Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies

*The Emerging Risk Factors Collaboration**

Summary

Background Uncertainties persist about the magnitude of associations of diabetes mellitus and fasting glucose concentration with risk of coronary heart disease and major stroke subtypes. We aimed to quantify these associations for a wide range of circumstances.

Methods We undertook a meta-analysis of individual records of diabetes, fasting blood glucose concentration, and other risk factors in people without initial vascular disease from studies in the Emerging Risk Factors Collaboration. We combined within-study regressions that were adjusted for age, sex, smoking, systolic blood pressure, and body-mass index to calculate hazard ratios (HRs) for vascular disease.

Findings Analyses included data for 698 782 people (52 765 non-fatal or fatal vascular outcomes; 8·49 million person-years at risk) from 102 prospective studies. Adjusted HRs with diabetes were: 2·00 (95% CI 1·83–2·19) for coronary heart disease; 2·27 (1·95–2·65) for ischaemic stroke; 1·56 (1·19–2·05) for haemorrhagic stroke; 1·84 (1·59–2·13) for unclassified stroke; and 1·73 (1·51–1·98) for the aggregate of other vascular deaths. HRs did not change appreciably after further adjustment for lipid, inflammatory, or renal markers. HRs for coronary heart disease were higher in women than in men, at 40–59 years than at 70 years and older, and with fatal than with non-fatal disease. At an adult population-wide prevalence of 10%, diabetes was estimated to account for 11% (10–12%) of vascular deaths. Fasting blood glucose concentration was non-linearly related to vascular risk, with no significant associations between 3·90 mmol/L and 5·59 mmol/L. Compared with fasting blood glucose concentrations of 3·90–5·59 mmol/L, HRs for coronary heart disease were: 1·07 (0·97–1·18) for lower than 3·90 mmol/L; 1·11 (1·04–1·18) for 5·60–6·09 mmol/L; and 1·17 (1·08–1·26) for 6·10–6·99 mmol/L. In people without a history of diabetes, information about fasting blood glucose concentration or impaired fasting glucose status did not significantly improve metrics of vascular disease prediction when added to information about several conventional risk factors.

Interpretation Diabetes confers about a two-fold excess risk for a wide range of vascular diseases, independently from other conventional risk factors. In people without diabetes, fasting blood glucose concentration is modestly and non-linearly associated with risk of vascular disease.

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This online publication has been corrected.
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Introduction

Diabetes mellitus is an established risk factor for coronary heart disease and ischaemic stroke,[1,2] but how much its effect varies by age, sex, or levels of conventional risk factors is uncertain.[3,4] The extent to which diabetes is associated with fatal versus non-fatal myocardial infarction or ischaemic versus haemorrhagic stroke is also unknown.[5,6] Furthermore, how much of the effect of diabetes on vascular risk can be accounted for by conventional vascular risk factors (eg, obesity, lipids, or blood pressure) is unresolved.[7] Different uncertainties apply to measures of dysglycaemia in people without diabetes. Fasting blood glucose has been reported to be log-linearly and importantly associated with risk of vascular disease at all concentrations, including below the threshold for diabetes of 7 mmol/L. Available data on this topic are, however, inconclusive.[8,9] In 2009, the US Preventive Services Task Force stated that prospective data for fasting blood glucose concentration and coronary heart disease were inconsistent and had serious limitations.[10] Furthermore, the value of assessment of fasting blood glucose concentration in vascular risk prediction—beyond measurement of conventional risk factors—is not established.[10] We report analyses of individual records of people without initial vascular disease in prospective studies. We aimed to produce reliable estimates of associations of diabetes and fasting blood glucose concentration with fatal or first-ever non-fatal incident ischaemic vascular disease (and deaths from other vascular disorders) for a wide range of circumstances.

Methods

Study design

Details of the Emerging Risk Factors Collaboration have been described previously.[11] By May, 2010, 121 prospective studies of vascular risk factors, involving a total of 1·27 million adults, had shared individual records (webappendix p 2). These studies: (1) did not select

See **Online** for webappendix

participants on the basis of previous vascular disease; (2) recorded cause-specific mortality or vascular morbidity, or both, using well defined criteria; and (3) accrued more than 1 year of follow-up. For registration of fatal outcomes, all contributing studies used coding from the International Classification of Diseases (ICD) to at least three digits (or using study-specific classification systems), and ascertainment was based on death certificates. The webappendix (pp 17–20) provides details of the 102 contributing studies that had information at baseline on history of diabetes and/or fasting blood glucose concentration (measured ≥8 h or overnight fasting). Acronyms and references for contributing studies are shown in the webappendix (pp 32–38).

Statistical analyses

We assessed baseline diabetes status (defined by self-report, medication usage, and/or baseline fasting blood glucose concentration ≥7 mmol/L) in relation to coronary heart disease (first-ever myocardial infarction or fatal coronary heart disease); stroke subtypes (fatal or non-fatal ischaemic, haemorrhagic, or unclassified stroke); and deaths attributed to the aggregate of other vascular disorders (consisting of heart failure, cardiac dysrrhythmia, sudden death, hypertensive disease, pulmonary embolism, and aortic aneurysm; webappendix p 21). We used a two-stage approach for analysis, with estimates of association calculated separately within each study, then pooled across studies by random-effects meta-analysis.[12,13] Hazard ratios (HRs) were calculated with Cox proportional hazards regression models that were stratified by sex (and, in the few contributing trials, stratified by allocated treatment group). We excluded studies with fewer than 11 cases of an outcome from the analysis of that outcome. In the figures presented, sizes of data markers are proportional to the inverse of the variance of the HRs. Participants contributed only their first non-fatal vascular outcome or death recorded at age 40 years or older (ie, deaths preceded by non-fatal vascular events were not included in the analyses). For the three individually matched nested case-control studies within prospective cohorts, we calculated odds ratios with conditional logistic regression. Since only 60760 participants had LDL cholesterol concentrations that had been directly measured, we used non-HDL cholesterol as the principal marker of cholesterol content in proatherogenic lipoproteins.

To characterise shapes of associations, study-specific HRs calculated within overall categories of baseline blood glucose concentration were pooled on the log scale, by multivariate random-effects meta-analysis, and plotted against pooled mean concentrations within each category. To restrict potential bias related to having a diagnosis of diabetes (eg, medication use, changes in lifestyle), we assessed separately individuals with and without a history of diabetes at baseline. 95% CIs were estimated from the variances that show the amount of information underlying each group (including the reference group).[14] We investigated effect-modification with formal tests of interaction, and calculated p values for interaction using continuous variables, when appropriate. Diversity between studies was investigated by grouping studies with recorded characteristics and meta-regression. We adjusted HRs for baseline age, sex, smoking status, BMI, systolic blood pressure, and lipids (and, in supplementary analyses, for additional factors). Evidence of association was shown by the Wald χ^2 statistic and of heterogeneity by the I^2 statistic.[15] We calculated measures of discrimination for censored time-to-event data (Harrell's C index) and reclassification, with methods described previously.[16] We estimated population-attributable fractions with HRs for vascular death,[17] and undertook sensitivity analyses allowing for potential misclassification of diabetes. Regression dilution ratios were obtained by regressing serial measurements taken from 307517 participants (mean interval 2·6 years) on baseline levels of the relevant characteristic and duration of follow-up. In further analyses, we corrected for regression dilution in fasting blood glucose concentration and covariates, with methods described previously.[12] We did all analyses using Stata (version 11). This study was approved by the Cambridgeshire ethics review committee.

