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RISKS ASSOCIATED WITH PERMANENT DISCONTINUATION OF BLOOD PRESSURE LOWERING MEDICATIONS IN PATIENTS WITH TYPE 2 DIABETES

--Manuscript Draft--

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Abstract:	Objective: The associations of discontinuation of the study medication on major outcomes were assessed in the ADVANCE Trial. Methods: ADVANCE was a factorial randomized controlled trial of blood pressure lowering (a fixed combination of perindopril and indapamide versus placebo) and intensive glucose control (vs standard glucose control) in patients with type 2 diabetes. Patients who permanently discontinued the randomised blood pressure lowering medication during the study period (n=1,557) were compared with others (n=9,583). Cox's proportional hazards models were used to estimate the effects of the discontinuation on the risks of macrovascular events, microvascular events together

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	and separately and all-cause mortality, using discontinuation as a time-dependent covariate. Results: In multivariable analyses, discontinuation was associated with increased risks of combined macro- and microvascular events (hazard ratio 2.24, 95% CI 1.96-2.57), macrovascular events (3.23, 2.75-3.79), microvascular events (1.38, 1.11-1.71), and all-cause mortality (7.99, 6.92-9.21), which were highest in the first year after discontinuation. These associations were similar in active and placebo groups, except in the first year after discontinuation during which event rates were lower in the active group than in the placebo group ($p \leq 0.01$). Conclusions: Discontinuation of study medication is a potent risk marker for identifying high risk patients. Thus it is important that clinicians seek to identify such patients early after discontinuation of treatment. Although some short-term residual effects of previous active treatment can be expected, patients who discontinue require further urgent investigation and management.

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Dear Professor Zanchetti

RE: JH-D-15-00746, entitled "RISKS ASSOCIATED WITH PERMANENT DISCONTINUATION OF BLOOD PRESSURE LOWERING MEDICATIONS IN PATIENTS WITH TYPE 2 DIABETES"

Thank you for the detailed review of our manuscript and the helpful comments. We have considered the comments and responded to each of the issues raised, as outlined in detail in the attached document, "Response to Reviewers re Discontinuation paper 29th Sept". We believe the manuscript is much improved as a result.

We also attached a clean copy of the new manuscript and a revised copy with all changes highlighted.

I hope these modifications to the manuscript meet the approval of the Reviewers and Editors.

Yours sincerely

John Chalmers

Affiliated with

THE UNIVERSITY OF SYDNEY

Reviewer 1:

Thank you for your useful suggestions. We have attempted to address your suggestions as follows:

Comment 1:

In the abstract (Results), it should be more clear that the increased risk for events was in comparison with patients who continued on randomized treatment.

Response 1:

Thank you for this comment. We clearly stated in the methods section of the abstract that patients who permanently discontinued the randomised blood pressure lowering medication during the study period (n=1,557) were compared with others (n=9,583). However, we take on board this comment and have stated, in the results section of the abstract, that "*In multivariable analyses, discontinuation was associated with increased risks of combined macro- and microvascular events (hazard ratio 2.24, 95% CI 1.96-2.57), macrovascular events (3.23, 2.75-3.79), microvascular events (1.38, 1.11-1.71), and all-cause mortality (7.99, 6.92-9.21)* ***compared to continuing administration of randomised medications during the trial period***,…"

Comment 2:

The ADVANCE trial had a factorial design. There is no information in the paper on the other treatment arms (glucose control). How many of the patients who stopped the randomized blood pressure treatment part did also quit the glucose control treatment part? And, how did these patients distribute between placebo and treatment groups etc. Could an imbalance between groups be a source of bias?

Response 2:

Thank you for this comment. The glucose control arm of the ADVANCE trial compared intensive vs standard treatment with different targets for HbA1c; intensive treatment with target HbA1c of <6.5% vs. standard treatment with local guideline recommended target. Furthermore, discontinuation of the study drug for this arm of the trial– gliclazide MR – was often associated with intensification of glucose control, when insulin was added to the intensive control regimen. Therefore, it is difficult to refer to "discontinuation" as this did not often happen unless the patients was lost to follow-up – a different matter altogether. Given this difference, and inherent complexity, we would propose not taking this matter up.

Comment 3:

It is unclear if the patients age used in the analyses was the age at randomization or if the age at stopping treatment was used in the discontinuation group. It seems likely that

the age when the follow-up started should be used (ie not at randomization in the discontinuation group).

Response 3:

The age used in the statistical analysis was the age at baseline. We used the Cox proportional hazard model with permanent discontinuation taken as a time-dependent variable, in which the information during the period from randomization until discontinuation contributes to the risk estimation in the persistent group, and that after discontinuation contributes to the risk estimation in the discontinuation group. In this setting, the age at baseline ought to be used; otherwise the effect of age would be wrongly estimated and affect the estimation of other variables.

However, we appreciate your concern, and the possibility that age at discontinuation could introduce a bias since the later patients discontinued, the older they would be. Therefore, we've performed a sensitivity analysis using a matched design, in which matching was made by age at the date of discontinuation as well as by sex, randomised treatment and prior history of vascular events at baseline. The pool of control patients in this analysis included persistent patients and patients who had not discontinued the study medication at the time of the case's discontinuation. This sensitivity analysis, which was clearly impervious to this bias, produced similar associations. Therefore, this potential bias does not appear to have affected the present results. This point has been acknowledged in Discussion as a limitation (see response 5).

Comment 4:

In the original publication, there is a statement that "at the end of follow-up, 4081 (73%) patients in the active treatment group and 4143 (74%) patients in the placebo group were adherent to randomized therapy". Please explain the difference between these published data and the data in this paper.

Response 4:

The definition of the permanent discontinuation in both situations was based on reports from local physicians or carers. The data published in the main paper included instances of permanent discontinuations resulting due to death of patients. In the present study, such discontinuations were considered to be "**due to death"** and not counted so that we could clearly define and count only those instances of discontinuation occurring before death.

Comment 5:

The limitations of the study, should be expanded with a more detailed discussion of potential sources of bias.

Response 5:

In accordance with this suggestion and comment 3, we have added the following sentence as a limitation since the age at discontinuation could be the potential bias in the 6th paragraph of the Discussion; "*Second, the difference of the age at discontinuation might have introduced a bias since patients who discontinued the study medication late during the trial would be older and have greater risk of vascular events. However, a sensitivity analysis using a matched design, which will be impervious to this bias, produced similar associations, thus, alleviating these concerns.*"

Reviewer 2

Thank you for your useful suggestions. We have attempted to address your suggestions as follows:

Comment 1:
The cause for permanent discontinuation other than death is reported, analysed and discussed but the reasons are too vague (wide) for providing precise information about the phenomenon of "sick stoppers" and "healthy adherents".

Response 1:

Thank you for your helpful comment. We agree that the analysis of different reasons is not very specific or precise. Therefore, we have provided further evidence through the analysis using left-censoring which supports our hypothesis from a different standpoint. However, we take on board the comment and have added the following sentence regarding Limitation in the 6th paragraph of the Discussion; "*Third, the reasons for discontinuation documented in case reports were very broad, making it difficult to clearly distinguish 'sick stoppers' and 'healthy adherers': However the analyses obtained with left-censoring produced reassurance regarding these findings, in terms of the main effect being due to 'sick stoppers'.*"

Comment 2:

Relevance of the information provided in the present study is derived from the data reported, in which discontinuation of placebo also increases risk during the first year, much more than the discontinuation of the active treatment. The authors give this data as evidence for a prolongued effect of the active medication after withdrawal. However, one relevant point for the discussion was missed, the fact that discontinuation due to side effects of medication in the active treatment is twice tan in the placebo group. In other words the reasons and may be the characteristics of the patients were different. This should be commented since this point has been considered a relevant one in the manuscript.

Response 2:

We agree and have added a sentence to the 5th paragraph of the Discussion, saying; "*This **may** suggest that the active medication continued to have a residual protective effect in the early months after cessation, and that this benefit was greater than any hazards due to withdrawal syndromes. **However, it should be noted that discontinuation due to side effects of the medication was greater in the actively treated group.***"

Comment 3:

Limitations of the post-hoc analysis should be mentioned.

Response 3:

As suggested, this point has been added in the 6th paragraph of the Discussion as a limitation as follows; "*Fifth, it should be noted that the present study constitutes a post-hoc observational analysis."*

Comment 4:

Description of the results is confuse in some moments and difficult to follow by the reader. Some effort in to clarify it should improve the manuscript.

Response 4:

Thank you for this suggestion. We have tried to clarify some of our descriptions in the Results, for example, in describing the data reported in some of our tables.

