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

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Summary

Background The effect of the α-glucosidase inhibitor acarbose on cardiovascular outcomes in patients with coronary heart disease and impaired glucose tolerance is unknown. We aimed to assess whether acarbose could reduce the frequency of 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.

Methods The Acarbose Cardiovascular Evaluation (ACE) trial was a randomised, double-blind, placebo-controlled, phase 4 trial, with patients recruited from 176 hospital outpatient clinics in China. Chinese patients with coronary heart disease and impaired glucose tolerance were randomly assigned (1:1), in blocks by site, by a centralised computer system to receive oral acarbose (50 mg three times a day) or matched placebo, which was added to standardised cardiovascular secondary prevention therapy. All study staff and patients were masked to treatment group allocation. The primary outcome was a five-point composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospital admission for unstable angina, and hospital admission for heart failure, analysed in the intention-to-treat population (all participants randomly assigned to treatment who provided written informed consent). The secondary outcomes were a three-point composite outcome (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke), death from any cause, cardiovascular death, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, hospital admission for unstable angina, hospital admission for heart failure, development of diabetes, and development of impaired renal function. The safety population comprised all patients who received at least one dose of study medication. This trial is registered with ClinicalTrials.gov, number NCT00829660, and the International Standard Randomised Controlled Trial Number registry, number ISRCTN91899513.

Findings Between March 20, 2009, and Oct 23, 2015, 6522 patients were randomly assigned and included in the intention-to-treat population, 3272 assigned to acarbose and 3250 to placebo. Patients were followed up for a median of 5·0 years (IQR 3·4–6·0) in both groups. The primary five-point composite outcome occurred in 470 (14%; 3·33 per 100 person-years) of 3272 acarbose group participants and in 479 (15%; 3·41 per 100 person-years) of 3250 placebo group participants (hazard ratio 0·98; 95% CI 0·86–1·11, p=0·73). No significant differences were seen between treatment groups for the secondary three-point composite outcome, death from any cause, cardiovascular death, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, hospital admission for unstable angina, hospital admission for heart failure, or impaired renal function. Diabetes developed less frequently in the acarbose group (436 [13%] of 3272; 3·17 per 100 person-years) compared with the placebo group (513 [16%] of 3250; 3·84 per 100 person-years; rate ratio 0·82, 95% CI 0·71–0·94, p=0·005). Gastrointestinal disorders were the most common adverse event associated with drug discontinuation or dose changes (215 [7%] of 3263 patients in the acarbose group *vs* 150 [5%] of 3241 in the placebo group [p=0·0007]; safety population). Numbers of non-cardiovascular deaths (71 [2%] of 3272 *vs* 56 [2%] of 3250, p=0·19) and cancer deaths (ten [<1%] of 3272 *vs* 12 [<1%] of 3250, p=0·08) did not differ 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.

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Introduction

People with coronary heart disease and impaired glucose tolerance are at increased risk of future cardiovascular events[1–3] and development of type 2 diabetes.[4] In 2006, the prevalence of impaired glucose regulation in Chinese adults who were admitted to hospital for coronary artery disease was reported to be 37·3%.[5]

The results of the STOP-NIDDM trial showed that acarbose, an α-glucosidase inhibitor, reduced the

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See Online for appendix

For the **ACE protocol** see http://www.dtu.ox.ac.uk/ACE/protocol.php

Research in context

Evidence before this study

We searched PubMed for reports of randomised trials and meta-analyses assessing the effects of acarbose or other α-glucosidase inhibitors on cardiovascular outcomes and incident diabetes published in English up to April 1, 2007, using the search terms "impaired glucose tolerance", "α-glucosidase inhibitors", "acarbose", "cardiovascular outcomes", and "new-onset diabetes". The results of the STOP-NIDDM trial showed that acarbose, an α-glucosidase inhibitor, decreased the incidence of diabetes in a population with impaired glucose tolerance who were at low risk of cardiovascular events. Findings from a prespecified analysis of the STOP-NIDDM study suggested a decreased risk of a cardiovascular composite outcome, although the absolute number of events was small. The results of a meta-analysis of seven short-term trials showed that acarbose reduced cardiovascular events by a third in patients with type 2 diabetes, although none of the included trials were specifically designed to test this hypothesis. The ABC trial, which assessed the α-glucosidase inhibitor voglibose, was discontinued for futility. The only large-scale trial to date that has examined the cardiovascular effect of targeting postprandial glucose excursions with an antihyperglycaemic drug in a population at high risk for cardiovascular events and with impaired glucose tolerance was the NAVIGATOR trial of the short-acting insulin secretagogue nateglinide. The findings of this trial showed no effect on the risk of cardiovascular events and suggested an increased risk for new-onset diabetes.