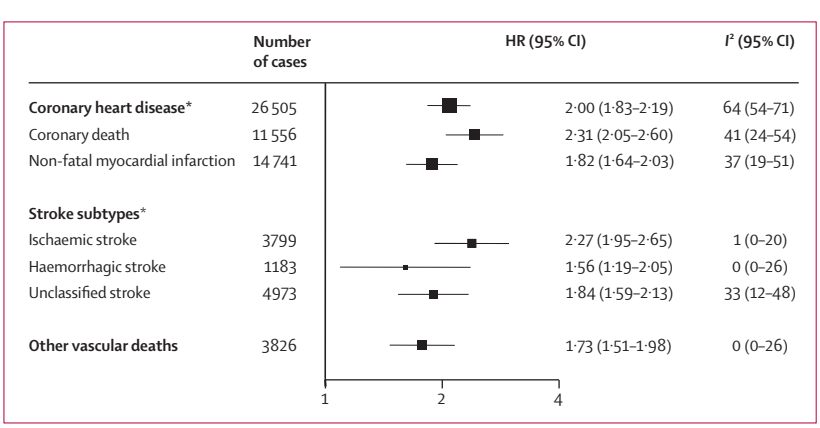

Figure 1: **Hazard ratios (HRs) for vascular outcomes in people with versus those without diabetes at baseline**
Analyses were based on 530083 participants. HRs were adjusted for age, smoking status, body-mass index, and systolic blood pressure, and, where appropriate, stratified by sex and trial arm. 208 coronary heart disease outcomes that contributed to the grand total could not contribute to the subtotals of coronary death or non-fatal myocardial infarction because there were fewer than 11 cases of these coronary disease subtypes in some studies. *Includes both fatal and non-fatal events.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. NS and JD had full access to all data in the study and had final responsibility to submit for publication.

Results

102 studies had relevant information for this analysis. From these studies, 698782 participants had no history of myocardial infarction, angina, or stroke at initial examination. 410299 of these had information recorded

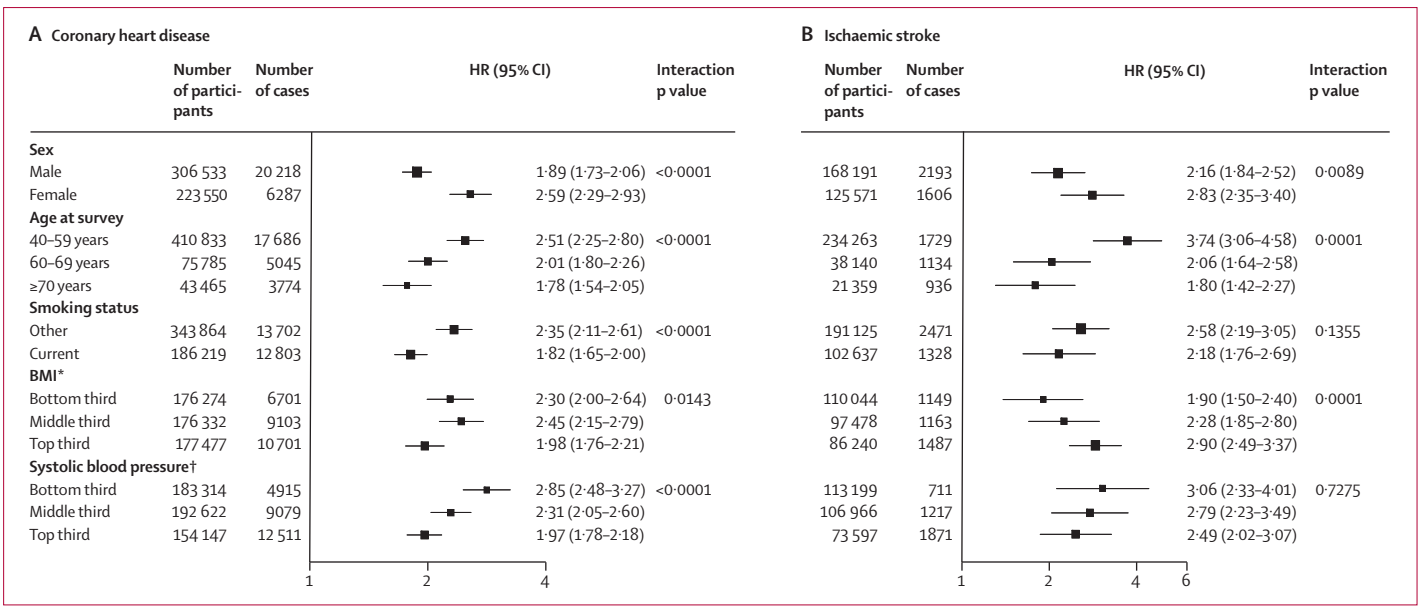

Figure 2: **Hazard ratios (HRs) for coronary heart disease and ischaemic stroke in people with versus those without diabetes at baseline, by individual characteristics**
HRs were adjusted as described in figure 1. BMI=body-mass index. *Bottom third=<23·8 kg/m² (mean 21·7 kg/m²); middle third=23·8–<27 kg/m² (mean 25·3 kg/m²); and top third=≥27 kg/m² (mean 30·7 kg/m²). †Bottom third=<123 mm Hg (mean 113 mm Hg); middle third=123–<141 mm Hg (mean 132 mm Hg); and top third=≥141 mm Hg (mean 157 mm Hg).

about self-reported history of diabetes, but not fasting blood glucose concentration; 195 390 had information on both self-reported diabetes and fasting blood glucose; and 93 093 had information for fasting blood glucose, but not self-reported diabetes (data for participants with information about fasting glucose but not self-reported diabetes contributed to analyses of fasting blood glucose concentration, but did not contribute to analyses of diabetes). 264 353 participants had complete information at baseline for self-reported history of diabetes, age, sex, smoking habits, systolic blood pressure, BMI, high-density lipoprotein (HDL) cholesterol, total cholesterol concentrations, and triglyceride concentration. Deaths were classified by ICD coding, and 70 of 102 contributing studies also used medical records, autopsy findings, and other supplementary sources. 73 studies used standard definitions of myocardial infarction that were based on WHO criteria. For 75 studies, investigators provided information about stroke subtype. For 59 studies, investigators reported diagnosis of strokes on the basis of typical clinical features and brain imaging. Information was generally not available for diabetes type (ie, whether type 1 or 2 diabetes) or diagnosis of diabetes and microvascular disease after baseline.

Overall, the mean age of participants at entry was 52 (SD 13) years, and 300 051 (43%) were women. 669 506 (96%) were in Europe, North America, and Australasia, with the remainder in Japan or the Caribbean. Of the participants with information on self-reported history of diabetes, 38 851 (7%) reported a history of diabetes at baseline. Diabetes prevalence varied across studies, partly affected by differences in sex distribution (webappendix p 3, 22). Baseline mean glucose concentrations were similar across studies (webappendix p 4). In people without known diabetes, glucose concentration was associated with obesity, blood pressure, lipid concentration, and inflammatory markers (webappendix p 5). In this group, serial measurements yielded an age-adjusted and sex-adjusted regression dilution ratio of 0·69 (95% CI 0·66–0·72; webappendix p 6) for fasting blood glucose concentration, 0·64 (0·62–0·65) for non-HDL cholesterol, and 0·51 (0·49–0·53) for systolic blood pressure. During 8·49 million person-years at risk (median 10·8 years to first outcome), 52 765 incident fatal or first-ever non-fatal vascular disease outcomes were recorded (webappendix pp 23–26).

In comparison of people with diabetes versus those without, HRs adjusted for age, sex, smoking status, BMI, and systolic blood pressure (basic covariates) were about two for coronary heart disease, ischaemic stroke, unclassified stroke, and deaths attributed to other vascular diseases (HR for haemorrhagic stroke was somewhat lower). HRs were about a third higher for coronary death than for non-fatal myocardial infarction (figure 1).

HRs for coronary heart disease with diabetes were significantly higher in women than in men, at 40–59 years than at 70 years or older, in non-smokers than in smokers, and at below average BMI or below average systolic blood pressure (figure 2). HRs for coronary heart disease did not vary much by other characteristics (including by geographical location or in people who are of white European ancestry versus those who are not; webappendix p 7). HRs for coronary heart disease did not change substantially after additional adjustment for non-HDL

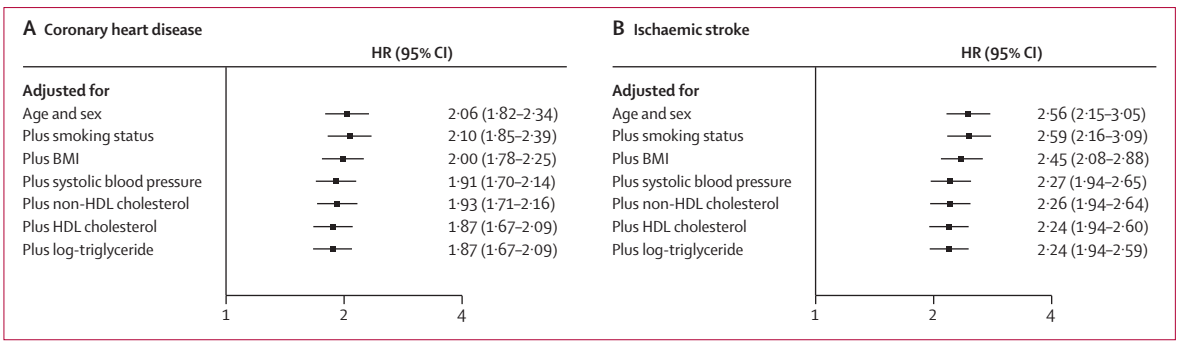

***Figure 3*: Hazard ratios (HRs) for coronary heart disease and ischaemic stroke in people with versus those without diabetes, progressively adjusted for baseline levels of conventional risk factors**

Analyses were based on 264 353 participants (11 848 cases) for coronary heart disease and 157 315 participants (2858 cases) for ischaemic stroke with complete information on all covariates listed. BMI=body-mass index.

