Holman, Rury R; Coleman, Ruth L; Chan, Juliana CN; Chiasson, Jean-Louis; Feng, Huimei; Ge, Junbo; Gerstein, Hertzel C; Gray, Richard; Huo, Yong; Lang, Zhihui; McMurray, John J; Rydn, Lars; Schrder, Stefan; Sun, Yihong; Theodorakis, Michael J; Tendera, Michal; Tucker, Lynne; Tuomilehto, Jaakko; Wei, Yidong; Yang, Wenying; Wang, Duolao; Hu, Dayi; Pan, Changyu; ACE Study Group, (2017) Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomised, double-blind, placebo-controlled trial. The lancet. Diabetes & endocrinology, 5 (11). pp. 877-886. ISSN 2213-8587 DOI: https://doi.org/10.1016/s2213-8587(17)30309-1

DOI: 10.1016/s2213-8587(17)30309-1

*Manuscript

Effects of Acarbose on Cardiovascular and Diabetes Outcomes in Patients with Coronary Heart Disease and Impaired Glucose Tolerance: A Randomised Controlled Trial

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Title:	130 characters with spaces (113 without)
Abstract:	300 words (Max 300)
Text:	3640 words (Max 4500)
Tables & Figures:	3 Tables, 2 Figures (Max 5)
References:	26 (Max 30)

Background

The impact of acarbose on cardiovascular outcomes in patients with coronary heart disease and impaired glucose tolerance is unknown.

Methods

Chinese patients with coronary heart disease and impaired glucose tolerance were randomised to double-blind acarbose 50 mg three times daily or placebo, added to standardised cardiovascular secondary prevention therapy. Acarbose was hypothesised to be superior to placebo for a composite outcome of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalisation for unstable angina or hospitalisation for heart failure. The completed study is registered with ClinicalTrials.gov NCT00829660 and ISRCTN 91899513.

Findings

Of 6526 patients randomised, 6522 were followed for median 5·0 years. The primary composite outcome occurred in 470 acarbose group participants (14·4%; 3·33 *per* 100 person-years) and in 479 placebo group participants (14·7%; 3·41 *per* 100 person-years). Acarbose was not superior to placebo for the primary outcome (hazard ratio 0·98; 95% Confidence Interval [CI] 0·86 to 1·11; P=0·73), with no significant subgroup interactions. No significant differences were seen between treatment groups for the secondary composite outcome (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke), death from any cause, cardiovascular death, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, hospitalisation for unstable angina, or hospitalisation for heart failure. Diabetes developed less frequently in the acarbose group (N=436, 13·3%; 3·17 *per* 100 person-years) compared with the placebo group (N=513, 15·8%; 3·84 *per* 100 person-years) (rate ratio 0·82; 95% CI 0·71 to 0·94; P=0·005). Gastrointestinal disorders were numerically more frequent with acarbose but adverse event rates did not differ significantly between groups.

Interpretation

In Chinese patients with coronary heart disease and impaired glucose tolerance, acarbose did not reduce the risk of major adverse cardiovascular events but did reduce the incidence of diabetes.

Funding

Bayer AG.

Introduction

People with coronary heart disease and impaired glucose tolerance are at increased risk of future cardiovascular events[1,2,3] and developing type 2 diabetes.[4] In 2006, the prevalence of impaired glucose regulation in Chinese adults hospitalised for coronary artery disease was 37·3%.[5]

After the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) reported that acarbose, an alpha-glucosidase inhibitor, reduced the incidence of type 2 diabetes by 25% in people with impaired glucose tolerance,[6] it was approved for treating this condition in China and elsewhere. A subsequent pre-specified STOP-NIDDM secondary analysis suggested a decreased risk of a cardiovascular composite outcome[7], although only 47 participants experienced such an event in the low cardiovascular risk population enrolled. Acarbose has also been shown to slow progression of carotid artery intima-media thickness in people with impaired glucose tolerance.[8] A meta-analysis of seven trials showed that acarbose reduced cardiovascular events by one third in patients with type 2 diabetes, although none were specifically designed to test this hypothesis.[9] These and other data support a possible cardiovascular disease prevention role for acarbose.[10]

The Acarbose Cardiovascular Evaluation (ACE) trial examined whether acarbose could reduce cardiovascular events in Chinese patients with established coronary heart disease and impaired glucose tolerance, and whether the incidence of type 2 diabetes could be reduced.[11,12]

Methods

Study Design

This randomised, double-blind, placebo-controlled, event-driven, Phase IV superiority trial was conducted at 176 sites in China.[11,12] Designed and overseen by a Steering Committee of 14 academic investigators and two Bayer employees, it was run independently by the University of Oxford Diabetes Trials Unit,[13] with the University of Oxford as the Sponsor. The protocol (available on-line at http://www.dtu.ox.ac.uk/ACE/protocol.php) was approved by the University of Oxford Tropical Research Ethics Committee, and by central or local ethics committees (as appropriate) at participating sites. Participants provided written informed consent. The Appendix contains organisational details and a list of participating sites and investigators. An independent Data and Safety Monitoring Board performed on-going safety surveillance with full access to unblinded data.

Participants

Selection criteria and baseline characteristics of participants have been published.[11,12,14] These are listed in the Appendix, but briefly those eligible were ≥50 years old with established coronary heart disease (defined as prior myocardial infarction, unstable angina or current stable angina), and impaired glucose tolerance (confirmed by a 75g oral glucose tolerance test) who had taken ≥80% of single-blind placebo study medication during a four-week run-in period. During the run-in period investigators were required to provide all participants with appropriate lifestyle advice with respect to diet, exercise and smoking. Also, existing cardiovascular therapy was optimised (if required) to be consistent with internationally accepted treatment guidelines, including antiplatelet agents, statins, beta-blockers, renin-angiotensin-aldosterone inhibitors, and blood pressure lowering therapy as appropriate.

