven risk factor management. It has been reported that coronary artery disease patients with diabetes are less well managed than subjects with normal glucose regulation. The present aim was to investigate the use of comprehensive pharmacological therapy defined as a combination of aspirin, β-blockade, Renin-Angiotensin-Aldosterone-System-blockade and a statin, and obtained treatment targets in a large cohort of coronary artery disease-patients with and without diabetes. Methods: EUROASPIRE III was a cross-sectional observational study of stable coronary artery disease-patients aged 18-80 years at 76 centres in 22 European countries during 2006-2007. The glucometabolic category (known, newly detected or no diabetes), guideline treatment target fulfilment and the use of pharmacological treatment were assessed at a study visit. Results: Of all patients investigated (females 25%) 4295 (57%) had no diabetes, 1541 (28%) known diabetes and 752 (15%) newly detected diabetes. Comprehensive pharmacological therapy was used in 50% of the patients with diabetes and 44% of the patients without. The proportion of coronary artery disease-patients with previously known diabetes who reached the treatment targets were 20% for blood pressure, 53% for LDL-cholesterol and 20% for HbA1c. Conclusion: This study demonstrates a low use of a comprehensive pharmacological therapy. This probably contributed to the poor adherence to treatment targets for cardiovascular prevention, particularly seen among patients with a combination of

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Professor Thomas F Lüscher
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Dear Professor Thomas F Lüscher

Attached please find the manuscript

Pharmacologic treatment in patients with established coronary artery disease and diabetes needs improvement: a report from the EUROASPIRE III cross-sectional study by Gyberg et al.

Which we hope will attract interest enough for publication in the journal.

We have compared pharmacologic treatment and target fulfilment in 6588 patients with coronary artery disease from 22 European countries. By comparing coronary artery disease patients with diabetes to those without it was possible to show that the patients with diabetes were prescribed more drugs. Despite this the adherence to recommended treatment targets for blood pressure and HbA1c was poor and remained unsatisfactory even if considerably higher targets were applied. Possible reasons, among them a less than optimal contact with caregivers are discussed.

It is our hope that this study will encourage physicians in charge of similar patients to pay further attention to this high risk group thereby improving their cardiovascular protection. This is a highly prioritised given the current increase of diabetes world wide.

Part of the contents in this manuscript was presented as a poster at the EuroPrevent conference in May this year.

We are grateful for your time and consideration of our paper.

Yours Sincerely,

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Pharmacologic treatment in patients with established coronary artery disease and diabetes needs improvement: a report from the EUROASPIRE III cross-sectional study

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Abstract

Purpose: Diabetes is common in patients with coronary artery disease and this combination is accompanied by a serious prognosis, which may be improved by a target driven risk factor management. It has been reported that coronary artery disease patients with diabetes are less well managed than subjects with normal glucose regulation. The present aim was to investigate the use of comprehensive pharmacological therapy defined as a combination of aspirin, β-blockade, Renin-Angiotensin-Aldosterone-System-blockade and a statin, and obtained treatment targets in a large cohort of coronary artery disease-patients with and without diabetes.

Methods and Results: EUROASPIRE III was a cross-sectional observational study of stable coronary artery disease-patients aged 18-80 years at 76 centres in 22 European countries during 2006–2007. The glucometabolic category (known, newly detected or no diabetes), guideline treatment target fulfilment and the use of pharmacological treatment were assessed at a study visit. Of all patients investigated (females 25%) 4295 (57%) had no diabetes, 1541 (28%) known diabetes and 752 (15%) newly detected diabetes. Comprehensive pharmacological therapy was used in 50% of the patients with diabetes and 44% of the patients without. The proportion of coronary artery disease-patients with previously known diabetes who reached the treatment targets were 20% for blood pressure, 53% for LDL-cholesterol and 20% for HbA1c.

Conclusion: This study demonstrates a low use of a comprehensive pharmacological therapy. This probably contributed to the poor adherence to treatment targets for cardiovascular prevention, particularly seen among patients with a combination of coronary artery disease and diabetes.

Key words:

Cardiovascular Disease, Diabetes Mellitus, Secondary Prevention, EUROASPIRE

Introduction

Cardiovascular disease is the major cause of death worldwide and in Europe alone 4 million people die from it every year, representing 50% of the regional mortality. [1, 2] Indeed, cardiovascular disease explain 31% of deaths in men and 26% of deaths in women before the age of 65 in Europe [1, 2] Diabetes is a rapidly increasingly cardiovascular risk factor, and around 30% of all patients with coronary artery disease have diabetes mellitus type 2 (from now on referred to as diabetes). [3-5] Patients with a combination of coronary artery disease and diabetes have a two times higher mortality than those without diabetes, making them a group at remarkably high risk for a second event and death. [6, 7] By using a comprehensive and target driven pharmacological treatment as recommended in available guidelines, the prognosis can be improved to almost become equivalent to that of patients without diabetes. [8, 9] Accounting for their higher absolute risk, the number needed to treat to avoid a cardiovascular event is substantially lower in coronary artery disease-patients with diabetes compared to those without it.[8] Despite some improvement over time, pharmacological therapy of cardiovascular patients is still inadequate, especially in those with diabetes. [8-10]

The aim of the present study was to investigate to what extent comprehensive pharmacological treatment is used and if treatment targets were reached in coronary artery disease patients with diabetes in the large cross sectional study EUROASPIRE III.