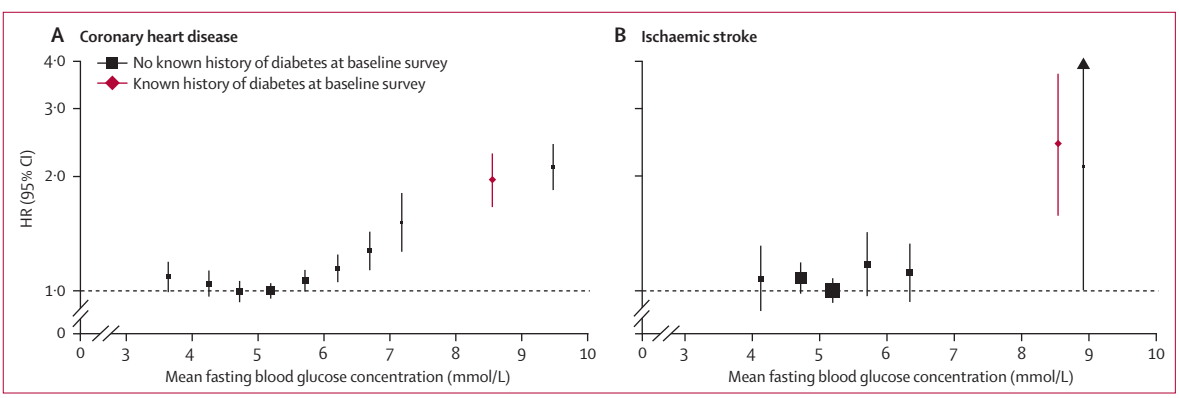

***Figure 4*: Hazard ratios (HRs) for coronary heart disease and ischaemic stroke by baseline fasting blood glucose concentration**

Analyses were based on 279 290 participants (14 814 cases) for coronary heart disease (CHD) and 175 542 participants (1754 cases) for ischaemic stroke. Participants without known diabetes at baseline were classified into groups of fasting glucose (CHD: <4·0, 4·0–4·5, 4·5–5·0, 5·0–5·5, 5·5–6·0, 6·0–6·5, 6·5–7·0, 7·0–7·5, and >7·5 mmol/L; ischaemic stroke: <4·5, 4·5–5·0, 5·0–5·5, 5·5–6·0, 6·0–7·0, and >7·0 mmol/L). HRs were adjusted as described in figure 1 and are plotted against mean fasting blood glucose in each group. Reference group for both outcomes is 5·0–5·5 mmol/L.

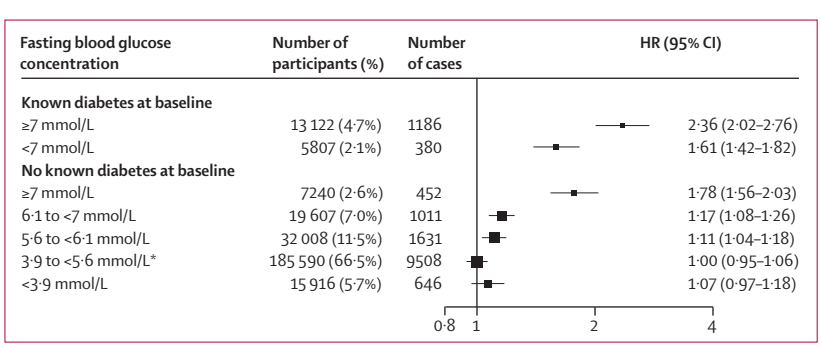

***Figure 5*: Hazard ratios (HRs) for coronary heart disease by clinically defined categories of baseline fasting blood glucose concentration**

Analyses were based on 279 290 participants (14 814 cases). HRs were adjusted as described in figure 1. HR (95% CI) in people with fasting glucose 5·60–6·99 mmol/L was 1·12 (1·06–1·18). *Reference group.

cholesterol, HDL cholesterol, and triglyceride concentration (figure 3). HRs for coronary heart disease were similar when: adjustment was made for apolipoprotein AI and apolipoprotein B instead of HDL cholesterol and non-HDL cholesterol, respectively; waist-to-hip ratio replaced BMI; or additional adjustment was made for fibrinogen, C-reactive protein, or estimated glomerular filtration rate (webappendix p 27). HRs for ischaemic stroke, adjusted for basic covariates, were higher in women, in people aged between 40 and 59 years, and in people with above average BMI (figure 2, webappendix p 7). HRs for ischaemic stroke did not change greatly after additional adjustment for lipids (figure 3).

In analyses adjusted for basic covariates, fasting blood glucose concentration was non-linearly related to risk of coronary heart disease or ischaemic stroke (figure 4), and unrelated to vascular risk between 3·90 and 5·59 mmol/L (webappendix p 8). In people with no history of diabetes at baseline, compared with people with fasting blood glucose concentrations of 3·90–5·59 mmol/L, risk of coronary heart disease was only modestly higher in those with fasting blood glucose concentrations between 5·60 mmol/L and 6·99 mmol/L (ie, impaired fasting glucose), but substantially higher in those with fasting blood glucose concentrations of 7 mmol/L or higher (figure 5). Compared with the same reference group, risk of coronary heart disease was substantially higher in people with a history of diabetes. HRs were about 50% higher in people with a history of diabetes and with fasting blood glucose concentrations

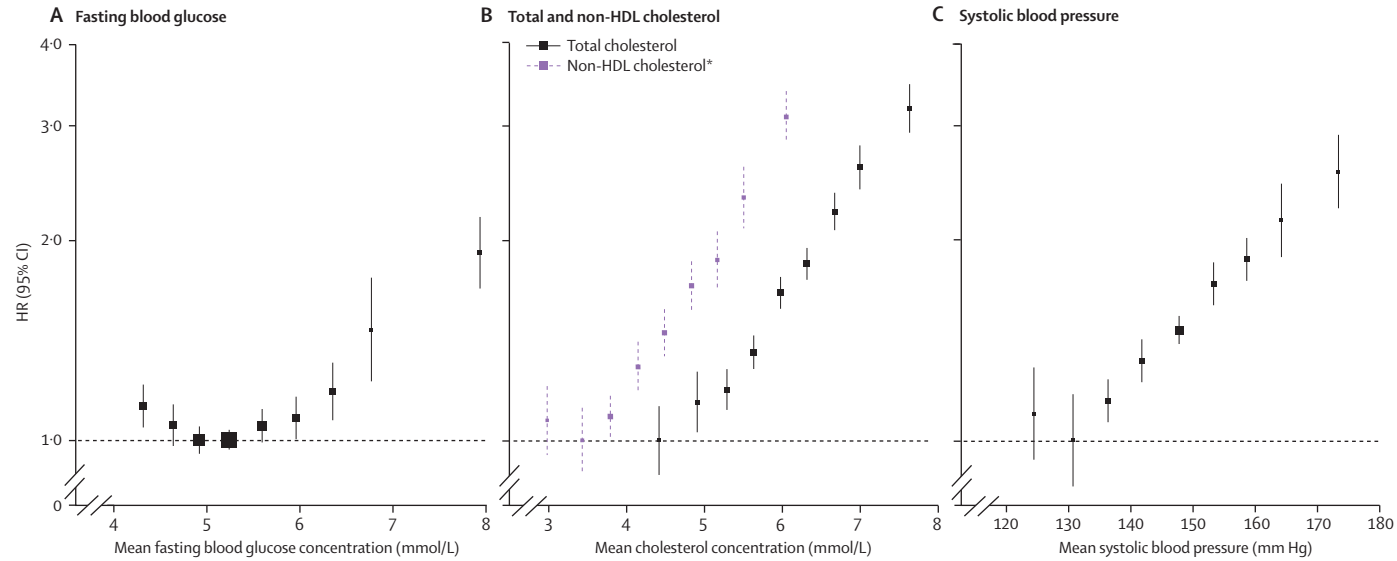

***Figure 6*: Comparison of hazard ratios (HRs) for coronary heart disease by long-term average concentrations of fasting blood glucose concentration, total (and non-HDL) cholesterol, and systolic blood pressure, in a common set of participants**