Randomisation and Masking

Participants were randomised 1:1 by a centralised computer system to acarbose 50mg three times daily with meals or to matching placebo, blocked within site. The 50mg acarbose dose was chosen because that was the usual dose used in China for people with impaired glucose tolerance and because of the high study medication discontinuation rate seen in STOP-NIDDM with a dose of 100mg three times daily (31% acarbose versus 19% placebo during median 3·3 years' follow-up, with 48% of these participants discontinuing in the first year), mainly secondary to gastrointestinal side effects which are dose dependent. The randomisation sequence (coded as "A" or "B") was generated by a Diabetes Trials Unit statistician unconnected to the trial and uploaded to the electronic Rave Trial Management System (rTMS, Medidata Rave, New York). Acarbose and matching placebo tablets were provided by Bayer packaged in four month quantities, each packet being labelled with a unique code. These codes were also uploaded to the rTMS with their corresponding "A" or "B" categorisation which was not visible to study staff. At the time of randomisation, and at subsequent visits, investigators were instructed by the rTMS which study medication packet should be given to each participant. They were required to enter two letters printed alongside the unique code on the packet label so that the rTMS could confirm the correct study medication had been dispensed. Up until database lock, the assignation of “A” or “B” to active or placebo was known only to the Bayer study medication packaging group and the Data Safety and Monitoring Board.

Procedures

Follow-up visits were performed at one, two, four, and then every four months to provide study medication, measure fasting plasma glucose, blood pressure and weight, and to ascertain clinical outcomes, monitor study medication adherence and collect serious adverse events that were not prespecified as study endpoints. At annual visits, oral glucose tolerance tests were conducted, glycated haemoglobin (HbA_{1c}) measured and serum creatinine measurements performed with estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease study equation, adapted for a Chinese population.[15] Whenever a four-monthly fasting plasma glucose value was ≥7·0 mmol/L an additional oral glucose tolerance test was scheduled to confirm the diagnosis of diabetes. Those who developed diabetes remained on blinded study medication with the addition of metformin or other glucose-lowering agents (except alphaglucosidase inhibitors), if required to maintain acceptable glycaemic control.

Non-serious adverse events were not collected unless related to the cessation or change in dose of study medication, as acarbose is licensed in China for treatment of impaired glucose tolerance. Adverse events were coded using the Medical Dictionary for Regulatory Activities Dictionary version 14·1.

Outcomes

During the trial, slow recruitment and lower than anticipated event rates required the Steering Committee to amend the protocol ahead of database lock.[14] This was done in a blinded manner with no involvement of the Data Safety and Monitoring Board. The primary composite cardiovascular outcome, a 3-point major cardiovascular adverse event [MACE] outcome (first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) was expanded to a 5-point MACE to include hospitalisation for unstable angina and hospitalisation for heart failure. Heart failure was included in the composite as a cardiovascular outcome that can no longer be ignored,[16] and given evidence that glucagon-like peptide-1, which is elevated by acarbose,[17] can improve left ventricular function.[18] The 3-point MACE became a secondary outcome.[14] In addition, the sample size was reduced from 7500 to 6500, and the power to detect a 20% reduction in the primary composite outcome was reduced from 90% to 85%, requiring ≥728 rather than ≥904 participants to have had a confirmed event.

The other secondary outcomes were all-cause death; cardiovascular death; nonfatal myocardial infarction; nonfatal stroke; hospitalisation for unstable angina; hospitalisation for heart failure; as well as the proportion of participants developing diabetes confirmed by two successive diagnostic plasma glucose values (defined as fasting plasma glucose ≥126 mg/dl [≥7·0 mmol/L] and/or two-hour plasma glucose ≥200 mg/dl [≥11·1 mmol/L]), with no intervening non-diagnostic values, or diagnosed outside of the study, and the proportion of participants developing impaired renal function (defined as ≥1 of eGFR <30 ml/min/1·73m^2, doubling of baseline serum creatinine level, or halving of baseline eGFR). To avoid confounding by competing mortality risks, we have chosen to report fatal or nonfatal myocardial infarction and fatal or nonfatal stroke as post hoc secondary endpoints, rather than nonfatal myocardial infarction and nonfatal stroke. The final secondary outcome is resource use, costs and cost effectiveness. These health economic outcomes are beyond the scope of this manuscript and will be reported elsewhere.

Participants were followed until study closeout whenever possible, regardless of whether they were taking study medication. Vital status ascertainment was completed by the investigator at study closeout visits, and for those lost to follow-up or who had withdrawn consent by searches conducted using local or national electronic health records, death registries, or other publicly available sources (where permitted by local ethics approvals).

Event Adjudication

Potential cardiovascular end points were reviewed and adjudicated in a blinded fashion by an independent Cardiovascular Endpoint Adjudication Committee. Each event was reviewed by two adjudicators, and was referred to the full committee if their categorisation of the event differed. Where it was not possible to fully adjudicate an event due to lack of source data (for example absence of cardiac biomarkers in a suspected MI) the committee had the option to classify the event as “probable” rather than “definite”. During the study the UK-based Cardiovascular Endpoint

Adjudication Committee was replaced by a China-based Cardiovascular Endpoint Adjudication Committee when it became apparent that supporting documents translated from Mandarin to English did not fully capture the information needed for a robust adjudication process.

An independent Diabetes Endpoint Adjudication Committee reviewed cases in a blinded fashion where diabetes was diagnosed, or participants are commenced on glucose lowering therapy, outside of the trial to decide if a diagnosis of diabetes was warranted.

Statistical Methods

We estimated that ≥728 participants with a confirmed composite primary outcome were required for the trial to have at least 85% power to detect a 20% risk reduction for acarbose, compared with placebo (two-sided alpha=0·05). For time-to event analyses, Kaplan-Meier curves were plotted and compared using log-rank tests according to randomised assignment. A Cox regression model with treatment arm as a predictor was used to derive the hazard ratio and 95% confidence interval (CI). As development of diabetes and impaired kidney function events are interval censored, they were analysed using discrete time proportional odds regression models. The analysis of the primary composite outcome was based only on events that were adjudicated as definite or probable, with a sensitivity analysis limited only to definite events. Sensitivity analyses for key endpoints were also performed in the on-treatment population, a subset of the intent-to-treat population that censored participants when they discontinued study medication.