Methods

A detailed report of European Action on Secondary and Primary Prevention by Intervention to Reduce Events III (EUROASPIRE III) has been given elsewhere. [11] In brief EUROASPIRE III was a cross-sectional observational study. Between 2006 and 2007 patients with established coronary artery disease were recruited from 76 volunteering centres in 22

European countries according to the following inclusion criteria: age 18-80 years and established coronary artery disease defined as: hospitalisation for either (1) elective or emergency coronary artery by-pass graft surgery; (2) elective or emergency percutaneous coronary intervention, (3) acute myocardial infarction (ST elevation and non-ST-elevation myocardial infarction); or (4) acute myocardial ischemia but no evidence of infarction (troponin negative). The index event had to be 6-36 months before the planned date of the patient interview. Consecutive patients were identified from diagnostic registries, hospital discharge lists or other valid sources and contacted by phone or mail. Trained research staff reviewed the medical records, interviewed and examined the patients and entered the data into an electronic central database.

The following measurements were performed:

a. Height and weight were measured in light indoor clothes without shoes (SECA scales model number 701 and measuring stick model 220, Hamburg, Germany). The scales were calibrated at the start of the survey.
b. Blood pressure was measured twice on the right upper arm in the sitting position using automatic digital sphygmomanometers (Omron M5-I, Illinois, USA).
c. Venous blood was retrieved for the analysis of serum total- and High Density Lipoprotein-cholesterol (HDL-cholesterol), triglycerides, calculated Low Density Lipoprotein cholesterol (LDL-cholesterol), plasma glucose (all patients) and in addition HbA1c in those with diabetes- All analyses were performed at the laboratory of Analytical Biochemistry, National Public Health Institute (Helsinki, Finland) fulfilling the requirements of the standard SFS-EN ISO/IEC 17025:2005 covering all analyses except glycated haemoglobin A1c (HbA1c).

Information about the patient's pharmacological treatment was collected at the time of the interview. The patient was asked to bring an updated list of medications or the medication itself.

For the purpose of this study patients were divided into three groups in relation to their glucose metabolism: known, newly detected and no diabetes. The diagnosis of newly detected diabetes was based on a fasting glucose of >7 mmol/L (126mg/dl) at the time of the study visit. The use of comprehensive pharmacological therapy in terms of types of the drugs was assessed. A comprehensive pharmacological therapy was defined as the combined use of aspirin, β-blockade, Renin-Angiotensin-Aldosterone-System (RAAS) blockade and a statin. Treatment target fulfilment was assessed for blood pressure, LDL-cholesterol and HbA1c. The used treatment targets for coronary artery disease-patients were those, which at the time for the investigation were recommended by the joint 2003 European guidelines on cardiovascular disease prevention [12] i.e. blood pressure <140/90 mmHg for patients without and <130/80 mmHg for patients with diabetes; total and LDL-cholesterol <4.5 mmol/L (175 mg/dL) and <2,5 mmol/L (97mg/dL) respectively; and HbA1c <6.1 DCCT % (43.2 mmol/mol). In addition tests were performed to investigate the proportions that reached more as well as less strict treatment targets.

Data management

Data management was undertaken at the ESC Euro Heart Survey department, European Heart House, Nice, France. Data were collected electronically using a unique identification number for country, center and individual. The data were submitted via Internet to the data management center where checks for completeness, internal consistency and accuracy were run. All data were stored under the provisions of the National Data Protection Regulations.

Ethical considerations

The study conformed to good clinical practice guidelines and followed the recommendations of the Helsinki Declaration. National coordinators obtained approvals from Local Research Ethics Committees and all participants signed a consent form following oral and written information.

Statistical analyses

All statistical analyses were performed at the Department of Public Health, Ghent University, Belgium by means of SAS statistical software release 9.1 (SAS Institute Inc., Cary, North Carolina, USA).

The distribution of patient characteristics across groups (Table 1) was compared according to the Chi-square test. Rates of pharmacological treatments, caregivers consulted as well as the percentages of patients reaching treatment targets for blood pressure, LDL-cholesterol and HbA1c were statistically compared between groups according to multilevel logistic modelling. [13] These hierarchical models accounted for the clustering of patients within centres. In addition these models adjusted for potential confounding due to differences in distributions of age and gender. A level of α=0.05 was *a priori* chosen to indicate statistical significance.

Results

A total of 13,935 medical records were reviewed and 8,966 patients interviewed. The present study population comprises 6,588 interviewed participants with available information on gluco-metabolic category. The proportion of patients with known diabetes was 23%, newly detected diabetes 11% and no diabetes 66%. The patients with newly detected and known

diabetes were older, less often smokers but more frequently obese. Pertinent patient characteristics are presented in Table 1.

The use of individual classes of drugs as well as the use of comprehensive pharmacological treatment is described in Table 2. The largest difference between the three groups was in the use of RAAS-blockers

In all three groups > 97% of the patients reported that they never or seldom missed or altered their medication.