Analyses were done in participants with no known history of diabetes at baseline. Analyses of fasting blood glucose concentration, total cholesterol, and systolic blood pressure were based on 140 624 participants (10 667 cases). For fasting blood glucose, participants were classified into groups of baseline fasting concentrations, as described in figure 4. For the other factors presented, participants were classified according to baseline values as follows: total cholesterol, <4·5, 4·5–5·1, 5·1–5·7, 5·7–6·3, 6·3–6·9, 6·9–7·5, 7·5–8·1, 8·1–8·7, ≥8·7 mmol/L; non-HDL cholesterol, <3, 3–3·6, 3·6–4·2, 4·2–4·8, 4·8–5·4, 5·4–6·0, 6·0–6·6, 6·6–7·2, ≥7·2 mmol/L; systolic blood pressure: <110, 110–120, 120–130, 130–140, 140–150, 150–160, 160–170, 170–180, ≥180 mm Hg). These categories approximately correspond to those used for fasting blood glucose concentration (ie, increments of half the SD of each factor). HRs were adjusted, where appropriate, for age, smoking status, BMI, systolic blood pressure, total cholesterol and fasting blood glucose, and stratified, where appropriate, by sex and trial arm. HRs were plotted against the mean value in each group. Long-term average values were calculated with information from serial measurements. The reference group for each factor is the category with the lowest HR. *Analyses of non-HDL cholesterol were based on a subset of 71 224 participants (4290 cases).

of at least 7 mmol/L than in people with a history of diabetes but fasting glucose concentrations lower than 7 mmol/L (figure 5). HRs for those with impaired fasting blood glucose did not vary materially by age, sex, or other recorded characteristics (webappendix p 9). At fasting blood glucose concentrations higher than 5·6 mmol/L, HR per 1 mmol/L higher concentration was 1·12 (1·08–1·15) for coronary heart disease, assuming existence of log-linear associations above this threshold (although data were insufficient to confirm or refute this assumption: webappendix p 15). Whereas long-term average (usual) concentrations of fasting blood glucose were non-linearly and moderately associated with risk of coronary heart disease, usual levels of total (or non-HDL) cholesterol and systolic blood pressure were nearly log-linearly and more strongly associated with such risk (figure 6). When added to a vascular risk-prediction model containing age, sex, smoking status, systolic blood pressure, and HDL and total cholesterol, information about history of diabetes significantly increased the C index (p<0·0001). By contrast, in people without diabetes at baseline, such addition of information on impaired fasting glucose status (p=0·24) or fasting blood glucose concentration (p=0·26) did not significantly increase the C index (webappendix p 28). Findings based on measures of reclassification for 10-year predicted risk yielded broadly similar results to those with the C index (webappendix p 28).

We noted similar findings in analyses that: used fixed-effect models, fractional polynomials, or spline terms (webappendix pp 10–11); compared larger and smaller studies (webappendix pp 12–13); assessed interactions by sex and age group; excluded initial follow-up (eg, the first 5 years); omitted 71 048 (10%) participants known to be receiving lipid-lowering, blood pressure-lowering, or other cardiovascular drugs at baseline; included fatal outcomes without censoring previous non-fatal outcomes; standardised glucose values in studies that used samples other than plasma;[18] and assessed associations with fasting blood glucose concentration, either ignoring history of diabetes at baseline (webappendix p 14) or excluding studies that did not record self-reported history of diabetes.

The overall age-adjusted prevalence of diabetes in adults was 7·0% (6·1–7·9%)—which is lower than some contemporary estimates of about 10% for developed countries.[19] Assuming a population-wide diabetes prevalence of 10% (ie, corresponding to a prevalence of 20% in cases of vascular death), 11% (10–12%) of vascular deaths are estimated to be attributable to diabetes (webappendix p 30), or 325 000 vascular deaths per year in the 49 high-income

countries defined by WHO.[20] For a hypothetical population-wide adult prevalence of diabetes of 20%, we estimated that 22% (20–23%) of vascular disease would be attributable to diabetes. Webappendix p 16 and p 31 provide sensitivity analyses, including estimation of the potential effect on HRs of misclassification of diabetes status.

Discussion

Our analysis has shown that diabetes confers about a two-fold excess risk for coronary heart disease, major stroke subtypes, and deaths attributed to other vascular causes. This pattern of strong associations of diabetes with each of several different vascular diseases contrasts with that of LDL cholesterol (or non-HDL cholesterol), which is strongly related to coronary heart disease, but modestly related to ischaemic stroke, and unrelated to haemorrhagic stroke in prospective observational studies.[12] Diabetes is about a third more strongly related to fatal than to non-fatal myocardial infarction, perhaps suggestive of more severe forms of coronary lesions in people with diabetes than in those without, differential response of the myocardium to ischaemia, or possibly in part, differential coding of deaths from coronary heart disease.[21–23] Although diabetes is a strong risk factor for coronary heart disease in all clinically relevant subgroups that we assessed, HRs are significantly greater in some groups at lower absolute risk of vascular disease—ie, in women, younger ages, non-smokers, and at lower-than-average blood pressure. Further investigation is needed to establish any implications of such effect modification. Because only a small part of the association between diabetes and ischaemic vascular disease is accounted for by several conventional and emerging risk factors, other mechanisms (including those as yet undiscovered) might be involved.

Our data suggest that in this decade about 10% of vascular deaths in populations in developed countries have been attributable to diabetes in adults, corresponding to an estimated 325 000 deaths per year in high-income countries alone (plus several-fold more people disabled by vascular disease). This burden will increase if the incidence of diabetes continues to rise,[19] even if rates of vascular disease continue to fall because of decreases in smoking, improvements in treatment, or other reasons. At a diabetes prevalence of 20% in the general adult population (ie, more than twice the present levels in developed countries), an estimated 20% of vascular deaths would be attributable to diabetes. Increasing rates of obesity worldwide will probably heighten the absolute risk for diabetes and vascular disease.[27] However, how these trends will modify the proportional effect of diabetes on risk of vascular disease is unclear. For example, HRs for ischaemic stroke seem somewhat greater at higher than at lower BMI, whereas HRs for coronary heart disease seem greater at lower than at higher BMI.

In contrast with the strong associations observed between diabetes and vascular outcomes, our study shows much more moderate associations of impaired fasting glucose status with coronary heart disease and stroke. Furthermore, there were no material associations with vascular risk at fasting blood glucose concentrations between 3·9 mmol/L and 5·6 mmol/L. By contrast, we have shown in a common set of participants that total (or non-HDL) cholesterol and systolic blood pressure each have much stronger and nearly log-linear associations with vascular risk. Additionally, we identified that, in people without diabetes, assessment of fasting blood glucose concentration or of impaired fasting glucose status does not significantly improve vascular disease prediction beyond the information provided by several conventional risk factors. Fasting blood glucose concentration is, of course, measured for other purposes, such as identification of diabetes.[24] Scientific guideline statements, risk assessment strategies, sample sizes for intervention studies, and burden of disease calculations have been premised on the existence of stronger and log-linear associations between fasting blood glucose concentration and vascular disease throughout the range of its values.[18,25,26] Review of these efforts might be useful, therefore, given the revised epidemiological estimates provided by our findings.

Our study was powered to characterise reliably several previously uncertain features, including: HRs for ischaemic vascular disease in several clinically relevant subgroups; HRs for vascular disease subtypes (eg, major stroke subtypes); shapes of relations across the range of fasting blood glucose concentrations; and predictive value of diabetes, impaired fasting glucose, and fasting blood glucose concentration for vascular risk assessment. Nevertheless, even more powerful analyses than those reported here are needed to characterise reliably shapes of associations in specific subgroups. For example, the present data seem to suggest the existence of some continuous association between fasting blood glucose concentration and coronary heart disease above an as yet imprecisely defined threshold.