Manuscript (all changes highlighted)

RISKS ASSOCIATED WITH PERMANENT DISCONTINUATION OF BLOOD PRESSURE LOWERING MEDICATIONS IN PATIENTS WITH TYPE 2 DIABETES

Short title: effects of discontinuation of medication

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Conflicts of interest

SZ reports grants from Servier, and personal fees from Servier, MSD, BMS/Astra Zeneca, Sanofi-Aventis, Novo-Nordisk and Amgen Australia; SH reports receiving honoraria from Servier, Takeda and Novartis; PH reports being a consultant to Servier; GM reports personal fees from Servier, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Novartis, Menarini International, Recordati, and Takeda; NP reports grants from Servier, Pfizer, DUK, BHF, and HTA, and personal fees from Servier, Takeda, Menarini, and Pfizer; BN reports grants from NHMRC, Servier, Roche, Abbvie, Janssen, Dr Reddy's Laboratories, and Merck Schering Plough and personal fees from Servier, Abbott, Novartis, and Pfizer.; BW reports personal fees from Servier, Novartis, Boerhinger Ingelheim, and MSD; MW reports grants from Servier; JC reports grants from Servier, administered through the University of Sydney as Co-Principal investigator for ADVANCE and ADVANCE-ON and personal fees from Servier. YH, HA, RW, QL, LL and AR all report no conflicts of interest.

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ABSTRACT

Objective: The associations of discontinuation of the study medication on major outcomes were assessed in the ADVANCE Trial.

Methods: ADVANCE was a factorial randomized controlled trial of blood pressure lowering (a fixed combination of perindopril and indapamide versus placebo) and intensive glucose control (vs standard glucose control) in patients with type 2 diabetes. Patients who permanently discontinued the randomised blood pressure lowering medication during the study period (n=1,557) were compared with others (n=9,583). Cox's proportional hazards models were used to estimate the effects of the discontinuation on the risks of macrovascular events, microvascular events together and separately and all-cause mortality, using discontinuation as a time-dependent covariate.

Results: In multivariable analyses, discontinuation was associated with increased risks of combined macro- and microvascular events (hazard ratio 2.24, 95% CI 1.96-2.57), macrovascular events (3.23, 2.75-3.79), microvascular events (1.38, 1.11-1.71), and all-cause mortality (7.99, 6.92-9.21) compared to continuing administration of randomised medications during the trial period, which were highest in the first year after discontinuation. These associations were similar in active and placebo groups, except in the first year after discontinuation during which event rates were lower in the active group than in the placebo group ($p \leq 0.01$).

Conclusions: Discontinuation of study medication is a potent risk marker for identifying high risk patients. Thus it is important that clinicians seek to identify such patients early after discontinuation of treatment. Although some short-term residual effects of previous active treatment can be expected, patients who discontinue require further urgent investigation and management.

Key words: Discontinuation of Medicine, Microvascular Disease, Macrovascular Disease, All-cause Mortality, Proportional Hazards Models, Prospective Study

Abbreviations: HbA1c, haemoglobin A1c; EMEs, established market economies

Introduction

Non-adherence to blood pressure lowering medication is a major problem which contributes to the burden of vascular events and deaths associated with hypertension [1-7]. Non-adherence, often defined as not taking medications as intended by the prescriber [8], can range from primary non-adherence (never starting the prescribed medication), to missing a few days of prescribed treatment, having 'drug holidays' for several days or weeks or to permanent discontinuation (i.e. permanently ceasing to take the medication and not re-starting). Permanent discontinuation is high for chronic conditions, with less than half of patients reporting persistent use of blood pressure lowering medication within one year of the initial prescription [9]. Stopping treatment may be expected to negate the benefits conferred by treatment in terms of cardiovascular event reduction. However, the picture is complex. Some data indicate ongoing benefits of long-term blood pressure lowering treatment [10,11] even after cessation of treatment (as also seen with statin [12], antiplatelet [13] and glucose lowering therapy [10,14]). There may also be rebound effects early, with short-term increases in blood pressure, particularly seen with drugs acting on the sympathetic nervous system, including beta blockers [15]: such rebound effects are associated with increased risk of cardiovascular events or death [6,16], as has been shown for anti-platelet agents [17-19] and statins [20]. Finally, stopping treatment can also be associated in a non-causal way with adverse outcomes: patients who are non-adherent to a wide range of beneficial interventions, in addition to medication, are at increased risk of adverse outcomes; and also a prodromal syndrome, clinical event, or diagnosis (eg. of cancer) may be associated with both a higher rate of stopping treatments and a higher rate of death.

Clinical trials provide an opportunity to help delineate the contributions of these

factors, with assessment of event rates following stopping of either placebo or active treatments. Such analyses could provide information relevant to the risks of non-adherence, and the importance of maintaining treatment and follow-up in clinical trials and clinical practice. We therefore examined the associations of discontinuation of study treatment on macrovascular events, microvascular events and mortality from any-cause, cardiovascular and non-cardiovascular diseases, amongst patients with type 2 diabetes using data from the ADVANCE Trial.

Methods

Study design of the ADVANCE trial

ADVANCE was a factorial randomized controlled trial of blood pressure lowering and intensive blood glucose control in patients with type 2 diabetes. Details have been described previously [21]. In brief, a total of 11,140 patients with type 2 diabetes aged 55 years or older who had a history of major macrovascular or microvascular disease or at least one other risk factor for vascular disease, were recruited from 215 collaborating centers in 20 countries from Asia, Australasia, Europe, and North America between November 2001 and March 2003. Approval for the trial was obtained from each center's institutional review board, and all participants provided written informed consent.

Participants were randomly assigned, in a factorial design, to fixed combination of perindopril and indapamide (2 mg/0.625 mg for the first 3 months and 4 mg/1.25 mg thereafter) or matching placebo for the blood-pressure–lowering comparison, and to either an intensive glucose control strategy (target HbA1c of ≤6.5%) or a standard glucose control strategy based on local guidelines for the glucose-control comparison.

Discontinuation of randomised study blood-pressure–lowering medication or placebo

Patients were seen at 3, 4 and 6 months after randomization, and then every 6 months until the end of the study. The patient's persistence with, or permanent discontinuation of, randomised study medication was confirmed at study visits and via reports from local physicians or carers together with the date of discontinuation where relevant. The reasons for permanent discontinuations were categorized as either the patients' inability or unwillingness to continue the study medication, or adverse events such as cough, dizziness/hypotension and serious adverse events, or other causes. Neither short interruptions of study medicine with re-administration, nor cessation due to death, were counted as permanent discontinuations which required cessation of perindopril/indapamide through to the end of randomised treatment.

Study outcomes

Primary outcomes were a composite of major macrovascular and major microvascular events, major macrovascular events, major microvasuclar events and all-cause mortality. Major macrovascular events were defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Major microvascular events were defined as new or worsening nephropathy (development of macroalbuminuria, defined as a urinary albumin:creatinine ratio of more than 300μg of albumin per milligram of creatinine, or doubling of serum creatinine level to at least 200 μmol per liter, the need for renal- replacement therapy, or death due to renal disease) or new or worsening retinopathy (development of proliferative retinopathy, macular edema or diabetes-related blindness or the use of retinal photocoagulation therapy). Secondary outcomes were the components of the primary outcomes such as cardiovascular death,

non-fatal myocardial infarction, non-fatal stroke, new or worsening retinopathy, new or worsening nephropathy and end-stage renal disease defined as the need for renal-replacement therapy or death due to renal disease. Deaths from non-cardiovascular causes were also investigated. An independent End Point Adjudication Committee adjudicated all the events and deaths.

Statistical analysis

Patients who permanently discontinued the randomised blood pressure lowering medication, before the trial was completed, were compared to the other participants. The effects of permanent discontinuation on the risks of outcomes were estimated using Cox's proportional hazards model, in which discontinuation was taken as a time-dependent covariate and was considered to be present only if it occurred before the index outcome. Multivariable adjustment was made for age, sex, randomized treatment and other covariates at baseline that were significantly associated with incident permanent discontinuation in unadjusted analyses. The effects of permanent discontinuation in subgroups were compared by adding an interaction term to the statistical model. The life-table method was used to estimate an event rate for each outcome occurring during each 12 month interval after permanent discontinuation. To assess whether reverse causality (essentially the same concept as imminent clinical events or prodromal syndrome) modified the results, further analyses were done after discounting the first year of follow-up after discontinuation in those who discontinued treatment, and the first year of follow-up after randomization in those who persisted with treatment throughout (i.e. after "left censoring"). Sensitivity analyses were performed using matched design, in which patients were enrolled as cases when they discontinued the study medication before

each outcome, and controls were randomly selected from patients who had not discontinued the study medication at the time of the case's discontinuation [22]. Matching was by age at discontinuation, sex, randomised treatment and prior history of vascular events at baseline, and three controls were selected for each case unless fewer matches could be identified. In order to evaluate the effects of discontinuation on change in hemodynamic parameters as well as blood glucose control, mean values of blood pressure, heart rate, haemoglobin A1c (HbA1c) and serum creatinine were calculated using the latest measurements before discontinuation compared with similar measurements in each 12 month interval after discontinuation. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). A two-sided $P<0.05$ was considered to be statistically significant.