Figure 1 shows the proportion of patients who reached different blood pressure levels (<150/100; <140/90; and <130/80 mmHg respectively). Half of the patients without and one fifth of those with diabetes reached the recommended blood pressure target of <140/90 mm Hg and <130/80 respectively. Applying a blood pressure target of <140/80 as prescribed in the 2012 prevention guidelines [14] 24% of the patients with diabetes reached the treatment target. As presented in figure 1 there were significant differences between the groups for all blood pressure levels.

Forty-four per cent of the patients without diabetes, 40% of those with newly detected diabetes and 53% with previously known diabetes reached the treatment target for LDL-cholesterol of < 2.5 mmol/l (< 97mg/dL) for all three groups. Figure 2 shows the proportion of patients who reached different LDL-levels (< 3.0; < 2.5; < 1.8 mmol/l = <116; <97; <70 mg/dL). There were significant differences between all three groups at all LDL-levels. The cholesterol target of <4,5 mmol/L (< 175 mg/dL) where reached by 49% of the patients without diabetes, 41% in the newly diagnosed diabetes group and 55% in the group with previously known diabetes. The differences between the groups were statistically significant ($p<0.0001$). Seventy-four per cent of the patients without diabetes, 64% of those with newly detected diabetes and 63% of patients with previously known diabetes had a HDL-cholesterol above 1.0 mmol/l (< 39 mmol/mol) and the differences between the groups

were significant ($p<0.0001$). Out of the patients with known diabetes 22% reached the guideline treatment target of HbA1c <6.1% (< 43 mmol/mol) as seen in Figure 3.

When asked about caregiver 17% of the patients with previously known diabetes reported that they were seen by an endocrinologist/diabetologist. As revealed by Table 3 a majority of the patients went to multiple caregivers.

Discussion

This study demonstrates a low use of a comprehensive pharmacological therapy, which probably contributed to the poor adherence to comprehensive treatment targets for cardiovascular prevention as particularly seen among patients with diabetes.

The findings confirm previous reports on a far from satisfactory use of pharmacologic treatment and target fulfilment in patients with coronary artery disease and diabetes. [9, 11, 15] In the EUROASPIRE II, conducted 1999-2000, 23% of the patients with coronary artery disease and diabetes used four or more out of eight specified drugs, and in the Euro Heart Survey, conducted 2003, the use of comprehensive pharmacological treatment was about 43%. Thus, the improvement in the care of patients with diabetes, of whom 50% used comprehensive pharmacological treatment in the present study, has been modest over time.

Higher levels for blood pressure, LDL-cholesterol and HbA1c were tested to counteract a frequently emphasised critique to studies of the present kind underlining that many patients, although reported as insufficiently managed, may be close to the targets. The pattern of poorly reached treatment targets remained when less stringent targets were tested. As revealed in Figures 1-3 many of the patients are well above the recommended targets and in need of improved attention. Another reason to present several levels outside those recommended in the 2003 European Guidelines for Cardiovascular Prevention is that the in

guidelines issued 2012 the targets changed for LDL-cholesterol (<1.8 mmol/L or <70 mg/dL), blood pressure (<140/90 mmHg without and <140/80 with diabetes) and HbA1c (<7.0% or <53 mmol/mol). [14]

Patients with diabetes received more pharmacological treatment than those without. This was, as in EUROASPIRE II and the Euro Heart Survey of diabetes and the heart, particularly due to a higher prescription of RAAS-blockade. [9, 15] Still blood pressure control was remarkably poor with only 20% of patients with diabetes within the recommended target, a similar proportion as in EUROASPIRE II (22%). Indeed 37% had a blood pressure exceeding 150/100 mmHg, which must be considered very high for this population. An adequate blood pressure control in patients with diabetes does often require two or three different antihypertensive drugs, thus a potential explanation might be that an insufficient number of drugs where used in too low dosages. [16]

A similar proportion of patients with and without diabetes were on statins, and the use of such drugs had increased considerably from EUROASPIRE II (54%) to EUROASPIRE III (85%). This also reflected that 53% of patients with diabetes had a LDL-cholesterol <2.5 mmol/l (< 97 mg/dL) compared to 25% in EUROASPIRE II. This shows that new knowledge can be widely adopted even if it takes time. Gaede and Pedersen [17] applied the UKPDS risk engine [18] to calculate the actual contribution of different risk factors for cardiovascular risk reduction in the extensively treated group of the STENO 2 population. They found that the most important contributor was lipid lowering (about 75 % of the impact) followed by glucose (13%) and blood pressure (11%).