Added value of this study

The results of the Acarbose Cardiovascular Evaluation (ACE) trial did not confirm the suggestion from the STOP-NIDDM trial that acarbose might reduce cardiovascular risk in people with impaired glucose tolerance. However, the results extend the knowledge of the safety of acarbose and its efficacy 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 seems 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 risk of cardiovascular events and with impaired glucose tolerance. The reduced incidence of diabetes seen with acarbose in the ACE trial might, however, help to reduce cardiovascular risk in the longer term by delaying the onset of diabetes in the high-risk population studied.

incidence of type 2 diabetes by 25% in people with impaired glucose tolerance,[6] after which it was approved for the treatment of this condition in China and in 52 other countries. Findings from a subsequent prespecified secondary analysis of STOP-NIDDM suggested a decreased risk of a composite cardiovascular outcome,[7] although only 47 participants had this type of event in the study population, which overall had low cardiovascular risk. Additionally, acarbose has also been shown to slow progression of carotid artery intima-media thickness in people with impaired glucose tolerance,[8] and findings from a meta-analysis of seven trials showed that acarbose reduced cardiovascular events by a third in patients with type 2 diabetes, although none of the trials were specifically designed to test this hypothesis.[9] These and other data support a possible role in cardiovascular disease prevention for acarbose.[10]

The Acarbose Cardiovascular Evaluation (ACE) trial was designed to examine 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]

Methods

Study design and participants

ACE was a randomised, double-blind, placebo-controlled, event-driven, phase 4 superiority trial done at 176 sites in outpatient clinics in tier 1 and tier 2 hospitals in China (appendix).[11] The study was designed and overseen by a steering committee of 14 academic investigators and two employees of the funder (Bayer AG), and was run independently by the University of Oxford Diabetes Trials Unit[12] with the University of Oxford (Oxford, UK) as the sponsor. An independent data and safety monitoring board did ongoing safety surveillance with full access to unmasked data. The protocol was approved by the University of Oxford Tropical Research Ethics Committee, and by central or local ethics committees (as appropriate) at participating sites. All participants provided written informed consent.

Selection criteria and baseline characteristics of study participants have been reported previously.[11,13] Briefly, eligible participants were aged 50 years or older and had established coronary heart disease (defined as previous myocardial infarction, previous unstable angina, or current stable angina), and impaired glucose tolerance (confirmed by a 75 g oral glucose tolerance test) who had taken at least 80% of single-blind placebo study medication during a 4 week run-in period (appendix). 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 the use of antiplatelet agents, statins, β blockers, renin–angiotensin–aldosterone system inhibitors, and blood pressure-lowering therapy, as appropriate.

Randomisation and masking

Participants were randomly assigned (1:1) by a centralised computer system to receive either acarbose or to matching placebo, in blocks of eight within site. 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, NY, USA). Acarbose and matching placebo tablets were provided by Bayer AG, packaged in 4-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 study 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 AG study medication packaging group and the data and safety monitoring board.