Results

Permanent discontinuation of randomised blood pressure lowering medication

Patient characteristics are summarized in Table 1. Mean age was 65.8 years, 42.5% were female, and 43.6% were recruited in established market economies (EMEs). Patients who discontinued the study medication were older compared to those who did not, and were more recruited in EMEs than in other regions. During a median follow-up period of 4.3 years, 1,557 of the 11,140 patients initially randomised (14.0%) permanently discontinued randomised blood pressure lowering medication; 809 patients in the active group (14.5%) and 748 in the placebo group (13.4%) (Table 2). The main reasons for permanent discontinuation were "inability or unwillingness to continue the study medicine" (41%) or "adverse events" (31%). Most discontinuations occurred during the first year of the study period (41%), particularly in the actively treated group (Figure 1).

As shown in online Supplemental Table S1 (Supplemental Digital Content 1), the risk of permanent discontinuation was significantly associated with older age, male sex, recruitment outside of Asia, prior history of macrovascular events, prior history of microvascular events, high systolic blood pressure, high total cholesterol, high BMI, long duration of diabetes, lower education level, any use of blood pressure lowering medication at baseline and presence of alcohol use at baseline. When the effects of these factors on discontinuation were compared between randomised groups using the interaction terms, there was significant attenuation of the effects of systolic blood pressure and any use of blood pressure lowering medication at baseline in the active group compared to the placebo group (Table S1, Supplemental Digital Content 1).

Impact of permanent discontinuation of randomised blood pressure lowering medication on outcomes

Permanent discontinuation of randomised blood pressure lowering medication (active or placebo) was associated with increased risks of combined macro- and microvascular events, macrovascular events, microvascular events and all-cause mortality in minimally and fully adjusted multivariable models (the left half of Table 3 and Table S2, Supplemental Digital Content 1). Likewise, there were positive associations between permanent discontinuation and the risks of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, new or worsening nephropathy, end-stage kidney disease and non-cardiovascular death (the left half of Table S3 and S4, Supplemental Digital Content 1). Similar associations were observed for each randomised group, perindopril-indapamide and placebo. These associations between permanent discontinuation and all outcomes were broadly similar when sensitivity analyses were performed using a matched design

(Table S5, Supplemental Digital Content 1). In subgroups defined by age groups (65 years and under/over 65 years), by gender (male/female), by prior history of vascular events at baseline (presence/absence) and by region (Asian, EMEs and Eastern Europe), permanent discontinuation was consistently associated with increased risks of combined macro- and microvascular events and all-cause mortality (Figure S1, Supplemental Digital Content 1). The positive association with combined macro- and micro vascular events was stronger among participants with prior history of vascular events at baseline than those without, whereas the association with all-cause mortality was stronger in Asian patients than patients in EMEs and eastern Europe (both $p<0.01$ for interaction). In analyses stratifying participants by the reason for permanent discontinuation, participants who were unable or unwilling to take the study medication were at higher risks of combined macro- and microvascular events, macrovascular events and all-cause mortality than those who discontinued medication for other reasons (Table S6, Supplemental Digital Content 1).

Among participants who permanently discontinued the study medication, event rates of combined macro- and microvascular events, macrovascular events and all-cause mortality were highest during the first 12 months, and during this period were lower in the active group than in placebo group (all $p \leq 0.01$). Thereafter the incidence of these outcomes decreased steeply and levelled off to the end of the study, at which time the event rates were equivalent between randomised groups (Figure 2). The mean difference in blood pressure between the active and placebo groups observed before discontinuation disappeared gradually after discontinuation (Figure S2, Supplemental Digital Content 1). On the other hand, there was no clear difference in mean values of heart rate, HbA1c and serum creatinine before and after discontinuation between randomised groups. When left-censoring by a year, we found the effects of permanent discontinuation on most of

outcomes were attenuated, but the association with macrovascular events and mortality remained significant (the right half of Table 3, S2, S3 and S4, Supplemental Digital Content 1). Similar results were obtained in the sensitivity analyses using left-censoring in the matched design comparison except that the significance was lost for macrovascular events, but retained for all-cause mortality (Table S7, Supplemental Digital Content 1).

Discussion

This is the first large-scale study to report the association of discontinuation of blood pressure lowering therapy with a variety of outcomes in patients with type 2 diabetes. Permanent discontinuation of randomised blood pressure lowering medication was associated with increased risks of macrovascular events, microvascular events and all-cause deaths. The associations were most pronounced in the first 12 months following discontinuation of treatment, with a greater effect seen in the placebo group for both all-cause mortality and major macrovascular events. After left-censoring by a year, the effects were attenuated for most of outcomes, but still remained significant for macrovascular events and mortality.

Several studies have shown that non-adherence to both placebo and active study medication is associated with increased risk of major adverse events [4-7, 10,13, 19]. A recent systematic review of randomised controlled trials reported that good placebo adherers had about 40% lower cardiovascular [23] and all-cause mortality [24] than poor placebo adherers. Apart from the short-term rebound effects of ceasing medications, the literature has generally attributed this to the ‘healthy adherer’ phenomenon, whereby patients who adhere to placebo are also thought to adhere to a range of other beneficial

treatments and behaviours. The ‘healthy adherer’ effect is a well-described theory in placebo-controlled trials assessing the effects of different levels of adherence to randomised treatment on clinical outcomes [25]. The benefits are not restricted to the key outcomes of the trial, but may include unrelated outcomes, such as motor vehicle accidents and work place accidents [26].

There is also the “sick stopper” phenomenon, whereby patients who are non-adherent are often sicker than those who are adherent either due to true clinical differences or non-use of other medication and of healthy behaviours [1,27,28]. It is also possible that patients who develop serious illness may be less willing or able to continue preventive treatments, or may even have them actively stopped. This could occur for major nonvascular conditions such as cancer or dementia, but also paradoxically, for vascular events, with more treatment discontinuation following an event [7].

While it might be thought that the healthy adherer and the sick stopper merely reflect two sides of the same coin, the different time courses of these two phenomena suggest there are real differences between them. As seen in the present analyses, both all-cause mortality and major macrovascular events increase maximally in the first year after discontinuation (Figure 2), a finding consistent with the sick stopper effect. On the other hand, the rates for all major outcomes after this first year post-discontinuation, remain constant and significantly raised (Figure 2 and Table 3), a finding consistent with the healthy adherer effect. The attenuation by left-censoring of the effects of discontinuation on all-cause mortality in particular (but on all outcomes to some extent),suggests a dominant effect of the sick stopper phenomena in this study, possibly reflecting “imminent adverse events” such as diagnosis of cancer and development of angina pectoris or of symptoms of heart failure.

The other important finding from the present analysis was that the event rate for both all-cause mortality and major macrovascular events in those that discontinued active treatment with perindopril/indapamide was lower than for those that discontinued placebo. This may suggest that the active medication continued to have a residual protective effect in the early months after cessation, and this benefit was greater than any hazards due to withdrawal syndromes. However, it should be noted that discontinuation, due to side effects of the medication was greater in the actively treated group. After a year, the event rates converged and were similar until the end of follow-up. This finding is consistent with the results of the ADVANCE-ON study, which recently reported results of six-year post-trial follow-up after ADVANCE finished [10]. At the end of follow-up the benefits of perindopril/indapamide on total and cardiovascular mortality that were seen at the end of the active phase of the trial were still present, albeit attenuated. A recent meta-analysis including 18 placebo-controlled blood pressure lowering trials with 132,854 patients also showed a persistent decrease in overall mortality following the end of the trial phase, despite equal numbers of patients in each group receiving active therapy post-trial [11].