Safety analyses were conducted in the safety population, a subset of the intent-to-treat population who received at least one study medication dose. Possible subgroup interactions for the primary composite outcome with sex, Chinese region, coronary heart disease inclusion criteria, prior heart failure, age at randomisation, as well as baseline HbA_{1c}, fasting plasma glucose, two-hour plasma glucose, systolic blood pressure, body mass index and eGFR were explored in stratified log-rank analyses. Differences in biochemical and clinical characteristics over time were analysed using a linear mixed regression model.

Continuous measures are summarised using descriptive statistics, mean, standard deviation, median and interquartile range as appropriate. For categorical variables, counts and percentage per treatment group are presented. All analyses were performed on the intention-to-treat (ITT) population unless specified otherwise, with two-sided tests at the 0·05 level of significance using SAS software, version 9·2 or higher (SAS Institute). Interaction P values were not adjusted for multiple testing.

Role of the Funding Source

This academically-led study was funded by Bayer but designed by the Steering Committee (two members of which were Bayer employees). It was sponsored by the University of Oxford with the funder having no role in data collection, analysis, interpretation of the data, or writing of this report. All analyses were performed independently by the Diabetes Trials Unit according to the prespecified statistical analysis plan, and verified by an independent statistician (DW). RRH, RLC and DW had full access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Study Participants

Of 6526 patients randomised between March 20th 2009 and October 23rd 2015, 6522 were included in the intent-to-treat population as written consent for four patients could not be located (N=3272 for acarbose, N=3250 for placebo). Planned closeout of participant follow-up was from 1 December 2016 to 18 April 2017. Vital status was ascertained for 94·4% of participants (Figure 1). Median follow up was 5·0 years (interquartile range [IQR] 3·4 to 6·0, maximum 7·9 years) in the acarbose group and 5·0 years (IQR 3·4 to 6·0, maximum 7·7 years) in the placebo group. The percentage of observed versus expected participant-years of follow-up for the primary composite outcome was 96·7% and 96·6% respectively. The mean percentage of time that participants received study drug was 77·5% and 76·4%, respectively, with premature study drug discontinuation primarily a participant decision (Appendix Figure S2). Overall, 29·8% and 31·4% respectively permanently discontinued study medication before completing the study with median treatment durations of 3·0 (1·3 to 5·0) and 3·0 (1·1 to 4·9) years.

Baseline characteristics and use of cardiovascular medications did not differ between treatment groups (Table 1). All participants had prior coronary heart disease, categorised overall as myocardial infarction (2712 of 6522, 41·6%), unstable angina (2715 of 6522, 41·7%) or stable angina (1417 of 6522, 21·7%) (not mutually exclusive). They were predominately male (4760 of 6522, 73·0%), of Han ethnicity (6327 of 6522, 97·0%), with mean (standard deviation [SD]) age 64·2 (8·1) years and body mass index 25·4 (3·1) kg/m^2. Their cardiovascular risk factors were well managed, with mean systolic blood pressure 130 (14) mmHg (73% of participants <140 mmHg), LDL-cholesterol 87 (31) mg/dl (2·3 (0·8) mmol/L), eGFR 91 (43) ml/min/1·73m^2 (6084 of 6522, 92·6% of participants ≥60 ml/min/1·73m^2), and 5697 of 6522 (87·3%) were non- or ex-smokers. Atrial fibrillation and prior heart failure were reported by the investigator in 274 of 6522 (4·2%) and 262 of 6522 (4·0%) of participants respectively.

Risk factor changes over time

At one year, mean (SD) HbA_{1c} was lower in the acarbose group compared with the placebo group (5·88 (0·65) versus 5·94 (0·65) %, P<0·0001), as were the 2-hour plasma glucose (8·4 (2·4) versus 8·7 (2·6) mmol/L, P<0·0001), triglycerides (1·49 (1·00) versus 1·62 (1·06) mmol/L, P<0·0001) and body weight (69·9 (10·9) versus 70·8 (11·0) kg, P<0·0001). These values remained lower in the acarbose group, compared with the placebo group, during the study with overall least-squares mean differences of −0·07% (95% confidence interval [CI] −0·04 to −0·10), −0·24% (95% CI −0·16 to −0·32), −0·09% (95% CI −0·07 to −0·12), and −0·64% (95% CI −0·53 to −0·75) respectively (Appendix Figure S1).

At one year, no significant differences were seen between treatment groups for systolic blood pressure (130·3 (15·4) versus 130·4 (14.9) mmHg, P=0·53), diastolic blood pressure (78·2 (9·5) versus 78·5 (9·6) mmHg, P=0·93) or LDL-cholesterol (2·4 (0·9) versus 2·4 (0·9) mmol/L, P=0·37). During the study, overall least-squares mean differences showed lower LDL-cholesterol (–0·03 mmol/L, 95% CI –0·05 to –0·01) and diastolic blood pressure (–0·32 mmHg, 95%CI –0·57 to –0·07) but not systolic blood pressure (–0·27 mmHg, 95%CI –0·67 to 0·13) in the acarbose group compared with the placebo group.

Outcomes

The primary outcome occurred in 470 of 3272 participants in the acarbose group (14·4%; 3·33 per 100 person-years) and 479 of 3250 in the placebo group (14·7%; 3·41 per 100 person-years) (hazard ratio 0·98; 95% CI 0·8 to 1·11; P=0·73) (Table 2, Figure 2). The results did not differ when primary outcomes adjudicated as probable (19 acarbose, 15 placebo) were excluded (hazard ratio 0·97, 95% CI 0·85 to 1·10, P=0·61), and the on-treatment analysis was similar (hazard ratio 1·07, 95% CI 0·92 to 1·24, P=0·41). Hazard rates for the components of the primary composite outcome did not differ by treatment group (Appendix Figure S3) and no significant interactions were seen in the prespecified subgroup analyses (Appendix Figure S4).

No statistically significant differences were seen between the acarbose and placebo groups for the 3-point MACE outcome (hazard ratio 0·95, 95% CI 0·81 to 1·11, P=0·51), death from any cause, cardiovascular death, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, hospitalisation for unstable angina, or hospitalisation for heart failure (Table 2).