Glucose control was poor in the patients with known diabetes with only 22% of the patients reaching the HbA1c target of < 6.1% (43 mmol/mol) and with 50% > 7.0% (53 mmol/mol). This is perhaps a less surprising finding in consideration of present uncertainties whether strict glucose control reduces macrovascular events. [19, 20] It should, however, not be

forgotten that microvascular complications undoubtedly increases with poor glucose control constituting a good reason to keep glycemia within reasonable limits. [20, 21] Noteworthy is that 15% of the investigated population were diagnosed with new diabetes via an elevated fasting glucose at the EUROASPIRE III study visit. This reasonably means that many of them remained undiagnosed 6-36 months after their index coronary event indicating a lack of knowledge or organisation to investigate glucose perturbations. [22]

A minority (17%) of patients with diabetes were seen by an endocrinologist, which might have had a negative impact on their treatment. Moreover, many patients were attended for by multiple caregivers, which might have led to no specific physician perceiving himself or herself as responsible for the complete care of the patient. It has previously been indicated that the transfer of patients to the outpatient care is suboptimal which might play a role. [23] A reasonable assumption is that the organisation of the care for these patients had an impact on the results from this survey. An organisational improvement could be to emphasise one responsible caregiver and/or a nurse led clinic providing comprehensive prevention including guided life style advice, smoking cessation and proper use of drugs. [24] In this perspective education, not only of the caregivers, but also the patients and their relatives may serve as a tool to accomplish better treatment with caregivers and patients taking joint responsibility working towards the same targets. [25]

Patient compliance was not believed to play a major role since > 97% of the patients responded that they never or seldom missed or altered their medication. Another and probably more likely explanation is that many patients did not receive a full combination of comprehensive medications. In this study we applied the same criteria for comprehensive pharmacological treatment as the one used in the Euro Heart Survey on diabetes and the heart. [9] It may be criticised as an oversimplification, insensitive to potential contraindications to individual drugs. Still it is reasonable to assume that patients with coronary artery disease and

diabetes should have a combination of aspirin, statin and ACE/ARB-inhibitors and quite frequently also a beta-blocker and even if there are contraindications to some of these drugs they are not very prevalent in a population of the present kind. Moreover such definition serves its purpose for comparisons between different surveys especially when the targets are far from being reached.

Study limitations

The classification of a patient as newly diagnosed diabetes was based on a single fasting glucose. This diagnosis should preferably be based on two fasting glucose values, which was impossible due to study logistics. The use of only fasting glucose will not diagnose patients with postprandial glucose disturbances that would have been disclosed by an oral glucose tolerance test or possibly by an HbA1c. [3, 26, 27] This means that the group free from diabetes likely contains some individuals with impaired glucose tolerance or diabetes. Never the less the proportion of 33% patients with diabetes concurs with findings from other studies reporting on glucose perturbations in patients with coronary artery disease. [15, 28] Since the major findings are primarily based on the differences between patients with known or no diabetes the potential misclassification is of limited importance in the present context. Furthermore, EUROASPIRE III may be afflicted by a positive selection bias. Participating centres volunteered and may have a keen interest in cardiovascular prevention compromising the generalisability of the results. If anything such bias will make the practice as reflected better than in average care in which the situation if anything can be assumed to be even worse.

Conclusion

Despite a fairly high use of individual drugs there was a low use of a comprehensive based pharmacologic therapy and treatment targets were often not reached. This was particularly apparent for blood pressure and glucose control in patients with diabetes, a serious combination with poor prognosis. It is believed that issues related to the caregiver and the care organization may be an important factor behind the present shortcomings.

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Competing interests

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Figure ledgends

Table 1: Patient characteristics. Data presented are % with number of patients in brackets if not stated otherwise.

Table 2: Use of pharmacological therapy in % (n/total n).

Table 3: Caregiver providing the care presented as % (n/total n).

Figure 1: Percentage of patients reaching blood pressure treatment target accounting for clustering of patients within centres and adjusted for age and gender.
Striped: <130/80 mmHg (differences between groups p<0.005). Grey: <140/90 mmHg (differences between groups p<0.0001). Dotted: <150/100 mmHg (differences between groups p<0.0001)

Figure 2: Percentage of patients reaching LDL treatment target accounting for clustering of patients within centres and adjusted for age and gender. Striped: LDL < 1.8 mmol/L (< 70 mg/dL) (differences between groups p<0.0001). Grey: LDL < 2.5 mmol/L (< 97 mg/dL) (differences between groups p<0.0001). Dotted: LDL < 3.0 mmol/L (< 116 mg/dL) (differences between groups p=0.0002).

Figure 3: Percentage of diabetes patients reaching HbA1c (DCCT) treatment targets accounting for clustering of patients within centres and adjusted for age and gender. Striped: HbA1c < 6.1% mmol/L (< 43 mmol/mol). Grey: HbA1c < 6.5% mmol/L (< 48 mmol/mol). Dotted: HbA1c < 7.0 mmol/L (< 53 mmol/mol).

Table 1: Patient characteristics. Data presented are % with number of patients in brackets if not stated otherwise.