The generalisability of our findings to populations in developed countries is supported by broadly consistent results across 102 cohorts in 25 countries. Because our data derive mostly from high-income countries, however, we could not estimate vascular disease burden attributable to diabetes for low-income and middle-income countries. Sensitivity analyses suggest that plausible degrees of misclassification were unlikely to change reported HRs substantially. Conversely, any preferential diagnosis of vascular disease in people with diabetes would have tended to overestimate HRs. We did not have information about duration or age of onset of diabetes or prevalence of diabetes type (type 1 or 2), although the age distribution suggests that the majority of participants with diabetes would have type 2 diabetes. Future prospective studies should aim to include additional markers of dysglycaemia and insulin resistance.[28–30]

Contributors

NS, SRKS, RG, and JD drafted the manuscript. PG and SK undertook the analyses. All members of the writing committee provided critical revisions. All investigators shared individual data and had an opportunity to contribute to interpretation of the results and to redrafting of the report. The data management team collated and standardised the data. All members of the coordinating centre contributed to the collection, standardisation, analysis, and interpretation of the data.

The Emerging Risk Factors Collaboration

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Conflicts of interest

JD has received research funding from the British Heart Foundation, BUPA Foundation, Denka, diaDexus, European Union, Evelyn Trust, Fogarty International Centre, GlaxoSmithKline, Medical Research Council, Merck Sharp and Dohme, National Heart, Lung and Blood Institute, National Institute of Neurological Disorders and Stroke, Novartis, Pfizer, Roche, Wellcome Trust, and UK Biobank, and has served on advisory boards for Merck and Novartis, for which he has received compensation. AT has received honoraria and reimbursement of costs for speaking at scientific meetings from GlaxoSmithKline. All other members of the writing committee declare that they have no conflicts of interest.

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CARDIO VASCULAR DIABETOLOGY

STUDY PROTOCOL Open Access

Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME™)

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Abstract

Background: Evidence concerning the importance of glucose lowering in the prevention of cardiovascular (CV) outcomes remains controversial. Given the multi-faceted pathogenesis of atherosclerosis in diabetes, it is likely that any intervention to mitigate this risk must address CV risk factors beyond glycemia alone. The SGLT-2 inhibitor empagliflozin improves glucose control, body weight and blood pressure when used as monotherapy or add-on to other antihyperglycemic agents in patients with type 2 diabetes. The aim of the ongoing EMPA-REG OUTCOME™ trial is to determine the long-term CV safety of empagliflozin, as well as investigating potential benefits on macro-/microvascular outcomes.

Methods: Patients who were drug-naïve (HbA_{1c} ≥7.0% and ≤9.0%), or on background glucose-lowering therapy (HbA_{1c} ≥7.0% and ≤10.0%), and were at high risk of CV events, were randomized (1:1:1) and treated with empagliflozin 10 mg, empagliflozin 25 mg, or placebo (double blind, double dummy) superimposed upon the standard of care. The primary outcome is time to first occurrence of CV death, non-fatal myocardial infarction, or non-fatal stroke. CV events will be prospectively adjudicated by an independent Clinical Events Committee. The trial will continue until ≥691 confirmed primary outcome events have occurred, providing a power of 90% to yield an upper limit of the adjusted 95% CI for a hazard ratio of <1.3 with a one-sided α of 0.025, assuming equal risks between placebo and empagliflozin (both doses pooled). Hierarchical testing for superiority will follow for the primary outcome and key secondary outcomes (time to first occurrence of CV death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for unstable angina pectoris) where non-inferiority is achieved.

Results: Between Sept 2010 and April 2013, 592 clinical sites randomized and treated 7034 patients (41% from Europe, 20% from North America, and 19% from Asia). At baseline, the mean age was 63 ± 9 years, BMI 30.6 ± 5.3 kg/m^2, HbA1c 8.1 ± 0.8%, and eGFR 74 ± 21 ml/min/1.73 m^2. The study is expected to report in 2015.

Discussion: EMPA-REG OUTCOME™ will determine the CV safety of empagliflozin in a cohort of patients with type 2 diabetes and high CV risk, with the potential to show cardioprotection.

Trial registration: Clinicaltrials.gov NCT01131676

Keywords: Blood pressure, Body weight, Empagliflozin, Glycemic control, Macrovascular, Microvascular, SGLT2 inhibitor, Type 2 diabetes

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Introduction

Type 2 diabetes mellitus (T2DM) is frequently associated with comorbidities that exacerbate cardiovascular (CV) risk, such as obesity and hypertension [1]. The risk of CV disease is increased approximately two to four-fold in adults with diabetes even after adjustment for conventional risk factors (age, sex, smoking status, body mass index [BMI], systolic blood pressure [BP], and lipids) [2]. Recommended strategies for reducing CV risk in patients with T2DM include glucose management, lipid lowering, BP control, smoking cessation, and weight loss [1]. Improved glycemic control has been associated with a reduction in microvascular events [3] and there is a clear association between microvascular complications such as albuminuria and an increased risk of CV events in patients with T2DM [4]. However, the impact of reducing blood glucose, and the potential benefit of specific glucose-lowering agents, on CV events in patients with T2DM remains unclear and highly controversial [5,6]. Moreover, treatment must likely occur over a substantial duration of time, since macrovascular outcome events are known to be late complications of a progressive multifaceted pathogenic process that spans decades [7,8]. Lately, regulatory authorities have issued guidance for evaluating the long-term CV safety of new anti-diabetes agents to ensure that CV safety is demonstrated with reasonable assurance [9,10]. These mandated trials provide an opportunity to potentially demonstrate CV as well as microvascular benefits of new anti-diabetes drugs.

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a new class of antidiabetes agents that reduce hyperglycemia in patients with T2DM by reducing renal glucose reabsorption and thus increasing urinary glucose excretion (UGE) [11]. Empagliflozin is a potent and selective inhibitor of SGLT2 [12]. In placebo-controlled phase III trials in patients with T2DM, empagliflozin used as monotherapy or add-on therapy improved hemoglobin A1c (HbA1c) approximately 0.7-1.0% -point (depending on baseline HbA1c and renal function) with a low risk of hypoglycemia, reduced body weight and BP, without increases in heart rate, and had small effects on plasma lipids (increase in HDL-cholesterol, increase in LDL-cholesterol, no change in LDL/HDL cholesterol ratio) [13-17]. In addition, empagliflozin has been shown to improve arterial stiffness and reduce glomerular hyperfiltration in patients with type 1 diabetes mellitus (T1DM) [18,19]. Moreover, SGLT2 inhibitors have also been reported to reduce other CV risk markers such as visceral fat mass [20,21] and proteinuria [22]. Based on these pleiotropic effects on CV risk factors, we hypothesized that empagliflozin may reduce CV risk in patients with T2DM.

The EMPA-REG OUTCOME™ trial was designed to determine the long-term CV safety of empagliflozin in patients with T2DM and to investigate its potential cardioprotective effects, as well as impact on microvascular outcomes, in a dedicated study that complied with current regulatory requirements.

Methods

The EMPA-REG OUTCOME™ trial (clinicaltrials.gov identifier: NCT01131676) is an ongoing, multicenter, randomized, double-blind, placebo-controlled trial. It was designed to assess the effect of empagliflozin (10 mg or 25 mg once daily) compared with placebo, in addition to standard of care, on CV events in adults with T2DM at high risk of CV events and with less than optimized glycemic control.

The study protocol was approved by the respective Institutional Review Boards, Independent Ethics Committees and Competent Authorities according to national and international regulations.

Trial population

Our goal was to recruit 7000 participants across 42 countries. Patients aged ≥18 years (≥20 years in Japan and also ≤65 years in India) with T2DM who were drug-naïve (no anti-diabetes agents for ≥12 weeks prior to randomization) with HbA1c ≥7.0% and ≤9.0% or taking any background anti-diabetes therapy (except pioglitazone in Japan) with HbA1c ≥7.0% and ≤10.0% despite diet and exercise counseling and who were at high risk of CV events were eligible for inclusion. The main inclusion criteria are provided in detail in Table 1. The dose of background glucose-lowering therapy was required to be unchanged for ≥12 weeks prior to randomization or, in the case of insulin, unchanged by >10% from the dose at randomization in the previous 12 weeks. Subjects were required to have a BMI ≤45 kg/m^2 at baseline. Detailed inclusion and exclusion criteria are listed in Additional file 1.