The strengths of our study include the large sample size and adjudication of major outcomes including microvascular events. A limitation is the small number of patients who stopped the study medication compared to that which may occur in clinical practice. Second, the difference of the age at discontinuation might have introduced a bias since patients who discontinued the study medication late during the trial would be older and have greater risk of vascular events. However, the sensitivity analysis using matched design, which will be impervious to this bias, produced the similar associations, thus, alleviating these concerns. Third, the reasons for discontinuation documented in case reports were very broad, making it difficult to clearly distinguish ‘sick stoppers’ and

'healthy adherers': However the analyses obtained with left-censoring produced reassurance regarding these findings, in terms of the main effect being due to 'sick stoppers'. Fourth, the possibility remains of residual confounding by unmeasured or unknown risk factors. Fifth, it should be noted that the present study constitutes a post-hoc observational analysis.

In conclusion, the association between discontinuation of randomised therapy with increased risks of vascular events and mortality in both active and placebo controlled arms appears to be most consistent with the previously described 'sick stopper' phenomenon. There is also evidence of persistent beneficial effect of blood pressure lowering therapy with perindopril/indapamide on mortality and macrovascular events following cessation of active treatment and a longer term 'healthy adherer' effect. The identification of high risk patients who wish to discontinue treatment may help to identify those who require additional intervention to prevent impending cardiovascular events.

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Conflicts of interest

SZ reports grants from Servier, and personal fees from Servier, MSD, BMS/Astra Zeneca, Sanofi-Aventis, Novo-Nordisk and Amgen Australia; SH reports receiving honoraria from Servier, Takeda and Novartis; PH reports being a consultant to Servier; GM reports personal fees from Servier, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Novartis, Menarini International, Recordati, and Takeda; NP reports grants from Servier, Pfizer, DUK, BHF, and HTA, and personal fees from Servier, Takeda, Menarini, and Pfizer; BN reports grants from NHMRC, Servier, Roche, Abbvie, Janssen, Dr Reddy's Laboratories, and Merck Schering Plough and personal fees from Servier, Abbott, Novartis, and Pfizer.; BW reports personal fees from Servier, Novartis, Boerhinger Ingelheim, and MSD; MW reports grants from Servier; JC reports grants from Servier, administered through the University of Sydney as Co-Principal investigator for ADVANCE and ADVANCE-ON and personal fees from Servier. YH, HA, RW, QL, LL and AR all report no conflicts of interest.

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Figure Legends

Figure 1. Permanent discontinuations of randomised blood pressure lowering medication according to time from randomisation in active and placebo blood pressure lowering groups

Active treatment denotes the fixed combination of perindopril and indapamide.

Figure 2. Event rates of outcomes after permanent discontinuation of randomised blood pressure lowering medication during each 12 months according to blood pressure randomised groups

The life-table method was used to estimate an event rates at the mid-point of each 12 month interval. All p values were >0.10 for the comparison between the active and placebo groups after 12 months.

Table 1. Baseline characteristics.

Variables	Overall (n=11,140)	Patients who did discontinue (n=1,557)	Patients who did not discontinue (n=9,583)
Demographics			
Age, y	65.8 (6.4)	67.4 (6.5)	65.5 (6.3)
Female, %	42.5	41.6	42.7
Regions of recruitment (%)*			
Asian countries	37.1	15.6	40.6
Established market economy countries	43.6	69.4	39.5
Eastern Europe	19.2	15.0	19.9
Medical and lifestyle history			
History of major macrovascular disease, %	32.2	37.5	31.4
History of major microvascular disease, %	10.3	14.7	9.6
Current smoking, %	15.1	15.4	15.0
Current alcohol intake, %	30.5	38.7	29.2
Duration of diabetes, y	7.9 (6.4)	8.2 (6.5)	7.9 (6.3)
Age of completion of highest education, y	18.4 (7.3)	18 (7.6)	18.5 (7.2)
Clinical risk factors			
Systolic blood pressure, mmHg	145 (21.5)	146.9 (21.9)	144.7 (21.5)
Diastolic blood pressure, mmHg	80.6 (10.9)	79.9 (10.8)	80.8 (11.0)
History of currently treated hypertension	68.7	69.4	68.6
HbA1c	7.5 (1.6)	7.5 (1.5)	7.5 (1.6)
Total cholesterol, mmol/L	5.2 (1.2)	5.1 (1.1)	5.2 (1.2)
High density lipoprotein cholesterol, mmol/l	1.3 (0.4)	1.2 (0.3)	1.3 (0.4)
Triglyceride, mmol/L	1.6 (1.2, 2.3)	1.7 (1.2, 2.3)	1.6 (1.2, 2.3)
BMI, kg/m^2	28.3 (5.2)	29.5 (5.6)	28.2 (5.1)
Nonstudy blood pressure–lowering drug, %	75.1	78.0	74.6
Nonstudy glucose-lowering treatment			
Oral glucose-lowering agent, %	90.9	90.2	91.0
Insulin, %	1.4	1.1	1.5
Randomized intensive glucose lowering, %	50.0	43.5	51.1
Randomized perindopril-indapamide, %	50.0	52.0	49.7

Values are mean (SD) for continuous variables except median (interquartile interval) for triglycerides, and percentage for categorical variables.

Asian countries comprise China, India, Malaysia and Philippines. EMEs comprises Australia, Canada, France, Germany, Ireland, Italy, Netherlands, New Zealand and United Kingdom. Eastern Europe countries comprise Czech Republic, Estonia, Hungary, Lithuania, Poland, Russia and Slovakia.

History of hypertension indicates use of blood pressure lowering drugs or blood pressure > 140/90 mmHg.

*The percentage shown for each region is of overall patients, of all those who discontinued and of all those who did not discontinue.

Table 2. The number of patients who permanently discontinued randomised blood pressure lowering medication according to randomised group and overall.

	Active N=5569	**Placebo N=5571**	**Overall N=11140**
Permanent discontinuation			
Number of patients (%)	809 (14.5)	748 (13.4)	1557 (14.0)
Reason for discontinuation*			
Unable or unwilling to continue	320 (40.0)	396 (52.9)	716 (46.0)
Adverse events	317 (39.2)	158 (21.1)	475 (30.5)
Other causes	172 (21.3)	194 (25.9)	366 (23.5)

Active treatment denotes the fixed combination of perindopril and indapamide.

Adverse events include cough, dizziness, hypotension and severe adverse events.

*The percentage shown is of all those who discontinued.

Table 3. The effects of permanent discontinuation of randomised blood pressure lowering medication on the risks of outcomes according to randomised groups and overall in the multivariable adjusted model.

	Whole study period				Left censoring by 1 year			
Outcome	**No. of events**	**HR (95%CI)**	**P**	**P for interaction**	**No. of events**	**HR (95%CI)**	**P**	**P for interaction**
Combined macro- and microvascular events								
Active	861	2.21 (1.83, 2.67)	<0.01	0.30	621	1.45 (1.11, 1.90)	<0.01	0.51
Placebo	938	2.54 (2.11, 3.05)	<0.01		675	1.27 (0.94, 1.72)	0.12	
Overall	1799	2.36 (2.07, 2.71)	<0.01		1296	1.37 (1.11, 1.67)	<0.01	
Major macrovascular events								
Active	480	3.08 (2.45, 3.87)	<0.01	0.09	315	1.79 (1.27, 2.52)	<0.01	0.86
Placebo	520	4.02 (3.23, 5.00)	<0.01		320	1.71 (1.17, 2.51)	<0.01	
Overall	1000	3.52 (2.99, 4.14)	<0.01		635	1.75 (1.35, 2.27)	<0.01	
Major microvascular events								
Active	439	1.49 (1.11, 1.99)	<0.01	0.52	353	1.22 (0.84, 1.77)	0.29	0.36
Placebo	477	1.30 (0.95, 1.77)	0.10		403	0.94 (0.61, 1.44)	0.78	
Overall	916	1.39 (1.12, 1.73)	<0.01		756	1.08 (0.82, 1.44)	0.58	
All-cause mortality								
Active	408	8.62 (7.03, 10.56)	<0.01	0.06	241	4.25 (3.17, 5.70)	<0.01	0.78
Placebo	471	11.18 (9.23, 13.55)	<0.01		256	4.01 (2.95, 5.44)	<0.01	
Overall	879	9.89 (8.55, 11.43)	<0.01		497	4.13 (3.32, 5.14)	<0.01	

The patients who permanently discontinued the randomised blood pressure lowering medication were compared to the other participants. Active treatment denotes the fixed combination of perindopril and indapamide.

†Adjustment was made for age, sex, randomised treatment, region, systolic blood pressure, total cholesterol, BMI, duration of diabetes, age of completion of highest education, history of microvascular event, history of macrovascular event, any use of blood pressure lowering medication at baseline, alcohol intake at baseline and interaction terms between randomised treatment and both systolic blood pressure and any use of blood pressure lowering medication at baseline.