Incident diabetes was lower in the acarbose group (N=436 of 3272, 13·3%; 3·17 per 100 person-years) compared with the placebo group (N=513 of 3250, 15·8%; 3·84 per 100 person-years) (rate ratio 0·82; 95% CI 0·71 to 0·94; p=0·005) during median 4·4 years' follow-up. Incident impaired kidney function did not differ between acarbose (N=41 of 3272, 1·3%, 0·33 *per* 100 person-years) and placebo (N=50 of 3250, 1·5%, 0·41 *per* 100 person-years) groups (rate ratio 0·81, 95% CI 0·54–1·23, P=0·33).

Safety outcomes

The number of participants reporting mild and severe hypoglycaemic episodes did not differ between acarbose and placebo groups (719 of 3272 [22·0%] versus 664 of 3250 [20·4%], and 65 of 3272 [2·0%] versus 63 of 3250 [1·9%] respectively). There were no clinically relevant differences in the incidence of events of clinical interest, serious adverse events or adverse events (Table 3), although bleeding events were more common with acarbose in participants whilst taking dual antiplatelet therapy (Appendix Table S1). Gastrointestinal disorders were numerically more frequent in the acarbose group compared with the placebo group for serious adverse events (92 of 3272 [2·8%] versus 65 of 3250 [2·0%] respectively, P=0·057) and adverse events associated with drug discontinuation or dose changes (252 of 3272 [7·7%] versus 179 of 3272 [5·5%] respectively, P=0·19). Neither non-cardiovascular death rates (71 of 3272 [2.2%] versus 56 of 3250 [1.7%], P=0·19) nor the incidence of cancer deaths (10 of 3272 [0.3%] versus 12 of 3250 [0.4%], P=0·08) differed between groups.

Discussion

Among Chinese patients with coronary heart disease and impaired glucose tolerance, addition of acarbose did not lower the rate of the primary composite outcome of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalisation for unstable angina or hospitalisation for heart failure, compared with placebo. No statistically significant impact was seen with acarbose on the risk of all-cause death, 3-point MACE, or its individual components. Acarbose, however, reduced the risk of incident diabetes by 18% compared with placebo, with the number-needed-to-treat to prevent one case of diabetes developing over 5 years being 41. There is no reason to believe that these findings cannot be extrapolated to equivalent but non-Chinese populations.

Acarbose was reported to reduce cardiovascular events in a secondary analysis of the STOP-NIDDM trial,[7] but with only 47 participants having the outcome in question this could be a chance finding.[19] The lack of any substantial benefit on cardiovascular events in ACE compared with STOP-NIDDM might reflect the lower dose of acarbose used (50 versus 100 mg three times daily), the younger population (54·5 versus 64·3 years), the different ethnic group, or the less-stringent cardiovascular risk targets in the 1990s. Few large-scale studies have examined the impact of antihyperglycaemic agents targeting postprandial glucose excursions, with none showing cardiovascular benefit. The UK Prospective Diabetes Study randomised 1946 people with type 2 diabetes double-blind to the addition of acarbose 100 mg three times daily or placebo for three years.[20] Those allocated to acarbose had lower mean HbA_{1c} values but no difference in "any diabetes-related end point" (hazard ratio 1·00, 95% CI 0·81 to 1·23) or microvascular disease (hazard ratio 0·91, 95% CI 0·61 to 1·35). The Assessment of an Alpha-Glucosidase Inhibitor to Block Cardiac Events in Patients With Myocardial Infarction and IGT (ABC) study with voglibose was terminated early as an interim analysis of the first 870 participants suggested a low probability of a positive outcome.[21] Nateglinide, a rapid-acting insulin secretagogue which reduces postprandial hyperglycemia by increasing circulating insulin levels, was evaluated in the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial.[22] In 9309 patients at high cardiovascular disease risk and with impaired glucose tolerance followed for median 5·0 years, nateglinide 120 mg once daily showed no effect on the risk of cardiovascular events and a 7% significant increased risk for new-onset diabetes.

Whilst no direct effect of acarbose was seen on cardiovascular outcomes in our trial, a possible indirect effect should not be dismissed. Development of diabetes doubles the risk for major adverse cardiovascular events[23] and it may be that in the longer term acarbose, by delaying or preventing diabetes in a people with coronary heart disease, could reduce their cardiovascular risk. Such a link was reported during the long-term passive follow-up of participants in the Da Qing diabetes prevention trial where individuals allocated to lifestyle modification who developed diabetes at a slower rate had a lower 23-year mortality rate than those allocated to the control group.[24]

The 18% statistically significant lower risk of incident diabetes seen in the ACE trial high risk cardiovascular population was less than the 25% reduction observed over mean 3·3 years in the STOP-NIDDM low cardiovascular risk population (4·8% with a prior cardiovascular event).[7] Notably, STOP-NIDDM subjects were required to have a fasting plasma glucose concentration of 5·6–7·7 mmol/L in addition to impaired glucose tolerance, increasing their risk of progression to diabetes 3·4 times more than having impaired fasting glucose alone.[25]

ACE study strengths include the long follow-up period, accumulation of sufficient participants with a primary composite outcome to provide 90% power, the fact that they were well-treated with respect to classical cardiovascular risk factors, independent adjudication of all outcomes, and high ascertainment of vital status.

Study limitations include the decline in study medication adherence over time reducing the possible impact of acarbose (although adherence did not differ between treatment groups), and the addition of hospitalisation for unstable angina and hospitalisation for heart failure components to the primary composite outcome which could mask more definitive cardiovascular events.[26]

In Chinese patients with impaired glucose tolerance and coronary heart disease, acarbose did not reduce the risk of major cardiovascular events but did reduce the risk of new-onset diabetes.

Contributors:

RRH, JCNC, JLC, JG, HCG, JJM, LR, MT, JT, WY, DH and CP help designed the study. RRH wrote the first draft of the manuscript. RLC, RG and DW provided statistical analysis. HF, YS, MJT, LT and YW provided study leadership. All authors contributed to the writing of the manuscript, assume responsibility for the accuracy and completeness of this report, and vouch for its fidelity to the trial protocol.