Variable	Diabetes			
	No	Newly Detected	Previously Known	Significance*
	n= 4295	n= 752	n= 1541	
Age				P<0.0001
< 50 years	12 (510/4295)	7 (52/752)	6 (86/1541)	
50–59 years	28 (1198/4295)	29 (218/752)	26 (406/1541)	
60–69 years	36 (1550/4295)	39 (292/752)	41 (625/1541)	
>70 years	24 (1037/4295)	25 (190/752)	28 (424/1541)	
Sex				P<0.0001
Women	24 (1008/4295)	21 (159/752)	30 (469/1541)	
Men	77 (3287/4295)	79 (593/752)	70 (1072/1541)	
Inclusion event				P=0.0002
CABG	18 (789/4295)	17 (128/752)	23 (360/1541)	
PCI	45 (1926/4295)	42 (319/752)	42 (639/1541)	
AMI	20 (874/4295)	21 (158/752)	19 (290/1541)	
Ischemia	16 (706/4295)	20 (147/752)	16 (252/1541)	
Non smoker	82 (3525/4289)	83 (619/750)	87 (1330/1538)	P=0.0005
BMI, kg/m^2				P<0.0001
<25	22 (934/4278)	14 (101/750)	12 (176/1528)	
>25- <30	50 (2119/4278)	44 (329/750)	41 (633/1528)	
≥30	29 (1225/4278)	43 (320/750)	47 (719/1528)	

*Significance of differences between the groups

Table 2: Use of pharmacological therapy in % (n/total n).

Ongoing therapy	Diabetes			
	No	Newly Detected	Previously Known	Significance*
Aspirin	91 (3902/4284)	93 (693/749)	91 (1400/1533)	P=0.34
β-blockers	79 (3391/4279)	84 (631/750)	81 (1243/1533)	P=0.01
RAAS-blockers	68 (2919/4277)	76 (567/749)	77 (1180/1532)	P<0.0001
Statins	79 (3385/4275)	80 (597/750)	80 (1230/1533)	P=0.72
All of the above	44 (1865/4271)	51 (384/749)	50 (766/1530)	P<0.0001
Glucose lowering				
Oral	-	-	60 (369/1520)	
Insulin	-	-	24 (916/1534)	

* Taking into account clustering of patients within centres and adjusted for age and gender

Table 3: Caregiver providing the care presented as % (n/total n).

Caregiver	Diabetes			
	No	Newly Detected	Previously Known	Significance[*1]
General practitioner	53 (2285/4290)	51 (383/752)	51 (775/1536)	P=0.66
Cardiologist	70 (3016/4290)	75 (561/752)	73 (1121/1536)	P=0.68
Endocrinologist/Diabetologist	1 (47/4290)	1 (8/752)	17 (267/1536)	P<0.0001
Cardiac specialist nurse	2 (80/4290)	1 (9/752)	2 (23/1536)	P=0.86
Cardiac Rehabilitation Program	35 (1504/4247)	33 (248/748)	32 (486/1522)	P=0.48

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Figure 1: Percentage of patients reaching blood pressure treatment target accounting for clustering of patients within centres and adjusted for age and gender.

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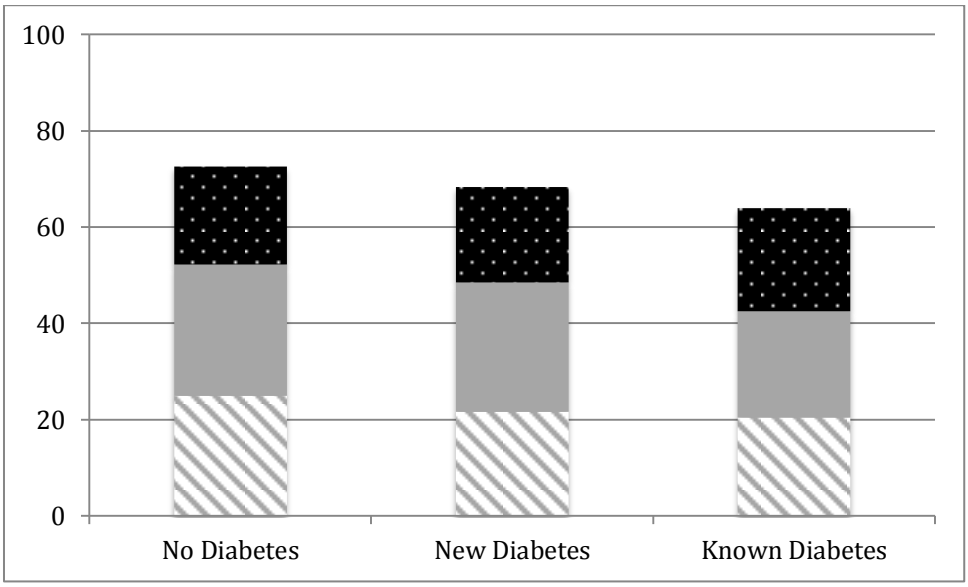