Procedures

Patients received either acarbose (50 mg given orally three times per day with meals) or matched placebo. The 50 mg dose was chosen because this is the most commonly used dose of acarbose 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 100 mg three times per day (31% acarbose *vs* 19% placebo during a median follow-up of 3·3 years, with 48% of these participants discontinuing in the first year), mainly because of gastrointestinal side-effects that were dose dependent.[6]

Follow-up visits took place at 1, 2, and 4 months, and then every 4 months until the end of the study to provide study medication; measure fasting plasma glucose, record hypoglycaemic episodes, blood pressure, and bodyweight; ascertain clinical outcomes; and monitor study medication adherence. During the trial, serious adverse events thought to be possible study endpoints were not reported as serious adverse events, although any other serious adverse events were reported to the sponsor and the China Food and Drug Administration (CFDA) according to the relevant regulations. Because acarbose was already licensed in China for the treatment of impaired glucose tolerance, there was no requirement to obtain data from adverse events routinely. However, adverse events were recorded when study medication was reduced or stopped as a result, or the event was thought to be related to study medication. Alanine aminotransferase concentrations, measured annually for safety, were reviewed unmasked by the data and safety monitoring board. At annual visits, patients did oral glucose tolerance tests, had HbA_{1c} and serum creatinine measured, and had estimated glomerular filtration rate (eGFR) calculated by use of the Modification of Diet in Renal Disease study equation, adapted for a Chinese population.[14] Whenever a 4-monthly fasting plasma glucose value was 7·0 mmol/L or higher, an additional oral glucose tolerance test was scheduled to confirm the diagnosis of diabetes. Participants who developed diabetes remained on masked study medication with the addition of metformin or other glucose-lowering agents (apart from α-glucosidase inhibitors), if required to maintain acceptable glycaemic control as identified by the treating physician.

Outcomes

During the trial, slow recruitment and lower than anticipated event rates required the steering committee to amend the protocol ahead of database lock.[13] Protocol amendments were done so that masking was preserved with no involvement of the data and safety monitoring board. The original primary composite cardiovascular outcome, a three-point major cardiovascular adverse event (MACE) outcome (first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) was expanded to a five-point MACE to also include hospital admission for unstable angina and hospital admission for heart failure. Heart failure was included in the composite outcome because it is being increasingly recognised as an important diabetes-related outcome in cardiovascular trials,[15] and because of evidence that glucagon-like peptide-1, which is increased by acarbose,[16] can improve left ventricular function.[17] The original three-point MACE became a secondary outcome.[13]

The other prespecified secondary outcomes were all-cause death; cardiovascular death; non-fatal myocardial infarction; non-fatal stroke; hospital admission for unstable angina; hospital admission for heart failure; the proportion of participants developing diabetes, as confirmed by two successive diagnostic plasma glucose values (defined as fasting plasma glucose ≥126 mg/dL [≥7·0 mmol/L] or 2 h 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 one or more of the following critera: eGFR <30 mL/min per 1·73 m², doubling of baseline serum creatinine concentration, or halving of baseline eGFR). To avoid confounding by competing mortality risks, we have chosen to report fatal or non-fatal myocardial infarction and fatal or non-fatal stroke as post-hoc secondary endpoints, rather than non-fatal myocardial infarction and non-fatal stroke as originally planned. Additional secondary outcomes were resource use, cost, and cost effectiveness; these health-economic outcomes will be reported elsewhere.

Non-serious adverse events were only recorded if they were related to the cessation or change in dose of study

medication, because acarbose is already licensed in China for treatment of impaired glucose tolerance. Adverse events were coded in accordance with the Medical Dictionary for Regulatory Activities Dictionary version 14.1.

Participants were followed up until the end of the study period whenever possible, irrespective of whether they were taking study medication. Vital status ascertainment was completed by the investigator at end-of-study visits, and for those lost to follow-up or who had withdrawn consent, by searches of local or national electronic health records, death registries, or other publicly available sources (where permitted by local ethics approvals). Data from participants lost to follow-up were censored at the last date their vital status could be ascertained.

Potential cardiovascular endpoint events were reviewed and adjudicated by an independent cardiovascular endpoint adjudication committee, which was masked to treatment allocation. Each event was reviewed by two adjudicators, and was referred to the full committee if their categorisation of the event differed. When it was not possible to fully adjudicate an event because of insufficient source data (eg, absence of cardiac biomarkers in a suspected myocardial infarction), 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 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 masked to treatment group allocation reviewed cases in which diabetes was diagnosed, or in which participants were commenced on other glucose-lowering drugs, outside of the trial to decide if a diagnosis of diabetes was warranted. Diagnosis of diabetes was not classified by type.