List of Supplemental Digital Content

Supplemental Digital Content 1. Supplementary tables and figures. docx

Manuscript

RISKS ASSOCIATED WITH PERMANENT DISCONTINUATION OF BLOOD PRESSURE LOWERING MEDICATIONS IN PATIENTS WITH TYPE 2 DIABETES

Short title: effects of discontinuation of medication

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ABSTRACT

Objective: The associations of discontinuation of the study medication on major outcomes were assessed in the ADVANCE Trial.

Methods: ADVANCE was a factorial randomized controlled trial of blood pressure lowering (a fixed combination of perindopril and indapamide versus placebo) and intensive glucose control (vs standard glucose control) in patients with type 2 diabetes. Patients who permanently discontinued the randomised blood pressure lowering medication during the study period (n=1,557) were compared with others (n=9,583). Cox's proportional hazards models were used to estimate the effects of the discontinuation on the risks of macrovascular events, microvascular events together and separately and all-cause mortality, using discontinuation as a time-dependent covariate.

Results: In multivariable analyses, discontinuation was associated with increased risks of combined macro- and microvascular events (hazard ratio 2.24, 95% CI 1.96-2.57), macrovascular events (3.23, 2.75-3.79), microvascular events (1.38, 1.11-1.71), and all-cause mortality (7.99, 6.92-9.21) compared to continuing administration of randomised medications during the trial period, which were highest in the first year after discontinuation. These associations were similar in active and placebo groups, except in the first year after discontinuation during which event rates were lower in the active group than in the placebo group ($p \leq 0.01$).

Conclusions: Discontinuation of study medication is a potent risk marker for identifying high risk patients. Thus it is important that clinicians seek to identify such patients early after discontinuation of treatment. Although some short-term residual effects of previous active treatment can be expected, patients who discontinue require further urgent investigation and management.

Key words: Discontinuation of Medicine, Microvascular Disease, Macrovascular Disease, All-cause Mortality, Proportional Hazards Models, Prospective Study

Abbreviations: HbA1c, haemoglobin A1c; EMEs, established market economies

Introduction

Non-adherence to blood pressure lowering medication is a major problem which contributes to the burden of vascular events and deaths associated with hypertension [1-7]. Non-adherence, often defined as not taking medications as intended by the prescriber [8], can range from primary non-adherence (never starting the prescribed medication), to missing a few days of prescribed treatment, having 'drug holidays' for several days or weeks or to permanent discontinuation (i.e. permanently ceasing to take the medication and not re-starting). Permanent discontinuation is high for chronic conditions, with less than half of patients reporting persistent use of blood pressure lowering medication within one year of the initial prescription [9]. Stopping treatment may be expected to negate the benefits conferred by treatment in terms of cardiovascular event reduction. However, the picture is complex. Some data indicate ongoing benefits of long-term blood pressure lowering treatment [10,11] even after cessation of treatment (as also seen with statin [12], antiplatelet [13] and glucose lowering therapy [10,14]). There may also be rebound effects early, with short-term increases in blood pressure, particularly seen with drugs acting on the sympathetic nervous system, including beta blockers [15]: such rebound effects are associated with increased risk of cardiovascular events or death [6,16], as has been shown for anti-platelet agents [17-19] and statins [20]. Finally, stopping treatment can also be associated in a non-causal way with adverse outcomes: patients who are non-adherent to a wide range of beneficial interventions, in addition to medication, are at increased risk of adverse outcomes; and also a prodromal syndrome, clinical event, or diagnosis (eg. of cancer) may be associated with both a higher rate of stopping treatments and a higher rate of death.

Clinical trials provide an opportunity to help delineate the contributions of these

factors, with assessment of event rates following stopping of either placebo or active treatments. Such analyses could provide information relevant to the risks of non-adherence, and the importance of maintaining treatment and follow-up in clinical trials and clinical practice. We therefore examined the associations of discontinuation of study treatment on macrovascular events, microvascular events and mortality from any-cause, cardiovascular and non-cardiovascular diseases, amongst patients with type 2 diabetes using data from the ADVANCE Trial.

Methods

Study design of the ADVANCE trial

ADVANCE was a factorial randomized controlled trial of blood pressure lowering and intensive blood glucose control in patients with type 2 diabetes. Details have been described previously [21]. In brief, a total of 11,140 patients with type 2 diabetes aged 55 years or older who had a history of major macrovascular or microvascular disease or at least one other risk factor for vascular disease, were recruited from 215 collaborating centers in 20 countries from Asia, Australasia, Europe, and North America between November 2001 and March 2003. Approval for the trial was obtained from each center's institutional review board, and all participants provided written informed consent.

Participants were randomly assigned, in a factorial design, to fixed combination of perindopril and indapamide (2 mg/0.625 mg for the first 3 months and 4 mg/1.25 mg thereafter) or matching placebo for the blood-pressure–lowering comparison, and to either an intensive glucose control strategy (target HbA1c of ≤6.5%) or a standard glucose control strategy based on local guidelines for the glucose-control comparison.

Discontinuation of randomised study blood-pressure–lowering medication or placebo

Patients were seen at 3, 4 and 6 months after randomization, and then every 6 months until the end of the study. The patient's persistence with, or permanent discontinuation of, randomised study medication was confirmed at study visits and via reports from local physicians or carers together with the date of discontinuation where relevant. The reasons for permanent discontinuations were categorized as either the patients' inability or unwillingness to continue the study medication, or adverse events such as cough, dizziness/hypotension and serious adverse events, or other causes. Neither short interruptions of study medicine with re-administration, nor cessation due to death, were counted as permanent discontinuations which required cessation of perindopril/indapamide through to the end of randomised treatment.

Study outcomes

Primary outcomes were a composite of major macrovascular and major microvascular events, major macrovascular events, major microvasuclar events and all-cause mortality. Major macrovascular events were defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Major microvascular events were defined as new or worsening nephropathy (development of macroalbuminuria, defined as a urinary albumin:creatinine ratio of more than 300μg of albumin per milligram of creatinine, or doubling of serum creatinine level to at least 200 μmol per liter, the need for renal- replacement therapy, or death due to renal disease) or new or worsening retinopathy (development of proliferative retinopathy, macular edema or diabetes-related blindness or the use of retinal photocoagulation therapy). Secondary outcomes were the components of the primary outcomes such as cardiovascular death,

non-fatal myocardial infarction, non-fatal stroke, new or worsening retinopathy, new or worsening nephropathy and end-stage renal disease defined as the need for renal-replacement therapy or death due to renal disease. Deaths from non-cardiovascular causes were also investigated. An independent End Point Adjudication Committee adjudicated all the events and deaths.

Statistical analysis

Patients who permanently discontinued the randomised blood pressure lowering medication, before the trial was completed, were compared to the other participants. The effects of permanent discontinuation on the risks of outcomes were estimated using Cox's proportional hazards model, in which discontinuation was taken as a time-dependent covariate and was considered to be present only if it occurred before the index outcome. Multivariable adjustment was made for age, sex, randomized treatment and other covariates at baseline that were significantly associated with incident permanent discontinuation in unadjusted analyses. The effects of permanent discontinuation in subgroups were compared by adding an interaction term to the statistical model. The life-table method was used to estimate an event rate for each outcome occurring during each 12 month interval after permanent discontinuation. To assess whether reverse causality (essentially the same concept as imminent clinical events or prodromal syndrome) modified the results, further analyses were done after discounting the first year of follow-up after discontinuation in those who discontinued treatment, and the first year of follow-up after randomization in those who persisted with treatment throughout (i.e. after "left censoring"). Sensitivity analyses were performed using matched design, in which patients were enrolled as cases when they discontinued the study medication before

each outcome, and controls were randomly selected from patients who had not discontinued the study medication at the time of the case's discontinuation [22]. Matching was by age at discontinuation, sex, randomised treatment and prior history of vascular events at baseline, and three controls were selected for each case unless fewer matches could be identified. In order to evaluate the effects of discontinuation on change in hemodynamic parameters as well as blood glucose control, mean values of blood pressure, heart rate, haemoglobin A1c (HbA1c) and serum creatinine were calculated using the latest measurements before discontinuation compared with similar measurements in each 12 month interval after discontinuation. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). A two-sided $P<0.05$ was considered to be statistically significant.

Results

Permanent discontinuation of randomised blood pressure lowering medication

Patient characteristics are summarized in Table 1. Mean age was 65.8 years, 42.5% were female, and 43.6% were recruited in established market economies (EMEs). Patients who discontinued the study medication were older compared to those who did not, and were more recruited in EMEs than in other regions. During a median follow-up period of 4.3 years, 1,557 of the 11,140 patients initially randomised (14.0%) permanently discontinued randomised blood pressure lowering medication; 809 patients in the active group (14.5%) and 748 in the placebo group (13.4%) (Table 2). The main reasons for permanent discontinuation were "inability or unwillingness to continue the study medicine" (41%) or "adverse events" (31%). Most discontinuations occurred during the first year of the study period (41%), particularly in the actively treated group (Figure 1).

