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Effects of blood pressure lowering on cardiovascular outcomes in different cardiovascular risk groups among participants with type 2 diabetes

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ABSTRACT

Aims: To asses differences in treatment effects of a fixed combination of perindopril–indapamide on major clinical outcomes in patients with type 2 diabetes across subgroups of cardiovascular risk.

Methods: 11,140 participants with type 2 diabetes, from the ADVANCE trial, were randomized to perindopril–indapamide or matching placebo. The Framingham equation was used to calculate 5-year CVD risk and to divide participants into two risk groups, moderate–high risk (<25% and no history of macrovascular disease), very high risk (>25% and/or history of macrovascular disease). Endpoints were macrovascular and microvascular events.

Results: The mean age of participants was 66 years (42.5% female). 1000 macrovascular and 916 microvascular events were recorded over follow-up of 4.3 years. Relative treatment effects were similar across risk groups, (all *P*-values for heterogeneity ≥0.38). Hazard ratios for combined macro- and microvascular events were 0.89 (0.77–1.03) for the moderate-high risk and 0.92 (0.81–1.03) for the very high risk. Absolute treatment effects tended to be greater in the high risk groups although differences were not statistically significant ($P > 0.05$).

Conclusions: Relative effects of blood pressure lowering with perindopril–indapamide on cardiovascular outcomes were similar across risk groups whilst absolute effects trended to be greater in the high risk group.

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1. Introduction

People with type 2 diabetes are considered to be at high risk for developing cardiovascular disease (CVD) [1]. Nevertheless, there is a gradation of CVD risk among people with type 2 diabetes as many factors contribute to this risk. Previous studies examining the effect of blood pressure lowering have focussed on treatment effects according to single risk factors [2–5]. Recently, there has been a shift from focussing on individual risk factors to absolute cardiovascular risk based on a combination of risk factors [6]. Moreover, contemporary cardiovascular, diabetes and hypertension management guidelines recommend integrating several risk factors into total cardiovascular risk assessment by using prediction models [7–9].

Several CVD prediction models have been developed over the past decade [10]; the most widely known and used models are Framingham and SCORE for primary prevention in the general population and the UKPDS risk engine for the population with diabetes [11–13]. The publicly available UKPDS risk engine only calculates the separate risk for either coronary heart disease or cerebrovascular disease [14,15]. While the Framingham risk equations are derived from general populations, free of prevalent disease, they do take diabetes into account and they calculate the risks for overall cardiovascular disease, including coronary heart disease and cerebrovascular disease [11,12]. As guidelines are increasingly recommending treatment according to absolute risk, it is important to define the absolute risks as well as the absolute effects of various interventions across cardiovascular risk groups, including those of blood pressure lowering in people with type 2 diabetes.

The recent Action in Diabetes and Vascular disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study investigated the effects of routine administration of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in participants with type 2 diabetes [16]. The aim of the present study was to assess differences in absolute and relative treatment effects of blood pressure lowering across subgroups defined by initial absolute cardiovascular risk.

2. Subjects, material and methods

2.1. Study design and participants

ADVANCE was a factorial randomized controlled trial evaluating the effects of routine blood pressure lowering and intensive blood glucose control on vascular outcomes and death in participants with type 2 diabetes. Detailed descriptions of the design have been published previously [16,17]. In brief, 11,140 participants with type 2 diabetes, aged 55 years or older, with a history of major macrovascular or microvascular disease, or at least one other risk factor for vascular disease, were recruited from 215 centres in 20 countries. Patients were excluded if they had a definite indication for, or contraindication to, any of the study treatments, a definite indication for long-term insulin treatment or were participating in any other clinical trial.

Approval for the trial was obtained from the institutional ethics committee of each centre and all participants signed an informed consent.

All potentially eligible participants entered a 6-week active run-in period during which they received a fixed combination of perindopril–indapamide (2 mg/0.625 mg). Participants who tolerated and were compliant with the run-in treatment were subsequently randomized to continued treatment with perindopril–indapamide (2 mg/0.625 mg) or matching placebo and to an intensive blood glucose control strategy aiming for a HbA1c $\leq$ 6.5% or a standard glucose therapy. The perindopril–indapamide dose was doubled to 4 mg/1.25 mg after three months. The use of concomitant treatments during follow-up, including blood pressure lowering therapy, remained at the discretion of the responsible physician with two exceptions, the use of thiazide diuretics was not allowed and open-label perindopril was the only ACE inhibitor allowed. Participants were seen at 2 pre-randomization visits, at 3, 4 and 6 months after randomization and subsequently every 6 months. The mean follow-up time was 4.3 years for the blood pressure arm of the study.

2.2. Outcomes

The primary outcomes were composites of major macrovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) and microvascular events (new or worsening nephropathy or retinopathy). The secondary outcomes included all-cause mortality, cardiovascular death, all coronary events (death due to coronary heart disease, including sudden death, nonfatal myocardial infarction, silent myocardial infarction, coronary revascularisation or hospital admission for unstable angina), all cerebrovascular events (death from cerebrovascular events, nonfatal stroke, transient ischemic attack or subarachnoid haemorrhage) and new or worsening nephropathy. An independent adjudication committee reviewed and validated all suspected primary endpoints and deaths.

2.3. Cardiovascular risk assessment

5-year cardiovascular disease risk was estimated using the Framingham Anderson equation for CVD [12], which is based on age, gender, smoking status, systolic blood pressure, the ratio of total/HDL cholesterol, left ventricular hypertrophy and diabetes status.

CVD risk at baseline was calculated for all participants using the risk equation. For the 35 participants with missing values for one of the characteristics included in the equation, values were imputed using mean substitution. The median calculated 5-year CVD risk was 18.8% with an interquartile range of 13.6%–23.5%.

Participants were divided into two risk groups: moderate-high risk (a calculated CVD risk of $\leq$25% over 5 years) and very high risk (a calculated CVD risk of $>$25% over 5 years). Only 7.1% (n = 789) of the patients had a calculated risk $<$10% and 10.8% (n = 85) of these participants had a major macrovascular or microvascular event. Combining this with the fact that guidelines classify all patients with type 2 diabetes to be at least at medium risk for a cardiovascular event [8,18], we did