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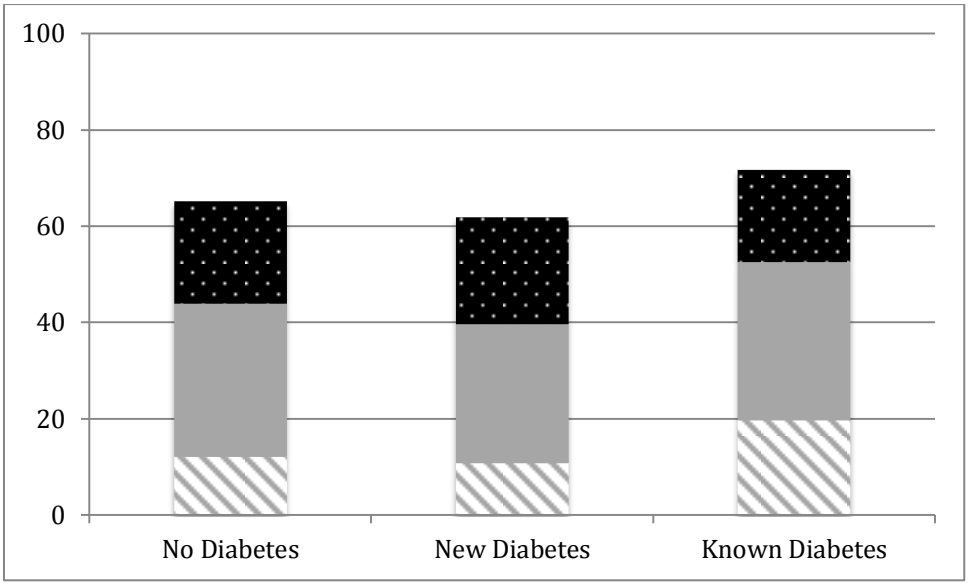

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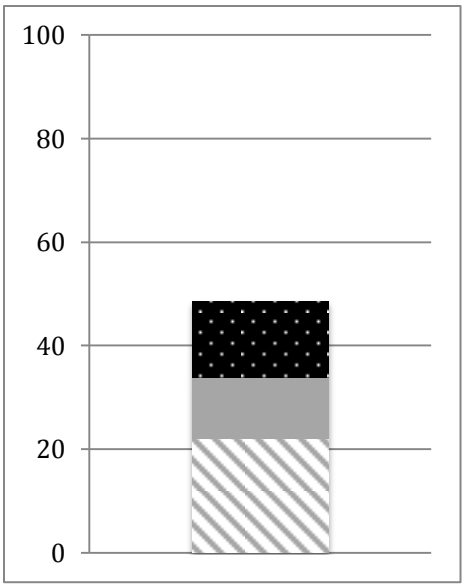

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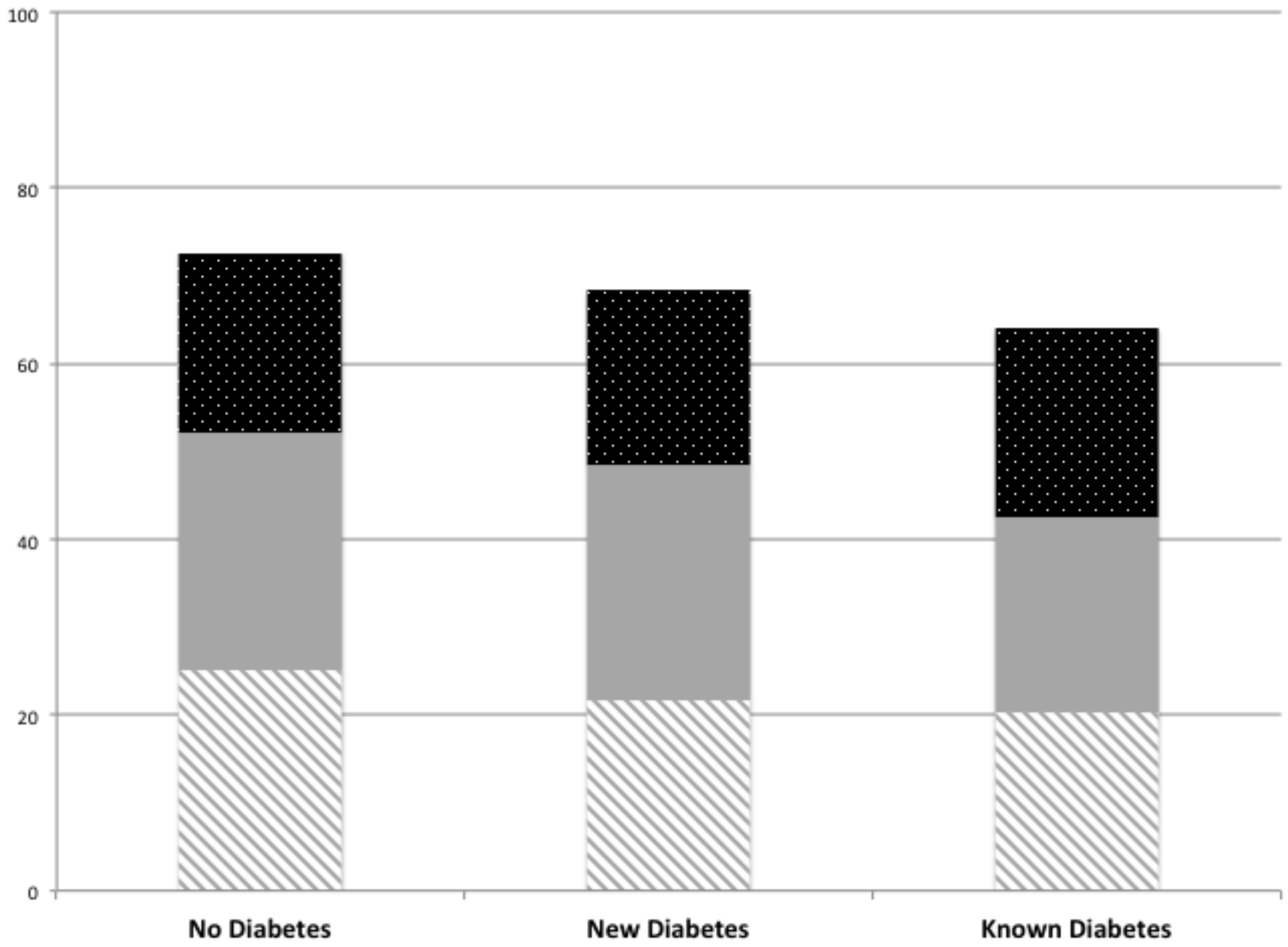