As shown in online Supplemental Table S1 (Supplemental Digital Content 1), the risk of permanent discontinuation was significantly associated with older age, male sex, recruitment outside of Asia, prior history of macrovascular events, prior history of microvascular events, high systolic blood pressure, high total cholesterol, high BMI, long duration of diabetes, lower education level, any use of blood pressure lowering medication at baseline and presence of alcohol use at baseline. When the effects of these factors on discontinuation were compared between randomised groups using the interaction terms, there was significant attenuation of the effects of systolic blood pressure and any use of blood pressure lowering medication at baseline in the active group compared to the placebo group (Table S1, Supplemental Digital Content 1).

Impact of permanent discontinuation of randomised blood pressure lowering medication on outcomes

Permanent discontinuation of randomised blood pressure lowering medication (active or placebo) was associated with increased risks of combined macro- and microvascular events, macrovascular events, microvascular events and all-cause mortality in minimally and fully adjusted multivariable models (the left half of Table 3 and Table S2, Supplemental Digital Content 1). Likewise, there were positive associations between permanent discontinuation and the risks of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, new or worsening nephropathy, end-stage kidney disease and non-cardiovascular death (the left half of Table S3 and S4, Supplemental Digital Content 1). Similar associations were observed for each randomised group, perindopril-indapamide and placebo. These associations between permanent discontinuation and all outcomes were broadly similar when sensitivity analyses were performed using a matched design

(Table S5, Supplemental Digital Content 1). In subgroups defined by age groups (65 years and under/over 65 years), by gender (male/female), by prior history of vascular events at baseline (presence/absence) and by region (Asian, EMEs and Eastern Europe), permanent discontinuation was consistently associated with increased risks of combined macro- and microvascular events and all-cause mortality (Figure S1, Supplemental Digital Content 1). The positive association with combined macro- and micro vascular events was stronger among participants with prior history of vascular events at baseline than those without, whereas the association with all-cause mortality was stronger in Asian patients than patients in EMEs and eastern Europe (both $p<0.01$ for interaction). In analyses stratifying participants by the reason for permanent discontinuation, participants who were unable or unwilling to take the study medication were at higher risks of combined macro- and microvascular events, macrovascular events and all-cause mortality than those who discontinued medication for other reasons (Table S6, Supplemental Digital Content 1).

Among participants who permanently discontinued the study medication, event rates of combined macro- and microvascular events, macrovascular events and all-cause mortality were highest during the first 12 months, and during this period were lower in the active group than in placebo group (all $p \leq 0.01$). Thereafter the incidence of these outcomes decreased steeply and levelled off to the end of the study, at which time the event rates were equivalent between randomised groups (Figure 2). The mean difference in blood pressure between the active and placebo groups observed before discontinuation disappeared gradually after discontinuation (Figure S2, Supplemental Digital Content 1). On the other hand, there was no clear difference in mean values of heart rate, HbA1c and serum creatinine before and after discontinuation between randomised groups. When left-censoring by a year, we found the effects of permanent discontinuation on most of

outcomes were attenuated, but the association with macrovascular events and mortality remained significant (the right half of Table 3, S2, S3 and S4, Supplemental Digital Content 1). Similar results were obtained in the sensitivity analyses using left-censoring in the matched design comparison except that the significance was lost for macrovascular events, but retained for all-cause mortality (Table S7, Supplemental Digital Content 1).

Discussion

This is the first large-scale study to report the association of discontinuation of blood pressure lowering therapy with a variety of outcomes in patients with type 2 diabetes. Permanent discontinuation of randomised blood pressure lowering medication was associated with increased risks of macrovascular events, microvascular events and all-cause deaths. The associations were most pronounced in the first 12 months following discontinuation of treatment, with a greater effect seen in the placebo group for both all-cause mortality and major macrovascular events. After left-censoring by a year, the effects were attenuated for most of outcomes, but still remained significant for macrovascular events and mortality.

Several studies have shown that non-adherence to both placebo and active study medication is associated with increased risk of major adverse events [4-7, 10,13, 19]. A recent systematic review of randomised controlled trials reported that good placebo adherers had about 40% lower cardiovascular [23] and all-cause mortality [24] than poor placebo adherers. Apart from the short-term rebound effects of ceasing medications, the literature has generally attributed this to the ‘healthy adherer’ phenomenon, whereby patients who adhere to placebo are also thought to adhere to a range of other beneficial

treatments and behaviours. The ‘healthy adherer’ effect is a well-described theory in placebo-controlled trials assessing the effects of different levels of adherence to randomised treatment on clinical outcomes [25]. The benefits are not restricted to the key outcomes of the trial, but may include unrelated outcomes, such as motor vehicle accidents and work place accidents [26].

There is also the “sick stopper” phenomenon, whereby patients who are non-adherent are often sicker than those who are adherent either due to true clinical differences or non-use of other medication and of healthy behaviours [1,27,28]. It is also possible that patients who develop serious illness may be less willing or able to continue preventive treatments, or may even have them actively stopped. This could occur for major nonvascular conditions such as cancer or dementia, but also paradoxically, for vascular events, with more treatment discontinuation following an event [7].

While it might be thought that the healthy adherer and the sick stopper merely reflect two sides of the same coin, the different time courses of these two phenomena suggest there are real differences between them. As seen in the present analyses, both all-cause mortality and major macrovascular events increase maximally in the first year after discontinuation (Figure 2), a finding consistent with the sick stopper effect. On the other hand, the rates for all major outcomes after this first year post-discontinuation, remain constant and significantly raised (Figure 2 and Table 3), a finding consistent with the healthy adherer effect. The attenuation by left-censoring of the effects of discontinuation on all-cause mortality in particular (but on all outcomes to some extent),suggests a dominant effect of the sick stopper phenomena in this study, possibly reflecting “imminent adverse events” such as diagnosis of cancer and development of angina pectoris or of symptoms of heart failure.

The other important finding from the present analysis was that the event rate for both all-cause mortality and major macrovascular events in those that discontinued active treatment with perindopril/indapamide was lower than for those that discontinued placebo. This may suggest that the active medication continued to have a residual protective effect in the early months after cessation, and this benefit was greater than any hazards due to withdrawal syndromes. However, it should be noted that discontinuation, due to side effects of the medication was greater in the actively treated group. After a year, the event rates converged and were similar until the end of follow-up. This finding is consistent with the results of the ADVANCE-ON study, which recently reported results of six-year post-trial follow-up after ADVANCE finished [10]. At the end of follow-up the benefits of perindopril/indapamide on total and cardiovascular mortality that were seen at the end of the active phase of the trial were still present, albeit attenuated. A recent meta-analysis including 18 placebo-controlled blood pressure lowering trials with 132,854 patients also showed a persistent decrease in overall mortality following the end of the trial phase, despite equal numbers of patients in each group receiving active therapy post-trial [11].

The strengths of our study include the large sample size and adjudication of major outcomes including microvascular events. A limitation is the small number of patients who stopped the study medication compared to that which may occur in clinical practice. Second, the difference of the age at discontinuation might have introduced a bias since patients who discontinued the study medication late during the trial would be older and have greater risk of vascular events. However, the sensitivity analysis using matched design, which will be impervious to this bias, produced the similar associations, thus, alleviating these concerns. Third, the reasons for discontinuation documented in case reports were very broad, making it difficult to clearly distinguish ‘sick stoppers’ and

'healthy adherers': However the analyses obtained with left-censoring produced reassurance regarding these findings, in terms of the main effect being due to 'sick stoppers'. Fourth, the possibility remains of residual confounding by unmeasured or unknown risk factors. Fifth, it should be noted that the present study constitutes a post-hoc observational analysis.

In conclusion, the association between discontinuation of randomised therapy with increased risks of vascular events and mortality in both active and placebo controlled arms appears to be most consistent with the previously described 'sick stopper' phenomenon. There is also evidence of persistent beneficial effect of blood pressure lowering therapy with perindopril/indapamide on mortality and macrovascular events following cessation of active treatment and a longer term 'healthy adherer' effect. The identification of high risk patients who wish to discontinue treatment may help to identify those who require additional intervention to prevent impending cardiovascular events.