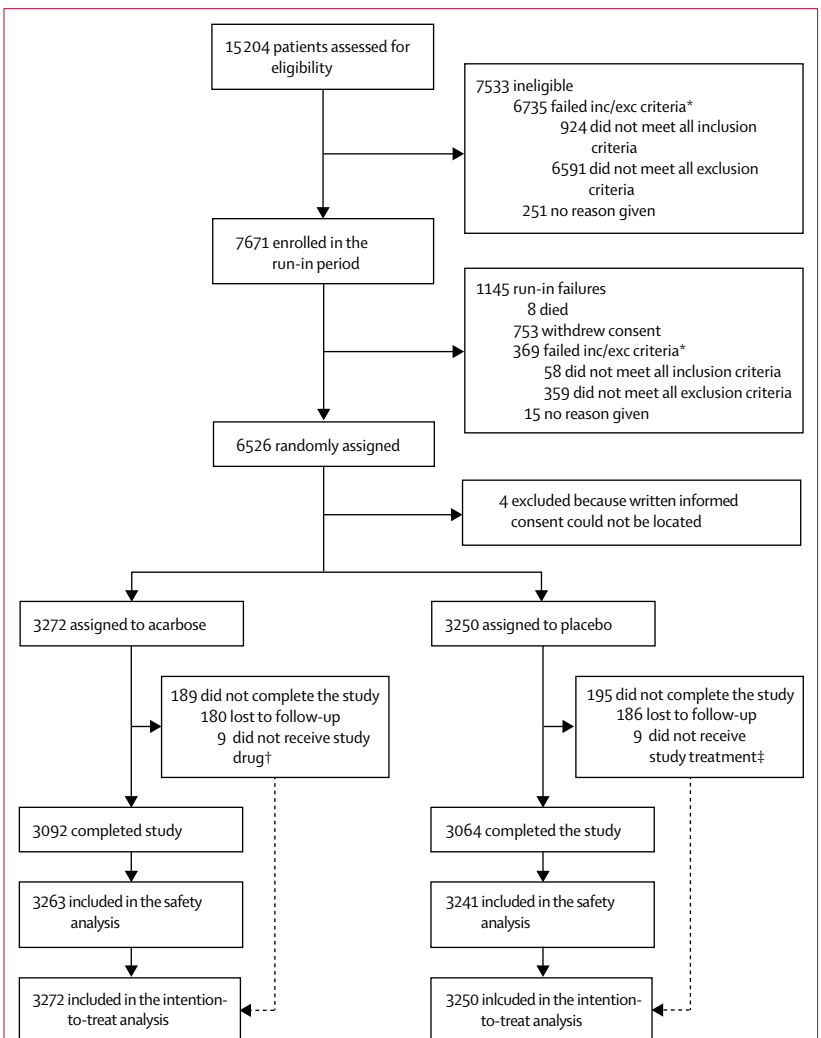

Figure 1: **Trial profile**
*Criteria were not mutually exclusive. †Of the nine patients who did not receive acarbose, six were patient refusal, two were other, and one was no reason given. ‡Of the nine patients who did not receive placebo, six were patient refusal, one was other, and two were no reason given.

Statistical analysis

At the time of the protocol amendment that changed the primary outcome to five-point MACE, the target study population size was also reduced from 7500 to 6500. With this revised sample size, we estimated that at least 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 α=0·05).

For time-to event analyses, we plotted Kaplan-Meier curves and compared analyses using log-rank tests according to randomised assignment. We used a Cox regression model with treatment group as a predictor to derive hazard ratios (HRs) and 95% CIs. Because development of diabetes and impaired kidney function events are interval censored, we analysed them using discrete time proportional odds regression models. We based the analysis of the primary composite outcome only on adjudicated events that were confirmed as definite or probable, with a sensitivity analysis limited only to definite events.

Analyses of primary and secondary outcomes were done in the intention-to-treat population, which included all participants randomly assigned to treatment who provided written informed consent. We also did prespecified sensitivity analyses for key endpoints in the on-treatment population, a subset of the intention-to-treat population in which participants were censored when they discontinued study medication.