Declarations of interests:

RRH reports grants from Bayer AG, during the conduct of the study; personal fees from Amgen, grants from AstraZeneca, personal fees from Bayer, grants and personal fees from Boehringer Ingelheim, other from Elcelyx, other from GSK, other from Jannsen, personal fees from Servier, other from Takeda, grants and personal fees from Merck Sharp & Dohme, outside the submitted work; **JCNC** reports grants and personal fees from Astra Zeneca, grants and personal fees from Bayer, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Eli Lilly, grants and personal fees from GlaxoSmithKline, grants and personal fees from Merck Sharp & Dohme, grants and personal fees from Novo Nordisk, grants and personal fees from Pfizer, grants and personal fees from Sanofi, during the conduct of the study; **HCG** reports personal fees from University of Oxford, during the conduct of the study; grants from Sanofi, personal fees from Sanofi, grants from Eli Lilly , personal fees from Eli Lilly, grants from Astra Zeneca, personal fees from Astra Zeneca, grants from Boehringer Ingelheim, personal fees from Boehringer Ingelheim, personal fees from Abbot, grants from Novo Nordisk, personal fees from Novo Nordisk, grants from Merck, personal fees from Merck, personal fees from Amgen, outside the submitted work; **LZ** reports other from Bayer, during the conduct of the study; **JJM** reports other from Novartis, other from Cardiorentis, other from Amgen, other from Novartis, other from Oxford University/Bayer, other from GlaxoSmithKline, other from Theracos, other from Abbvie, other from DalCor, other from Pfizer, other from Merck, other from AstraZeneca, other from Bristol Myers Squibb (BMS), other from Kidney Research UK (KRUK)/Kings College Hospital, London/Vifor-Fresenius Pharma, outside the submitted work; **LR** reports grants from Swedish Heart Lung

Foundation, grants from Swedish Diabetes Foundation, grants from Family E Perssons foundation, grants from Amgen, grants and personal fees from Bayer AG, grants and personal fees from Boehringer Ingelheim, grants and personal fees from MSD, grants and personal fees from Novo Nordisk, outside the submitted work; **SS** reports other from Bayer, during the conduct of the study; **MT** reports personal fees from University of Oxford, during the conduct of the study; personal fees from Bayer, personal fees from Celyad, personal fees from Kowa, personal fees from Janssen Cilag, personal fees from PERFUSE Group, personal fees from Servier, outside the submitted work; **JT** has received research grants, served as a consultant to and/or a member of advisory boards for, and/or gave lectures organised by AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Impeto-Medical, Merck, MSD, Sanofi-Aventis, Novartis, Novo Nordisk and Servier. **WY** reports personal fees from Novo Nordisk, grants and personal fees from AstraZeneca, personal fees from Bayer, Sanofi Aventis, Merck Sharp & Dohme China, Eli Lilly, Boehringer-Ingelheim, and Servier, personal fees from Merck & Co., Inc, outside the submitted work; **DW** reports grants from Oxford University, during the conduct of the study. **CP** has received lecture honoraria from Bayer Healthcare Company Ltd. **RLC, JLC, HF, JG, RG, YH, YS, MJT, LT, YW** and **DH** have nothing to disclose.

Acknowledgements:

Supported by Bayer AG.

We thank the patients, without whom this study and these analyses would not have been possible, the ACE China Project Office staff, and the contract research organisation Chiltern.

RRH is a National Institute for Health Research (NIHR) Senior Investigator.

Research in Context:

Evidence before this study

The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) demonstrated that acarbose, an alphaglucosidase inhibitor, decreased the incidence or diabetes in a population with impaired glucose tolerance and at low cardiovascular risk. A pre-specified analysis of this study suggested a decreased risk of a cardiovascular composite outcome, but only 47 participants in total experienced such an event. A meta-analysis of seven short term trials showed that acarbose reduced cardiovascular events by one third in patients with type 2 diabetes, although none were specifically designed to test this hypothesis. A Japanese trial, the Assessment of an Alpha-Glucosidase Inhibitor to Block Cardiac Events in Patients With Myocardial Infarction and IGT (ABC), using another alphaglucosidase inhibitor (voglibose) was discontinued for futility. The only large-scale trial to date that has examined the cardiovascular impact of targeting postprandial glucose excursions with an antihyperglycaemic agent in a population at high cardiovascular risk and with impaired glucose tolerance was the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial. This showed no effect on the risk of cardiovascular events and an increased risk for new-onset diabetes.

Added value of this study

This trial did not confirm the earlier STOP-NIDDM trial suggestion that acarbose might reduce cardiovascular risk in people with impaired glucose tolerance. It did, however, extend the known utility and safety of acarbose for delaying the onset of diabetes to a population with both coronary heart disease and impaired glucose tolerance.

Implications of all the available evidence

On the basis of the data from this trial and the NAVIGATOR study it would appear that, despite the strong epidemiological data linking postprandial hyperglycaemia to increased cardiovascular risk, directly targeting postprandial hyperglycaemia does not directly reduce the risk of cardiovascular events in populations at high cardiovascular risk and with impaired glucose tolerance. The reduced incidence of diabetes seen with acarbose in the ACE trial may, however, help reduce cardiovascular risk in the longer term by delaying the onset of diabetes in the high-risk population studied.

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Figure Legends

Figure 1. Enrollment, Follow-up, and Vital Status

Figure 2. Rates of the primary cardiovascular outcome (composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalisation for unstable angina or hospitalisation for heart failure) (Panel A), the secondary cardiovascular outcome (composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) (Panel B), cardiovascular death (Panel C), and new-onset diabetes (Panel D) in the acarbose and placebo groups.