Study design

Eligible patients underwent a 2-week, open-label, placebo run-in period (Figure 1) during which background glucose-lowering therapy was continued unchanged. The purpose of the run-in period was to evaluate participants' willingness to adhere to the long-term treatment and follow-up planned in the trial. Following the placebo run-in, patients still meeting the inclusion/exclusion criteria were randomized (1:1:1) to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily in addition to their background therapy. Background glucose-lowering therapy was to remain unchanged for the first 12 weeks after randomization if possible, although rescue therapy could be initiated (details in Additional file 2). After this period, therapy could be adjusted to achieve desired glycemic control at the investigator's discretion to achieve best standard of care according to local guidelines. Investigators

Table 1 Key inclusion criteria

Insufficient glycemic control	High risk of cardiovascular events (≥1 of the following)
• ***Drug-naive subjects*:** HbA_{1c} ≥7.0% and ≤9.0% at screening	• History of myocardial infarction >2 months prior to informed consent
	• Evidence of multi-vessel CAD i.e. in ≥ 2 major coronary arteries or the left main coronary artery, documented by any of the following:
• ***Subjects on background therapy*:** HbA_{1c} ≥7.0% and ≤10.0% at screening	– Presence of significant stenosis: ≥50% luminal narrowing during angiography (coronary or multi-slice computed tomography)
	– Previous revascularization (percutaneous transluminal coronary angioplasty ± stent or coronary artery bypass graft >2 months prior to consent
	– The combination of revascularization in one major coronary artery and significant stenosis (≥50% luminal narrowing) in another major coronary artery
	• Evidence of single-vessel CAD, ≥50% luminal narrowing during angiography (coronary or multi-slice computed tomography) not subsequently successfully revascularized, with at least 1 of the following:
	– A positive non-invasive stress test for ischemia
	– Hospital discharge for unstable angina ≤12 months prior to consent
	• Unstable angina >2 months prior to consent with evidence of single- or multi-vessel CAD
	• History of stroke (ischemic or hemorrhagic) >2 months prior to consent
	• Occlusive peripheral artery disease documented by any of the following:
	– Limb angioplasty, stenting, or bypass surgery
	– Limb or foot amputation due to circulatory insufficiency
	– Evidence of significant peripheral artery stenosis (>50% on angiography, or >50% or hemodynamically significant via non-invasive methods) in 1 limb
	– Ankle brachial index <0.9 in ≥1 ankle

CAD, coronary artery disease.

were encouraged to treat all other CV risk factors according to local standard of care.

Randomization and follow-up

Randomization was undertaken using a computer-generated random sequence and an interactive voice and web response system. Patients were stratified by HbA_{1c} at screening (<8.5%, ≥8.5%), BMI at randomization (<30 kg/m^2, ≥30 kg/m^2), region (North America [plus Australia and New Zealand], Latin America, Europe, Africa, Asia), and renal function (eGFR using the Modification of Diet in Renal Disease [MDRD] equation) at screening (Chronic Kidney Disease [CKD] stage 1: ≥90 ml/min/1.73 m^2; CKD stage 2: 60–89 ml/min/1.73 m^2; CKD stage 3: 30–59 ml/min/1.73 m^2). Patients are instructed to attend the clinic at pre-specified times over the duration of the study including a follow-up visit 30 days after the end of the treatment period (Figure 1). Patients who prematurely discontinue study medication are asked to attend all visits as originally planned.

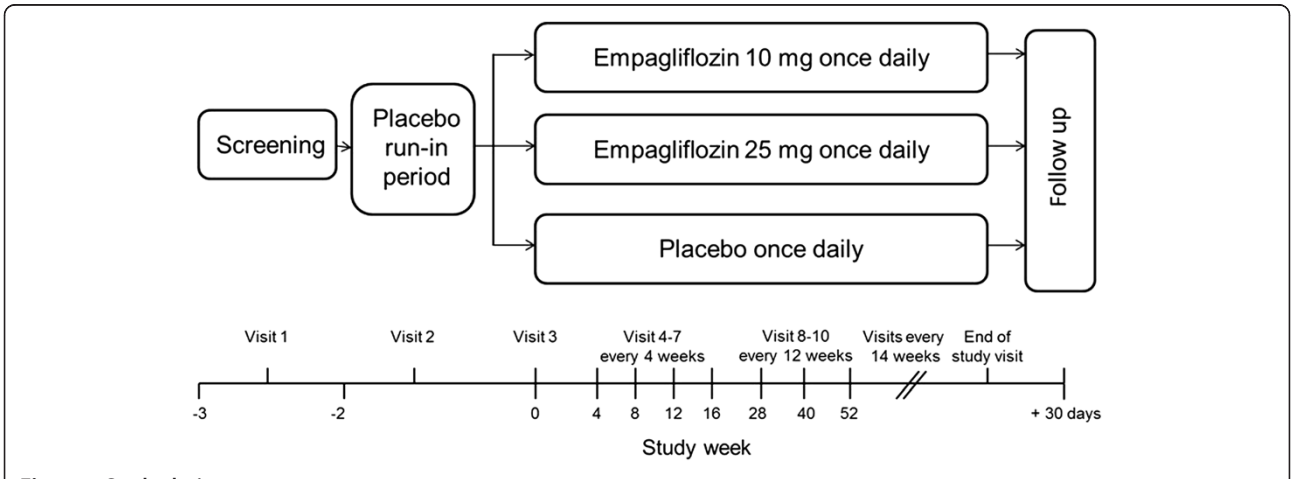

Figure 1 Study design.

Outcomes and outcome adjudication

The primary outcome of the study is time to first occurrence of CV death, non-fatal myocardial infarction (MI, excluding silent MI), or non-fatal stroke *i.e.,* 3-point major adverse cardiovascular events (3P-MACE). The key secondary outcome expands the primary composite outcome to include time to first occurrence of hospitalization for unstable angina (4P-MACE). Further CV outcomes are the individual components of the 4P-MACE, as well as individual occurrence of and time to silent MI, heart failure requiring hospitalization, all-cause mortality, transient ischemic attack (TIA) and coronary revascularization procedures. All CV outcome events and deaths are being prospectively adjudicated by the Clinical Events Committee (one for cardiac events and one for neurological events), as recommended in FDA guidelines (FDA [9]). Definitions of the major clinical outcomes are presented in Additional file 3 and a non-exhaustive list of further CV outcomes (secondary, tertiary and exploratory) in Additional file 4.

Additional secondary outcomes include the occurrence of and time to new onset albuminuria (urinary albumin: creatinine ratio ≥30 mg/g) and new onset of macroalbuminuria (urinary albumin:creatinine ratio ≥300 mg/g). Other outcomes include the occurrence of and time to a composite microvascular outcome comprising the initiation of laser therapy for retinopathy, vitreous hemorrhage, diabetes-related blindness, and new or worsening nephropathy (new onset macroalbuminuria [albumin:creatinine ratio ≥300 mg/g]; doubling of serum creatinine accompanied by eGFR ≤45 mL/min/1.73 m^2; initiation of renal replacement therapy; or death due to renal disease) as well as the individual components of this composite.

The short (12 weeks), medium (52 weeks), and long-term (annually, at end of study, and at follow-up) effects of the two doses of empagliflozin on HbA_{1c}, fasting plasma glucose (FPG), body weight, waist circumference, and BP will be assessed, as well as the proportion of patients who meet the composite outcome of HbA_{1c} reduction ≥0.5%, systolic BP reduction >3 mmHg, and body weight reduction >2%.

The prognostic impact of, and the modulating potential of empagliflozin on, the renal biomarker cystatin C and the CV biomarkers high-sensitivity C-reactive protein and high sensitivity troponin T will be assessed in sub-studies, as will potential associations between genetic variations and drug response.