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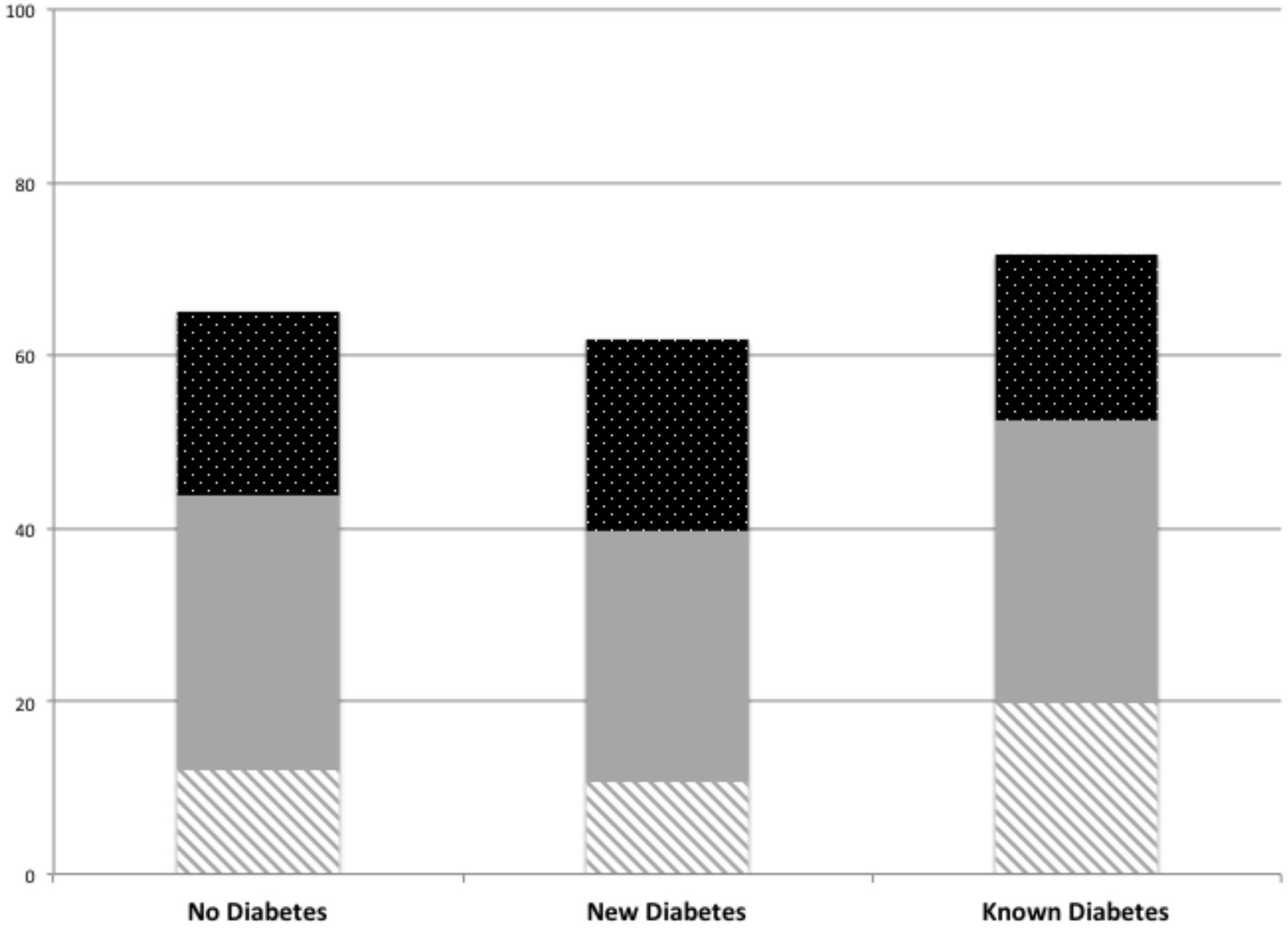