Table 1. Baseline Characteristics of the Trial Participants, According to Assigned Study Treatment

	Acarbose (N=3272)	Placebo (N=3250)	All participants (N=6522)
Patient Demographics			
Age (years)	64.4 (8.2)	64.3 (8.0)	64.3 (8.1)
<65	1794 (54.8%)	1823 (56.1%)	3617 (55.5%)
≥65	1478 (45.2%)	1427 (43.9%)	2905 (44.5%)
Sex			
Male	2395 (73.2%)	2365 (72.8%)	4760 (73.0%)
Female	877 (26.8%)	885 (27.2%)	1762 (27.0%)
Race			
Han	3183 (97.3%)	3144 (96.7%)	6327 (97.0%)
Other	89 (2.7%)	106 (3.3%)	195 (3.0%)
Region			
Beijing and Tianjin	515 (15.7%)	519 (16.0%)	1034 (15.9%)
Central	474 (14.5%)	471 (14.5%)	945 (14.5%)
South and Southwest	654 (20.0%)	634 (19.5%)	1288 (19.8%)
West and East	1125 (34.4%)	1124 (34.6%)	2249 (34.5%)
Northeast	485 (14.8%)	483 (14.9%)	968 (14.8%)
Hong Kong	18 (0.6%)	17 (0.5%)	35 (0.5%)
Clinical Characteristics			
Weight (kg)	70.1 (10.7)	70.3 (11.0)	70.2 (10.8)
Height (m)	1.66 (7.5)	1.66 (7.7)	1.66 (7.6)
Body mass index (kg/m^2)	25.3 (3.1)	25.5 (3.1)	25.4 (3.1)
<25	1543 (47.2%)	1473 (45.4%)	3016 (46.1%)
25-30	1514(46.3%)	1517 (46.7%)	3031 (46.3%)
≥30	211 (6.5%)	257 (7.9%)	468 (7.2%)
Waist circumference (cm)	91.0 (8.8)	91.5 (8.9)	91.2 (8.9)
Systolic blood pressure (mmHg)	130 (14.2)	129 (14.1)	130 (14.2)
Systolic blood pressure <140 mmHg	2399 (73.3%)	2344 (72.1%)	4743 (72.7%)
Diastolic blood pressure (mmHg)	78 (9.2)	78 (9.2)	78 (9.2)
Smoking			
Never	1321 (40.4%)	1312 (40.6%)	2640 (40.5%)
Ex	1551 (47.4%)	1506 (46.3%)	3057 (46.9%)
Current	398 (12.2%)	425 (13.1%)	823 (12.6%)
Consuming alcohol			
Yes	309 (9.4%)	299 (9.2%)	608 (9.3%)
No	2961 (90.6%)	2951 (90.8%)	5912 (90.7%)
Biochemical Characteristics			

Fasting plasma glucose (mmol/l)	5.5 (0.86)	5.5 (0.78)	5.5 (0.82)
Two-hour plasma glucose (mmol/l)	9.3 (1.1)	9.3 (1.1)	9.3 (1.1)
HbA_{1c}			
(mmol/mol)	41 (8)	41 (7)	41 (7.8)
(%)	5.9 (0.8)	5.9 (0.7)	5.9 (0.7)
Haemoglobin (g/L)	141 (15)	141 (15)	141 (15)
Mean red cell corpuscular volume (fL)	91 (5.5)	92 (5.6)	92 (5.5)
White blood cell count ($x10^{9/l}$)	6.3 (1.6)	6.4 (1.7)	6.4 (1.7)
Platelet count ($x10^{9/l}$)	200 (57)	200 (57)	200 (57)
Haematocrit	0.42 (0.05)	0.42 (0.04)	0.42 (0.04)
Plasma alanine aminotransferase (U/L)	25.9 (14.6)	25.9 (15.2)	25.9 (14.9)
Plasma creatinine (µmol/L)	79 (19)	79 (20)	79 (20)
eGFR ($ml/min/1.73m^2$)	88 (75 - 103)	89 (75 - 103)	88 (75 - 103)
$<60\ ml/min/1.73m^2$	234 (7.2%)	249 (7.7%)	438 (7.4%)
Total cholesterol (mmol/L)	4.1 (1.1)	4.1 (1.0)	4.1 (1.0)
HDL-cholesterol (mmol/L)	1.18 (0.31)	1.18 (0.30)	1.18 (0.30)
LDL-cholesterol (mmol/L)	2.27 (0.82)	2.25 (0.78)	2.26 (0.80)
Triglycerides (mmol/L)	1.37 (1.00 to 1.91)	1.36 (0.99 to 1.91)	1.36 (1.00 to 1.91)
Coronary Heart Disease Inclusion Criteria			
Previous myocardial infarction	1350 (41.3%)	1362 (41.9%)	2712 (41.6%)
Previous unstable angina	1352 (41.3%)	1363 (42.0%)	2715 (41.7%)
Current stable angina	727 (22.2%)	690 (21.2%)	1417 (21.7%)
Cardiovascular therapies			
Lipid-lowering therapy			
Statins	3038 (93.0%)	3028 (93.3%)	6066 (93.2%)
Fibrate	35 (1.1%)	32 (1.0%)	67 (1.0%)
Niacin	13 (0.4%)	9 (0.35%)	22 (0.3%)
Antiplatelet therapy			
Any	3198 (97.9%)	3186 (98.2%)	6384 (98.0%)
Aspirin	3063 (93.8%)	3063 (94.4%)	6126 (94.1%)
Clopidrogel	2000 (61.3%)	1983 (61.1%)	3983 (61.2%)
Other	40 (1.2%)	38 (1.2%)	78 (1.2%)
Other cardiovascular therapy			
Beta-blocker	2141 (65.6%)	2160 (66.5%)	4301 (66.1%)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	1930 (59.1%)	1909 (58.8%)	3839 (59.0%)
Calcium channel blocker	967 (29.6%)	938 (28.9%)	1905 (29.3%)

Nitrates	1191 (36.5%)	1217 (37.5%)	2408 (37.0%)

Table 2: Rates of Composite Cardiovascular Outcomes and Secondary Outcomes in Randomised Groups by Intention-to-Treat Analysis.