Acknowledgement

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Conflicts of interest

SZ reports grants from Servier, and personal fees from Servier, MSD, BMS/Astra Zeneca, Sanofi-Aventis, Novo-Nordisk and Amgen Australia; SH reports receiving honoraria from Servier, Takeda and Novartis; PH reports being a consultant to Servier; GM reports personal fees from Servier, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Novartis, Menarini International, Recordati, and Takeda; NP reports grants from Servier, Pfizer, DUK, BHF, and HTA, and personal fees from Servier, Takeda, Menarini, and Pfizer; BN reports grants from NHMRC, Servier, Roche, Abbvie, Janssen, Dr Reddy's Laboratories, and Merck Schering Plough and personal fees from Servier, Abbott, Novartis, and Pfizer.; BW reports personal fees from Servier, Novartis, Boerhinger Ingelheim, and MSD; MW reports grants from Servier; JC reports grants from Servier, administered through the University of Sydney as Co-Principal investigator for ADVANCE and ADVANCE-ON and personal fees from Servier. YH, HA, RW, QL, LL and AR all report no conflicts of interest.

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Figure Legends

Figure 1. Permanent discontinuations of randomised blood pressure lowering medication according to time from randomisation in active and placebo blood pressure lowering groups

Active treatment denotes the fixed combination of perindopril and indapamide.

Figure 2. Event rates of outcomes after permanent discontinuation of randomised blood pressure lowering medication during each 12 months according to blood pressure randomised groups

The life-table method was used to estimate an event rates at the mid-point of each 12 month interval. All p values were >0.10 for the comparison between the active and placebo groups after 12 months.

Table 1. Baseline characteristics.

Variables	Overall (n=11,140)	Patients who did discontinue (n=1,557)	Patients who did not discontinue (n=9,583)
Demographics			
Age, y	65.8 (6.4)	67.4 (6.5)	65.5 (6.3)
Female, %	42.5	41.6	42.7
Regions of recruitment (%)*			
Asian countries	37.1	15.6	40.6
Established market economy countries	43.6	69.4	39.5
Eastern Europe	19.2	15.0	19.9
Medical and lifestyle history			
History of major macrovascular disease, %	32.2	37.5	31.4
History of major microvascular disease, %	10.3	14.7	9.6
Current smoking, %	15.1	15.4	15.0
Current alcohol intake, %	30.5	38.7	29.2
Duration of diabetes, y	7.9 (6.4)	8.2 (6.5)	7.9 (6.3)
Age of completion of highest education, y	18.4 (7.3)	18 (7.6)	18.5 (7.2)
Clinical risk factors			
Systolic blood pressure, mmHg	145 (21.5)	146.9 (21.9)	144.7 (21.5)
Diastolic blood pressure, mmHg	80.6 (10.9)	79.9 (10.8)	80.8 (11.0)
History of currently treated hypertension	68.7	69.4	68.6
HbA1c	7.5 (1.6)	7.5 (1.5)	7.5 (1.6)
Total cholesterol, mmol/L	5.2 (1.2)	5.1 (1.1)	5.2 (1.2)
High density lipoprotein cholesterol, mmol/l	1.3 (0.4)	1.2 (0.3)	1.3 (0.4)
Triglyceride, mmol/L	1.6 (1.2, 2.3)	1.7 (1.2, 2.3)	1.6 (1.2, 2.3)
BMI, kg/m^2	28.3 (5.2)	29.5 (5.6)	28.2 (5.1)
Nonstudy blood pressure–lowering drug, %	75.1	78.0	74.6
Nonstudy glucose-lowering treatment			
Oral glucose-lowering agent, %	90.9	90.2	91.0
Insulin, %	1.4	1.1	1.5
Randomized intensive glucose lowering, %	50.0	43.5	51.1
Randomized perindopril-indapamide, %	50.0	52.0	49.7

Values are mean (SD) for continuous variables except median (interquartile interval) for triglycerides, and percentage for categorical variables.

Asian countries comprise China, India, Malaysia and Philippines. EMEs comprises Australia, Canada, France, Germany, Ireland, Italy, Netherlands, New Zealand and United Kingdom. Eastern Europe countries comprise Czech Republic, Estonia, Hungary, Lithuania, Poland, Russia and Slovakia.

History of hypertension indicates use of blood pressure lowering drugs or blood pressure > 140/90 mmHg.

*The percentage shown for each region is of overall patients, of all those who discontinued and of all those who did not discontinue.

Table 2. The number of patients who permanently discontinued randomised blood pressure lowering medication according to randomised group and overall.

	Active N=5569	**Placebo N=5571**	**Overall N=11140**
Permanent discontinuation			
Number of patients (%)	809 (14.5)	748 (13.4)	1557 (14.0)
Reason for discontinuation*			
Unable or unwilling to continue	320 (40.0)	396 (52.9)	716 (46.0)
Adverse events	317 (39.2)	158 (21.1)	475 (30.5)
Other causes	172 (21.3)	194 (25.9)	366 (23.5)

Active treatment denotes the fixed combination of perindopril and indapamide.

Adverse events include cough, dizziness, hypotension and severe adverse events.

*The percentage shown is of all those who discontinued.

Table 3. The effects of permanent discontinuation of randomised blood pressure lowering medication on the risks of outcomes according to randomised groups and overall in the multivariable adjusted model.

	Whole study period				Left censoring by 1 year			
Outcome	**No. of events**	**HR (95%CI)**	**P**	**P for interaction**	**No. of events**	**HR (95%CI)**	**P**	**P for interaction**
Combined macro- and microvascular events								
Active	861	2.21 (1.83, 2.67)	<0.01	0.30	621	1.45 (1.11, 1.90)	<0.01	0.51
Placebo	938	2.54 (2.11, 3.05)	<0.01		675	1.27 (0.94, 1.72)	0.12	
Overall	1799	2.36 (2.07, 2.71)	<0.01		1296	1.37 (1.11, 1.67)	<0.01	
Major macrovascular events								
Active	480	3.08 (2.45, 3.87)	<0.01	0.09	315	1.79 (1.27, 2.52)	<0.01	0.86
Placebo	520	4.02 (3.23, 5.00)	<0.01		320	1.71 (1.17, 2.51)	<0.01	
Overall	1000	3.52 (2.99, 4.14)	<0.01		635	1.75 (1.35, 2.27)	<0.01	
Major microvascular events								
Active	439	1.49 (1.11, 1.99)	<0.01	0.52	353	1.22 (0.84, 1.77)	0.29	0.36
Placebo	477	1.30 (0.95, 1.77)	0.10		403	0.94 (0.61, 1.44)	0.78	
Overall	916	1.39 (1.12, 1.73)	<0.01		756	1.08 (0.82, 1.44)	0.58	
All-cause mortality								
Active	408	8.62 (7.03, 10.56)	<0.01	0.06	241	4.25 (3.17, 5.70)	<0.01	0.78
Placebo	471	11.18 (9.23, 13.55)	<0.01		256	4.01 (2.95, 5.44)	<0.01	
Overall	879	9.89 (8.55, 11.43)	<0.01		497	4.13 (3.32, 5.14)	<0.01	

The patients who permanently discontinued the randomised blood pressure lowering medication were compared to the other participants. Active treatment denotes the fixed combination of perindopril and indapamide.

†Adjustment was made for age, sex, randomised treatment, region, systolic blood pressure, total cholesterol, BMI, duration of diabetes, age of completion of highest education, history of microvascular event, history of macrovascular event, any use of blood pressure lowering medication at baseline, alcohol intake at baseline and interaction terms between randomised treatment and both systolic blood pressure and any use of blood pressure lowering medication at baseline.

List of Supplemental Digital Content

Supplemental Digital Content 1. Supplementary tables and figures. docx

Abbreviations: HbA1c, haemoglobin A1c; EMEs, established market economies

Supplemental Digital Content 1

Click here to download Supplemental Data File (.doc, .tif, pdf, etc.): Y Hirakawa_SDC1_clean.docx

Condensed Abstracts: Permanent discontinuation of randomised blood pressure lowering medication with perindopril-indapamide (both active and placebo) was associated with the increase in risk of vascular events and of mortality in patients with type 2 diabetes. During the first year after discontinuation, the risk of both all-cause mortality and major macrovascular events was lower in those that discontinued active treatment with perindopril/indapamide than for those that discontinued placebo, suggesting the residual benefit of active blood pressure lowering therapy. Discontinuation of study medication is a potent risk marker for identifying high risk patients. Patients who discontinue require further urgent investigation and management.