Safety will be assessed based on adverse events (AEs) reported throughout the study and up to 7 days after the last dose of study medication (coded using the Medical Dictionary for Drug Regulatory Activities [MedDRA]), clinical laboratory tests, vital signs, 12-lead electrocardiogram (ECG), physical examination, and the use of rescue medication. Pre-specified AEs of special interest (AESI) include confirmed hypoglycemic adverse events (plasma glucose ≤70 mg/dL (3.9 mmol/L) and/or requiring assistance), those reflecting volume depletion, bone fracture, hepatic events, malignancies, urinary tract infection (UTI), and genital infection. Events may be defined by either abnormal laboratory values and/or relevant adverse events identified using prospectively defined search categories or both. For qualifying events, relevant source documentation will be requested including lab values, histological analysis, results of ultrasound, CT, MRI, scintigraphy, hospital discharge letters, and medical reports from other physicians. All evaluations will be performed in a blinded fashion.

A list of efficacy and safety outcomes is presented in Additional file 4.

Study oversight and organization

The trial was jointly designed by employees of Boehringer Ingelheim (BI) and the academic investigators who were members of the Steering Committee. The Steering Committee, which was led by the academic investigators and included members who were employees of the sponsor, supervised the trial design and operation. The independent data and safety monitoring committee (DMC) reviews interim safety data every 90 days or on an ad hoc basis on request. A list of committees involved in the trial conduct is presented in Additional file 5.

Statistical considerations

Sample size and power calculations

The primary hypothesis aims to show non-inferiority on 3P-MACE for empagliflozin versus placebo based on a non-inferiority margin of < 1.3 (upper limit of the adjusted 95% confidence interval (CI)) for the hazard ratio. The upper limit of the adjusted 95% CI for the HR of <1.3 was based on FDA guidance for CV trials evaluating new anti-hyperglycemic therapies for T2DM [9]. Patients who receive either 10 mg or 25 mg of empagliflozin will be pooled into a common treatment group for the purposes of the primary analysis. A 4-step hierarchical testing strategy will be followed: 1) non-inferiority test of the primary outcome (3P-MACE), 2) non-inferiority test of the key secondary outcome (4P-MACE), 3) superiority test of the primary outcome (3P-MACE) and 4) superiority test of the key secondary outcome (4P-MACE). A minimum of 691 confirmed primary outcome events are required to provide 90% power with a one-sided α level of 0.025, assuming equal risk between the placebo and empagliflozin groups. With a minimum of 691 events, the trial will also have at least 80% power to detect a hazard ratio of 0.785 (corresponding to a 21.5% risk reduction in CV outcome events) for the primary outcome.

Interim analysis

In order to support a CV meta-analysis of all CV events occurring in the phase III trials involving empagliflozin, as required for all New Drug Applications to be submitted to the FDA [9], CV outcome data from the ongoing EMPA-REG OUTCOME™ was extracted. The cut off for the data extraction was preplanned and ~ 150 4P-MACE were included in the project level CV meta-analysis. This resulted in addition of a Haybittle-Peto correction for the interim analysis (i.e., 0.0001 of the α was spent on the data extraction for the interim analysis), and subsequent reduction of the final α level to 0.0249 (in order to maintain the experiment-wise α level of 0.025).

The need to prevent the release of any data from the data extraction or interim analysis that could define the effects of empagliflozin on CV outcomes was fundamental to the study design [23]. Accordingly, procedures, including restricted access to electronic systems, were put in place to ensure that the effect estimate remained blinded and data review by the regulators would not require premature disclosure of the effects of empagliflozin on CV outcome. The data extraction, interim analysis and the following phase III CV meta-analysis were performed by a group independent from the EMPA-REG OUTCOME™ trial team, so that the trial's operational team and the academic Steering Committee remained blinded to the results. The DMC is the sole group with access to unblinded results beyond the strictly firewalled "CV meta-analysis group" of the sponsor.

Analysis plan

Three analysis populations are defined for this trial: 1) The treated set (TS), consisting of all patients who were treated with at least one dose of study drug, 2) The on-treatment set (OS), consisting of patients who received the drug for at least 30 days (cumulative) in whom events will be considered that occurred within 30 days of the off-treatment period or until the end of the entire trial, whichever will be earlier (patients who did not experience the primary outcome will be censored at the end of the treatment period, if the patient completes treatment as planned, or at the end of the 30 day period) and 3) the Full Analysis Set (FAS), consisting of all patients randomized, treated with at least one dose of study drug and with a baseline HbA1c value.

The primary analysis will be based on a Cox proportional hazards model with treatment (with empagliflozin 10 mg and 25 mg pooled into a single group), age, gender, baseline BMI (<30 kg/m^2, ≥30 kg/m^2), baseline HbA_{1c} (<8.5%, ≥8.5%), baseline eGFR as well as geographical region (classified as North America, Latin America, Europe, Africa and Asia) as factors. The same Cox proportional hazards model as for the primary outcome will be employed in all steps of the hierarchical testing strategy (3P-MACE and 4P-MACE).

The time to the occurrence of the primary outcome and the key secondary outcomes event will be computed as (event date – randomization date) +1. Patients who do not have the event during the trial period will be censored at the individual day of trial completion. The time to censoring will be computed as (individual day of trial completion – randomization date) + 1. For patients who have more than one primary outcome event during the trial, the time to the first occurrence of the primary outcome event will be considered for the primary analysis. All adjudicated and confirmed events will be used for the primary analysis.

The TS is the basis for the primary analysis and the FAS is the basis for the intention-to-treat (ITT) analysis for efficacy analyses. As sensitivity analyses the primary analysis will also be performed for the OS. Secondary analyses of the primary analysis with pooled active treatment arms will be performed by comparing the active treatments individually versus the placebo arm. Sensitivity analyses of the primary and key secondary outcomes will be performed that include the additional factor of naïve/experienced drug status in the Cox model. The secondary and tertiary further cardiovascular outcomes will be analyzed in a Cox proportional hazards model similar to the primary analysis for the treated set. Of note is that also other sensitivity analysis will be conducted employing other statistical methods, as well as an assessment of outcomes per individual dosages (i.e., empagliflozin 10 mg and empagliflozin 25 mg).

Subgroups to be considered in the analyses will be defined based on, but not limited to, age, HbA1c, BMI, weight, geographical region, race, gender, ethnicity, time since diagnosis of T2DM, renal function, BP, eGFR, glucose-lowering and CV prophylactic medication, CV complications and cohort, all defined at study baseline or screening. In addition, outcomes in patients experiencing severe hypoglycaemia vs those not experiencing severe hypoglycaemia will be assessed. Further details as to the specific categories to be employed for each subgroup factor are provided in Additional file 6.

Patient recruitment and baseline characteristics

Recruitment into the EMPA-REG OUTCOME™ trial began in September 2010 and was completed in April 2013. In total 11507 patients were screened and 7042 participants were randomized to receive study treatment at 592 clinical sites in 42 countries. The main reason for screen-failure was that the HbA1c fell outside protocol specifications. Of those randomized, 7034 participants were treated. The baseline characteristics of treated participants are shown in Table 2. Most came from Europe (41%) or North-America (20%) with 19% from Asia, 15.4% from Latin America and 4% from South-Africa. The mean age of participants was 63 years, with

Table 2 Baseline characteristics (treated set; n = 7034)

Age (years), mean (SD)	63.1 (8.6)
≥ 75 years of age, n (%)	652 (9)
Male, n (%)	5026 (72)
Race, n (%)	
White	5089 (72)
Asian	1518 (22)
Black/African American	357 (5)
Other*	70 (1)
Ethnicity, n (%)	
Hispanic or Latino	1268 (18)
Smoking history, n (%) Current/Ex-smoker	930 (13)/3216 (46)
Time since diagnosis, n (%)	
≤5 years	1265 (18)
>5-10 years	1754 (25)
>10 years	4015 (57)
Region, n (%)	
Europe	2885 (41)
North America/Australia/New Zealand	1408 (20)
Latin America	1081 (15)
Africa	313 (4)
Asia	1347 (19)
Northeast Asia	586 (8)
South/South-East Asia	761 (11)
CV risk factors, any of the below, n (%)	6978 (99)
History of MI	3275 (47)
Single-vessel CAD	743 (11)
Multi-vessel CAD	3285(47)
CABG	1738(25)
History of stroke	1631 (23)
Peripheral occlusive arterial disease	1449 (21)
Glucose-lowering therapy at baseline, n (%)	
None	128 (2)
Monotherapy	2055 (29)
Metformin (% of monotherapy)	745 (36)
Insulin (% of monotherapy)	954 (46)
Dual therapy	3188 (45)
Metformin + sulfonylurea (% of dual therapy)	1383 (43)
Metformin + insulin (% of dual therapy)	1420 (45)
Other therapies (n, %)	
Acetylsalicylic acid	5990 (85)
Statins	5387 (77)
Fibrates	630 (9)
Any antihypertensive therapy (n, %)	6641 (94)
Blockers of the renin-angiotensin system	5651 (80)
Beta-blockers	4537 (64)
Calcium channel blockers	2114 (30)

*American Indian/Native Alaskan/Native Hawaiian/Pacific Islander/missing.
Results (based on a pre-final version of the database of this ongoing trial) may change slightly once trial is completed.