Outcome	**Acarbose N=3272**		**Placebo N=3250**		**Hazard Ratio (95% CI)**	**P Value**
	No. (%)	**No. per 100 person-yrs.**	**No. (%)**	**No. per 100 person-yrs.**		
Primary cardiovascular outcome (5-point MACE)	470 (14.4)	3.33	479 (14.7)	3.4.	0.98 (0.86 to 1.11)	0.73
Secondary outcomes						
Cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (3-point MACE)	285 (8.7)	1.93	299 (9.2)	2.04	0.95 (0.81 to 1.11)	0.51
Death from any cause	216 (6.6)	1.42	219 (6.7)	1.45	0.98 (0.81 to 1.19)	0.85
Cardiovascular death	145 (4.4)	0.96	163 (5.0)	1.03	0.89 (0.71 to 1.11)	0.23
Fatal or non-fatal myocardial infarction	122 (3.7)	0.82	108 (3.3)	0.73	1.12 (0.87 to 1.46)	0.38
Fatal or non-fatal stroke	75 (2.3)	0.50	77 (2.4)	0.52	0.97 (0.70 to 1.33)	0.83
Hospitalisation for unstable angina	174 (5.3)	1.19	170 (5.2)	1.17	1.02 (0.82 to 1.26)	0.87
Hospitalisation for heart failure	65 (2.0)	0.43	73 (2.2)	0.49	0.89 (0.63 to 1.24)	0.48
Developed diabetes	436 (13.3)	3.17	513 (15.8)	3.84	0.82 (0.71 to 0.94)*	0.005
Developed impaired kidney function[†]	41 (1.3)	0.33	50 (1.5)	0.41	0.81 (0.54 to 1.23)*	0.33

*Rate ratios. [†] eGFR <30 ml/min/1.73m^2, doubling of baseline serum creatinine level, or halving of baseline eGFR

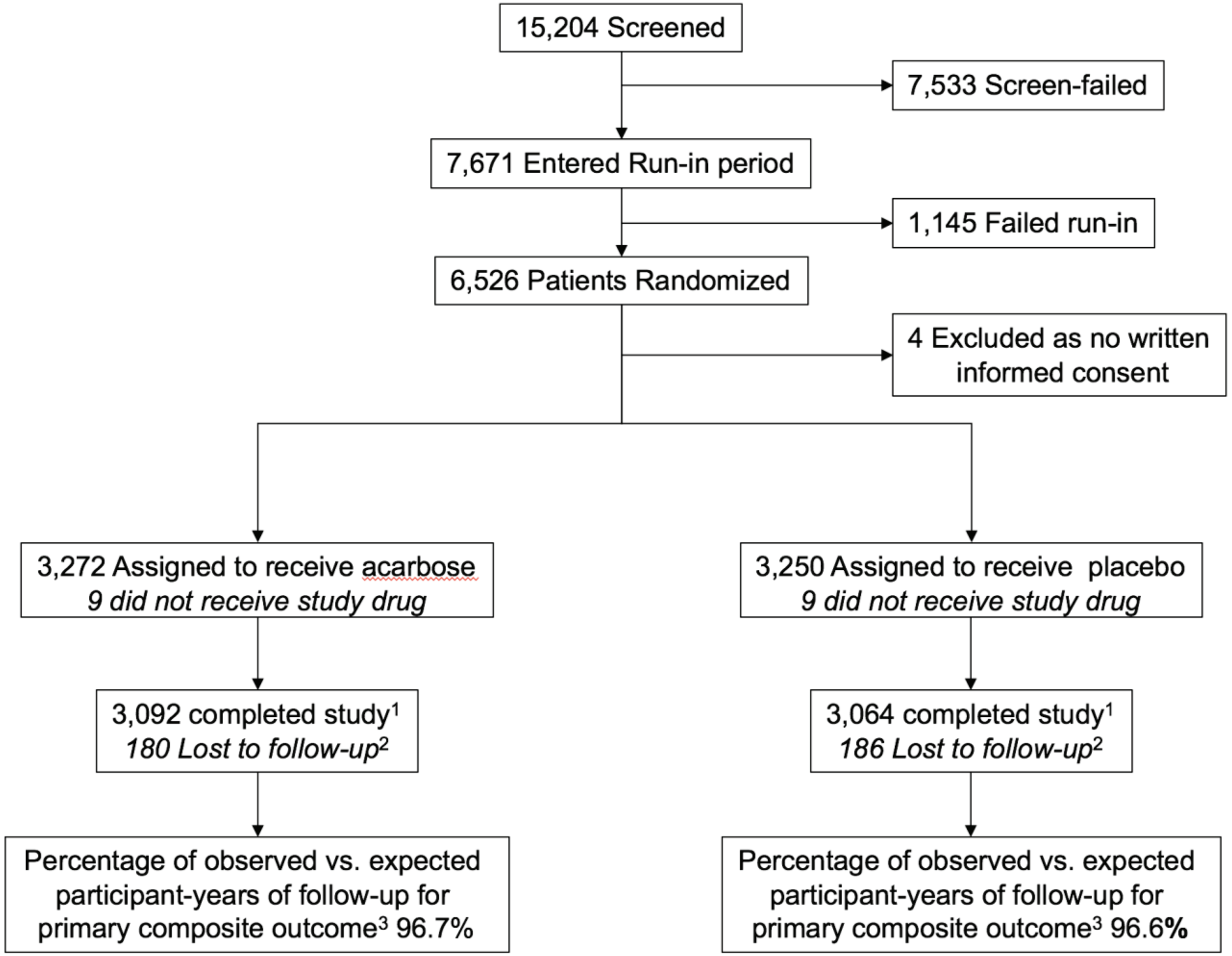
Table 3: Adverse Events Reported During the Trial According to System Organ Class

	Acarbose (N=3263)		Placebo (N=3241)	
	Patients	Events	Patients	Events
Serious adverse events*				
Neoplasms benign, malignant and unspecified	91 (2.8%)	109	90 (2.8%)	101
Infections and infestations	79 (2.4%)	87	77 (2.4%)	86
Gastrointestinal disorders	90 (2.8%)	94	66 (2.0%)	71
Vascular disorders	49 (1.5%)	52	37 (1.1%)	43
Nervous system disorders	39 (1.2%)	41	26 (0.8%)	62
Musculoskeletal and connective tissue disorders	33 (1.0%)	34	22 (0.7%)	23
Adverse events†				
Gastrointestinal disorders	250 (7.7%)	277	179 (5.5%)	187

* Serious adverse events are reported where they occur in ≥1% of participants in either treatment group.