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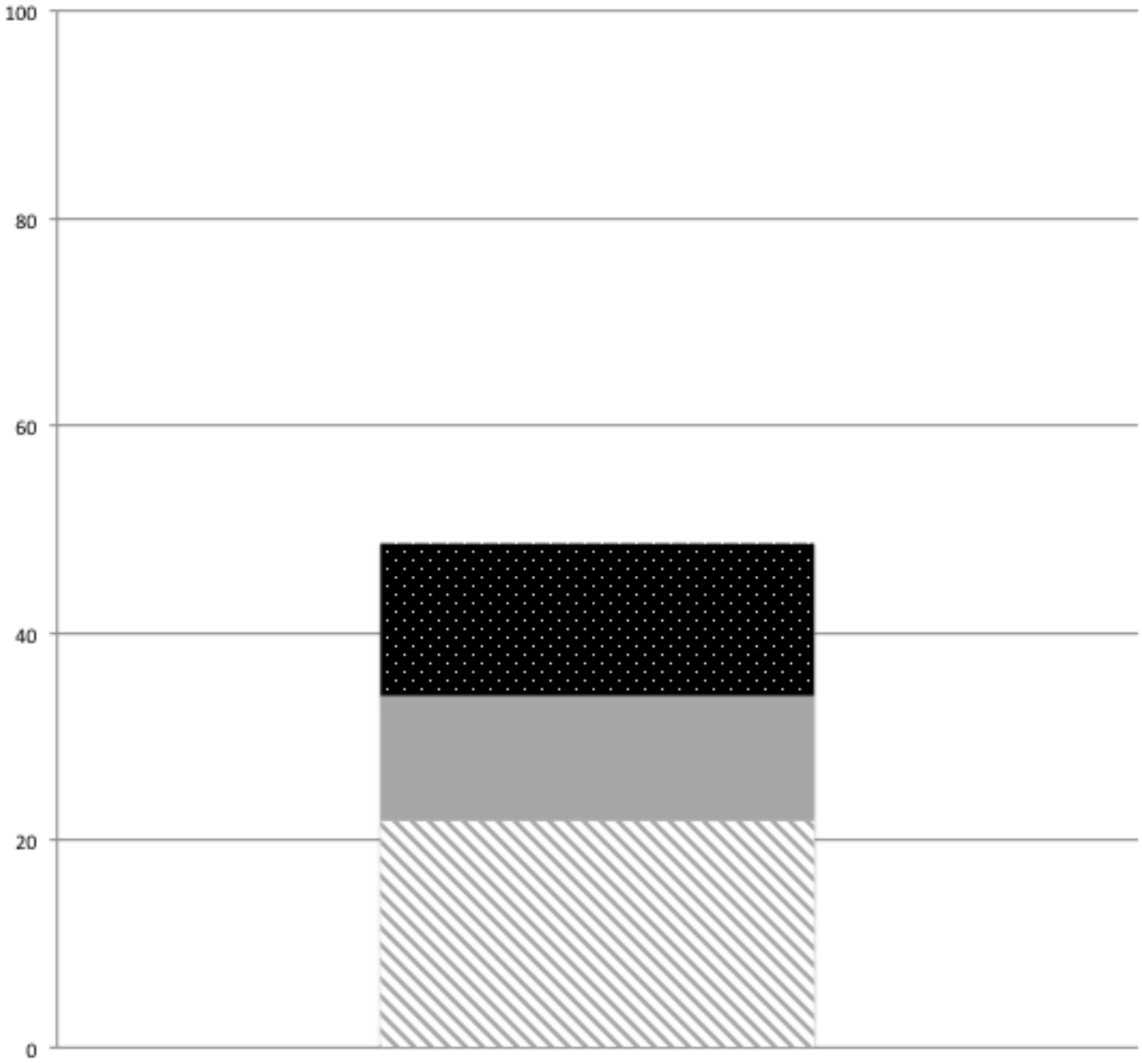

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Pharmacologic treatment in patients with established coronary artery disease and diabetes needs improvement: a report from the EUROASPIRE III cross-sectional study

Viveca Gyberg[1,2], Kornelia Kotseva[3], Jean Dallongeville[4], Guy De Backer[5], Linda Mellbin[1], Lars Rydén[1], David Wood[3], Dirk De Bacquer[5] for the EUROASPIRE Study Group.

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Abstract

Purpose: Diabetes is common in patients with coronary artery disease and this combination is accompanied by a serious prognosis, which may be improved by a target driven risk factor management. It has been reported that coronary artery disease patients with diabetes are less well managed than subjects with normal glucose regulation. The present aim was to investigate the use of comprehensive pharmacological therapy defined as a combination of aspirin, β-blockade, Renin-Angiotensin-Aldosterone-System-blockade and a statin, and obtained treatment targets in a large cohort of coronary artery disease-patients with and without diabetes.

Methods and Results: EUROASPIRE III was a cross-sectional observational study of stable coronary artery disease-patients aged 18-80 years at 76 centres in 22 European countries during 2006–2007. The glucometabolic category (known, newly detected or no diabetes), guideline treatment target fulfilment and the use of pharmacological treatment were assessed at a study visit. Of all patients investigated (females 25%) 4295 (57%) had no diabetes, 1541 (28%) known diabetes and 752 (15%) newly detected diabetes. Comprehensive pharmacological therapy was used in 50% of the patients with diabetes and 44% of the patients without. The proportion of coronary artery disease-patients with previously known diabetes who reached the treatment targets were 20% for blood pressure, 53% for LDL-cholesterol and 20% for HbA1c.

Conclusion: This study demonstrates a low use of a comprehensive pharmacological therapy. This probably contributed to the poor adherence to treatment targets for cardiovascular prevention, particularly seen among patients with a combination of coronary artery disease and diabetes.

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