9% aged ≥75 years. Seventy-two per cent are male, and 72% are white. Time since diagnosis of T2DM was ≤5 years in 18% of participants and >10 years in 57%. At baseline, mean HbA_{1c} was 8.1% (Table 3) with 68% of participants having HbA_{1c} <8.5%. Only 2% of participants were drug-naïve; 29% were receiving monotherapy, and 45% were receiving dual therapy. Insulin was used by 36% of participants (as monotherapy or part of dual therapy). A history of CV complications or CV events was demonstrated in 99% of participants and in total 47% had a history of MI and 23% a history of stroke. Fifty-two per cent of participants had an eGFR ≥ 60 and <90 mL/min/1.73 m^2 (i.e., stage 2 CKD) and 26% had an eGFR ≥ 30 and <60 mL/min/1.73 m^2 (i.e., stage 3 CKD). Albuminuria (UACR ≥30 mg/g) was present in 40% of participants. At baseline, 77% of patients were receiving a statin, 9% were receiving a fibrate, 85% were being treated with an acetylsalicylic acid agent, and 94% were receiving any drug for BP reduction (80% on blockers of the renin-angiotensin system).

Discussion

The EMPA-REG OUTCOME™ trial is an ongoing, randomized, placebo-controlled, clinical outcomes trial powered to establish the CV safety of empagliflozin with the potential to demonstrate cardioprotection in patients with T2DM at high risk of CV events who are receiving standard of care.

The pragmatic inclusion of patients on any background glucose-lowering agents will enable an assessment of the long-term CV effects of empagliflozin in a representative cohort and in a setting similar to real-life clinical practice. Of further note is that the trial will be able to assess the impact of empagliflozin on CV risk, in particularly vulnerable patient groups since ~ 25% patients have eGFR < 60 and ~10% were ≥75 years of age at baseline. Further, given the diversity of background therapy being allowed, CV outcomes according to type of background therapy can be derived. Recruitment into the study is complete and the baseline characteristics of the 7034 treated participants indicate that, as planned, they are at high risk of CV events and we anticipate that the pre-specified number of 3P-MACE will be reached in 2015. Thus, this trial will be one of the first, if not the first, to report final CV outcome data amongst the ongoing

Table 3 Key baseline laboratory data (treated set; n = 7034)

HbA_{1c} (%), mean (SD)	8.1 (0.8)
HbA_{1c} <8.5%, n (%)	4811 (68)
Fasting plasma glucose (mmol/L), mean (SD)	8.5 (2.4)
Body mass index (kg/m^2), mean (SD)	30.6 (5.3)
≥ 35 kg/m^2, n (%)	1426 (20)
Weight (kg), mean (SD)	86.4 (18.9)
Waist circumference (cm), mean (SD)	105 (14)
Systolic/diastolic blood pressure (mmHg), mean (SD)	135 (17)/77 (10)
Lipids (mmol/L), mean (SD)	
Total cholesterol	4.2 (1.1)
LDL-cholesterol	2.2 (0.9)
HDL-cholesterol	1.2 (0.3)
Triglycerides	1.9 (1.4)
eGFR according to MDRD (mL/min/1.73 m^2), mean (SD)	74 (21)
eGFR according to MDRD (mL/min/1.73 m^2), n (%)	
≥90	1534 (22)
60 to <90	3671 (52)
30 to <60	1796 (26)
ACR albumin ratio (mg/g), median (Q1, Q3)	17.7 (7.1, 72.5)
ACR ratio (mg/g), n (%)	
≥ 30 – 300	2011 (29)
≥ 300	771 (11)

Results (based on a pre-final version of the database of this ongoing trial) may change slightly once trial is completed.

SGLT2i CV outcome trials: DECLARE-TIMI58 (clinicaltrials.gov identifier: NCT01730534) involving dapagliflozin, CANVAS (clinicaltrials.gov identifier: NCT01032629) involving canagliflozin [24] and the ertugliflozin CV outcome study (clinicaltrials.gov identifier: NCT01986881), which all according to public sources will complete 2017–2020.

With 7034 patients enrolled and treated, the trial is in keeping with the 2008 FDA guidance on evaluating the CV risk of new therapies to treat T2DM [9] but may also provide insights beyond CV safety, including impact on microvascular, in particular renal outcomes, as detailed above. A theoretical basis for renal protection with SGLT2 inhibitors has been proposed, encompassing reduction in tubular stress as well as glucose-induced inflammation and fibrotic markers in the proximal tubule *in vitro* and in animal models, as well as improvement in glucose and BP control, reduction in plasma uric acid and albuminuria, and reduction in glomerular hyperfiltration with improvement in glomerular capillary hypertension [19,22,25-28].

Since the majority (i.e., 78%) of participants in EMPA-REG OUTCOME™ had some degree (i.e. CKD 2 or 3) of renal impairment at baseline, including 11% with macroalbuminuria, this trial is also expected to provide valuable information on the effect of empagliflozin on renal outcomes. Of note, renal outcomes comprise the dedicated scope for two other SGLT2i outcome trials, i.e., the CANVAS-R trial (clinicaltrials.gov identifier NCT01989754) which will investigate the effects of canagliflozin on progression of albuminuria in 5700 patients with T2DM and the CREDENCE trial (clinical trials.gov identifier NCT02065791) which will investigate the effects of canagliflozin on the incidence of end-stage kidney disease, serum- creatinine doubling and renal and CV death in 3627 patients with T2DM and stage 2 and 3 CKD and macroalbuminuria, estimated to report in 2017 and 2019, respectively.

In summary, it is expected that the results of the EMPA-REG OUTCOME™ trial will provide evidence concerning the CV safety of empagliflozin, as well as provide insights on the potential benefits of empagliflozin on CV and microvascular outcomes. Thus the results of the EMPA-REG OUTCOME™ trial will help to inform clinical decision-making for patients with T2DM.

Additional files

Additional file 1: Inclusion and exclusion criteria.
Additional file 2: Criteria for the institution of rescue therapy.
Additional file 3: Outcome definitions for major clinical outcomes.
Additional file 4: Study outcomes (non-exhaustive list).
Additional file 5: Study organization.
Additional file 6: Selected subgroups of interest.

Abbreviations

3P-MACE: 3-point major adverse cardiovascular events; 4P-MACE: 4-point major adverse cardiovascular events; ACR: Albumin/creatinine ratio; AE: Adverse event; AESI: Adverse events of special interest; BI: Boehringer Ingelheim; BP: Blood pressure; BMI: Body mass index; CV: Cardiovascular; CG: Cockcroft-Gault; CKD: Chronic kidney disease; DBP: Diastolic blood pressure; DMC: Data monitoring committee; eGFR: Estimated glomerular filtration rate; FAS: Full analysis set; FPG: Fasting plasma glucose; HbA1c: Glycosylated hemoglobin; HR: Hazard ratio; ITT: Intention to treat; LOCF: Last observation carried forward; MACE: Major adverse cardiovascular events; MDRD: Modified diet renal disease formula; MI: Myocardial infarction; MMRM: Mixed model repeated measures; OS: On-treatment set; qd: Once daily; SBP: Systolic blood pressure; SGLT2: Sodium glucose cotransporter 2; SGLT2i: Sodium glucose cotransporter 2 inhibitor; T2DM: Type 2 diabetes mellitus.

Competing interests

BZ, SEI, JML, CW, RF and DF have received fees for advisory services to BI. EB, SH, JKH, JN, OEJ, HJW and UCB are employees of BI, the developer of empagliflozin.

Authors' contributions

All authors contributed to the development of the manuscript and read and approved the final manuscript.

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