Figure

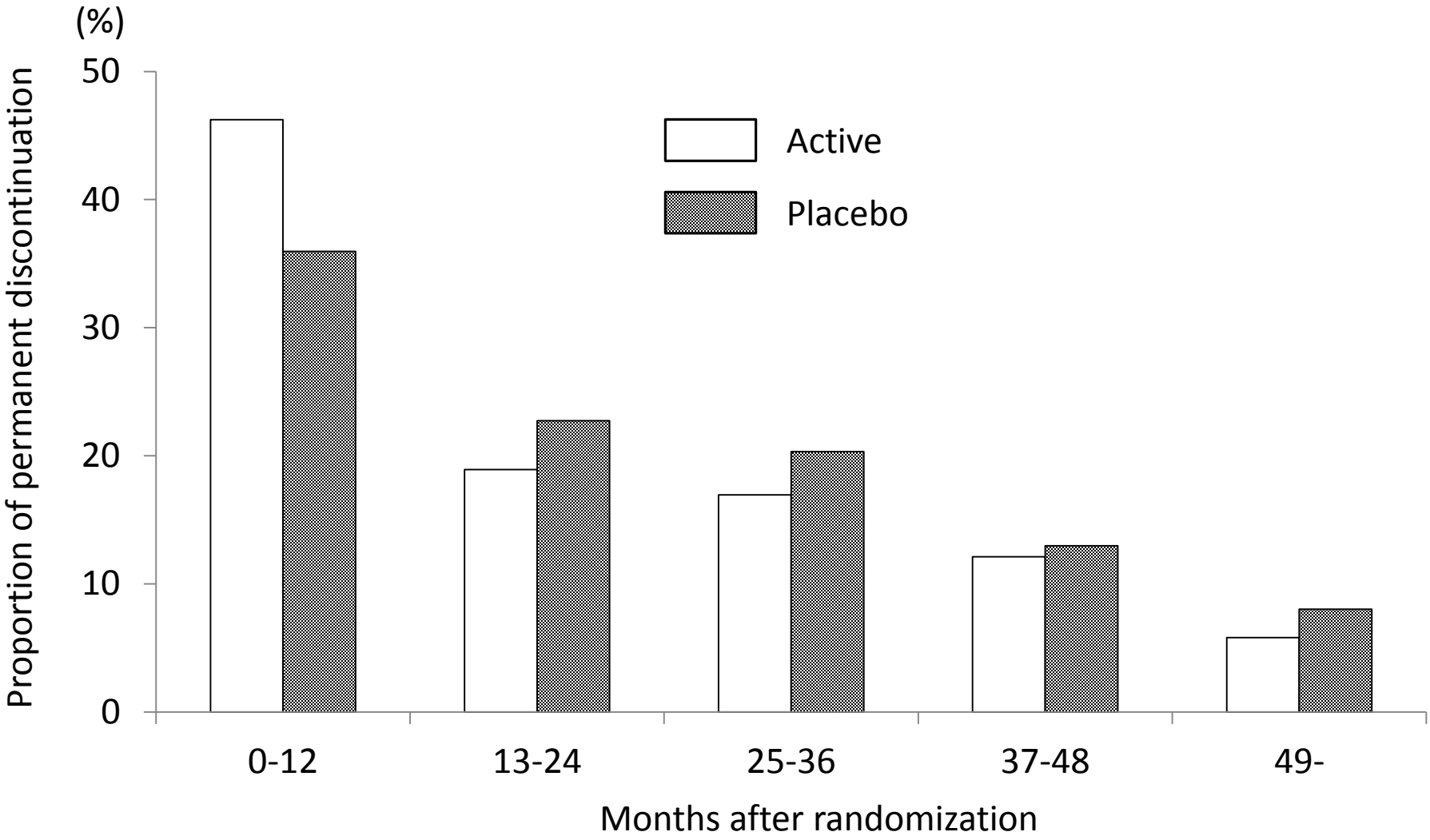
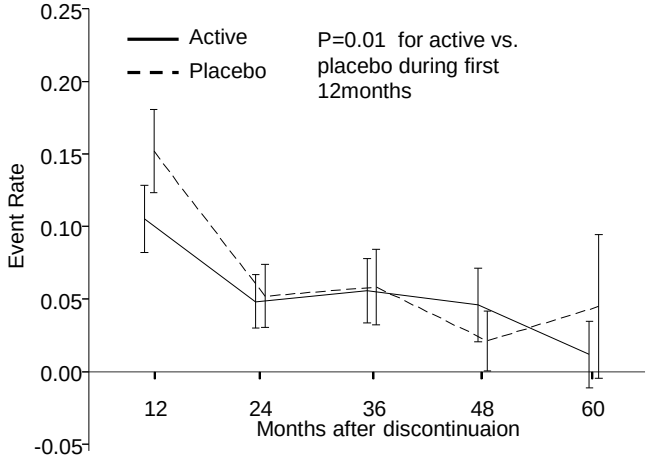


Figure 1.

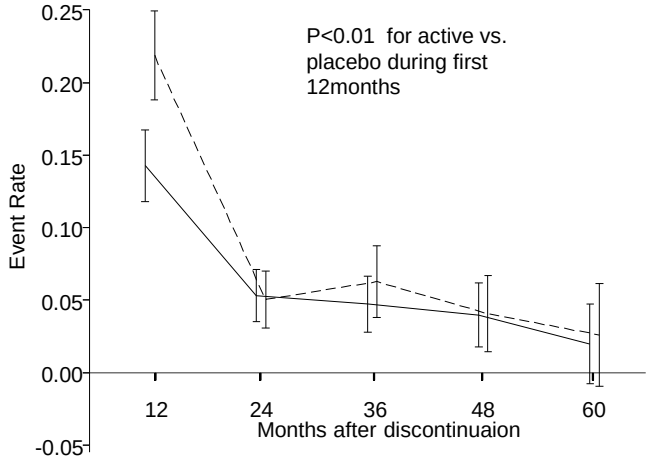
Combined macro - and microvascular events



No. of events / Adjusted No. at risk

Active	72/683	125/517.5	23/413	12/261	1/84.5
Placebo	90/592.5	21/404.5	18/309	4/188.5	3/67

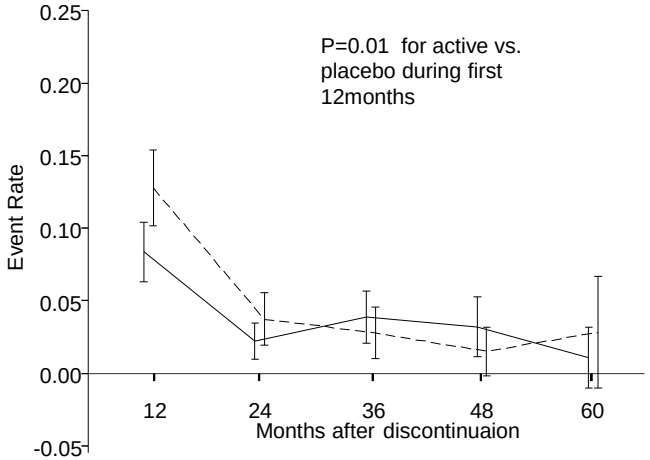
All-cause mortality



No. of events / Adjusted No. at risk

Active	110/770.5	31/583.5	22/466.5	12/302	2/100.5
Placebo	154/704	24/476.5	23/367	9/221.5	2/77

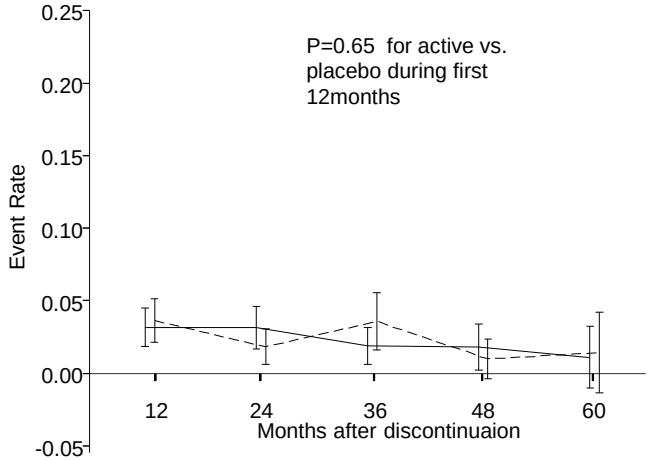
Major macrovascular events



No. of events / Adjusted No. at risk

Active	59/705.5	12/542	17/440.5	9/281	1/92
Placebo	79/618	16/428.5	9/325	3/199.5	2/71

Major microvascular events



No. of events / Adjusted No. at risk

Active	22/694.5	17/542	8/426	5/274.5	1/91.5
Placebo	22/605.5	8/438.5	12/336	2/202	1/70

Figure 2.

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