† Adverse events associated with drug discontinuation or dose changes were reported where they occur in ≥5% in either treatment group.

Figure 1:

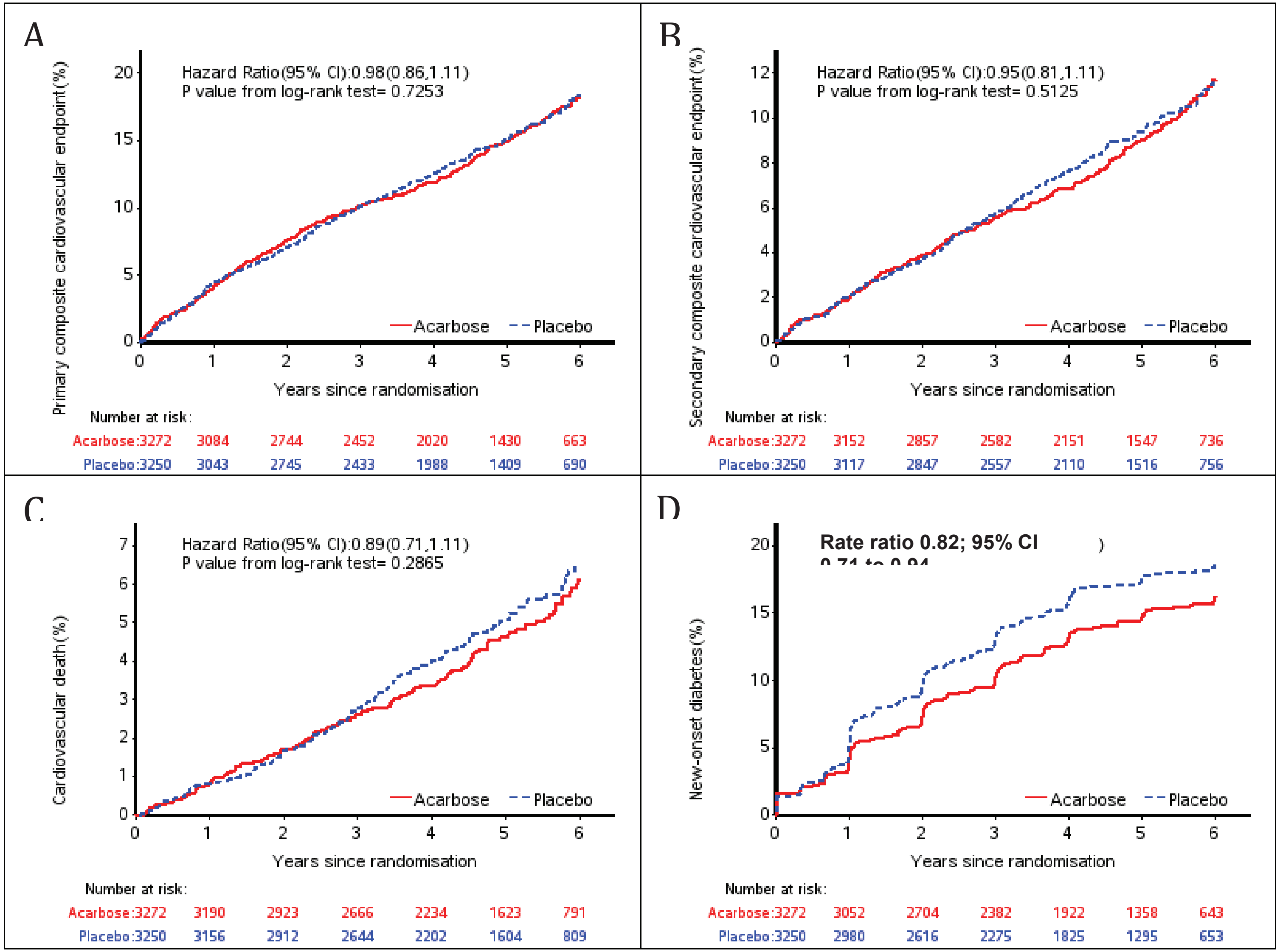


1 Subjects were counted as completers if they had vital status assessed as alive or deceased at the trial termination visit and had not withdrawn consent.

2 Subjects were counted as lost to follow-up if they were lost and their vital status could not be determined at the trial termination visit.

3 Time from randomization to the time of first primary composite outcome or the time when censored for first primary composite outcome according to the primary censoring scheme for event-free subjects, divided by the time from randomization to the time of first primary composite outcome or the expected follow-up time for event-free subjects as follows: vital status date at the trial termination visit for subjects counted as completers assessed as alive, the date of death for subjects counted as completers assessed as deceased, and the study cut-off date (1 Dec 2016) for subjects who were counted as lost to follow-up or withdrew consent.

Figure 2:


A
Primary composite cardiovascular endpoint (%)
Hazard Ratio (95% CI):0.98(0.86,1.11)
P value from log-rank test= 0.7253
Acarbose
Placebo
Years since randomisation
Number at risk:
Acarbose:3272 3084 2744 2452 2020 1430 663
Placebo:3250 3043 2745 2433 1988 1409 690
B
Secondary composite cardiovascular endpoint (%)
Hazard Ratio (95% CI):0.95(0.81,1.11)
P value from log-rank test= 0.5125
Acarbose
Placebo
Years since randomisation
Number at risk:
Acarbose:3272 3152 2857 2582 2151 1547 736
Placebo:3250 3117 2847 2557 2110 1516 756
C
Cardiovascular death (%)
Hazard Ratio (95% CI):0.89(0.71,1.11)
P value from log-rank test= 0.2865
Acarbose
Placebo
Years since randomisation
Number at risk:
Acarbose:3272 3190 2923 2666 2234 1623 791
Placebo:3250 3156 2912 2644 2202 1604 809
D
New-onset diabetes (%)
Rate ratio 0.82; 95% CI
Acarbose
Placebo
Years since randomisation
Number at risk:
Acarbose:3272 3052 2704 2382 1922 1358 643
Placebo:3250 2980 2616 2275 1825 1295 653