Safety analyses were done in the safety population, a subset of the intention-to-treat population who received at least one study medication dose. In prespecified subgroup analyses, we investigated possible subgroup interactions for the primary composite outcome with sex, Chinese region, coronary heart disease inclusion criteria,

previous heart failure, and age at randomisation, as well as baseline HbA_{1c}, fasting plasma glucose, 2 h plasma glucose, systolic blood pressure, BMI, and eGFR in stratified log-rank analyses. We analysed differences in biochemical and clinical characteristics over time using a linear mixed regression model.

Continuous measures are summarised using descriptive statistics (mean and SD or median and IQR, as appropriate). For categorical variables, counts and percentages per treatment group are presented.

We used two-sided tests at the 0·05 level of significance for all statistical comparisons. Interaction p values were not adjusted for multiple testing. All statistical analyses were done with SAS (version 9.2 or later).

Role of the funding source

The study was designed by the trial steering committee, two members of which were employed by the study funder. The funder of the study had no role in data collection, data analysis, data interpretation, or writing of the report. All analyses were done independently by the Diabetes Trials Unit (University of Oxford, Oxford, UK) in accordance with the prespecified statistical analysis plan, and verified by an independent statistician (DW). RRH, RLC, and DW had full access to the raw trial data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 20, 2009, and Oct 23, 2015, 15 204 patients were screened, of whom 6526 were deemed eligible and completed the run-in period. Of these patients, four were excluded from all analyses because written informed consent could not be located, and 6522 were included in the intention-to-treat population, with 3272 randomly assigned to acarbose and 3250 to placebo (figure 1). The participant follow-up period for the end of study was from Dec 1, 2016, to April 18, 2017. Vital status was ascertained for 6160 (94·4%) of 6522 participants.

Median follow up was 5·0 years (IQR 3·4–6·0; maximum 7·9) in the acarbose group and 5·0 years (IQR 3·4–6·0; maximum 7·7) in the placebo group. The percentage of observed versus expected participant-years of follow-up for the primary composite outcome was 97% in both groups. The mean percentage of time that participants received study drug was 78% in the acarbose group and 76% in the placebo group, with premature study drug discontinuation primarily a participant decision (appendix). Overall, 1771 (49%) of 3272 participants in the acarbose group and 1809 (51%) of 3250 in the placebo group permanently discontinued study medication before completing the study, with median treatment durations of 3·0 years (IQR 1·3–5·0) and 3·0 years (1·1–4·9), respectively.

Baseline characteristics and use of cardiovascular medications did not differ between treatment groups (table 1). All participants had previous coronary heart disease, categorised overall as myocardial infarction, unstable angina, or stable angina (some patients had more than one condition).

At 1 year after the start of the study, mean HbA_{1c} was slightly lower in the acarbose group than in the placebo group (40·8 mmol/mol [5·88%], SD 7, *vs* 41·4 [5·94%], SD 8, p<0·0001), as were 2 h plasma glucose (8·4 mmol/L [2·4] *vs* 8·7 mmol/L [2·6], p<0·0001), triglycerides (1·49 mmol/L [1·00] *vs* 1·62 [1·06], p<0·0001) and bodyweight (69·9 kg (10·9) *vs* 70·8 (11·0), p<0·0001). These values remained lower in the acarbose group than in the placebo group during the study, with overall least-squares mean differences of –0·07% for HbA_{1c} (95% CI –0·04 to –0·10), –0·24

	Acarbose group (n=3272)	Placebo group (n=3250)	All participants (n=6522)
Demographic characteristics			
Age, years	64·4 (8·2)	64·3 (8·0)	64·3 (8·1)
<65	1794 (55%)	1823 (56%)	3617 (56%)
≥65	1478 (45%)	1427 (44%)	2905 (45%)
Sex			
Male	2395 (73%)	2365 (73%)	4760 (73%)
Female	877 (27%)	885 (27%)	1762 (27%)
Race			
Han	3183 (97%)	3144 (97%)	6327 (97%)
Other	89 (3%)	106 (3%)	195 (3%)
Region			
Beijing and Tianjin	515 (16%)	519 (16%)	1034 (16%)
Central	474 (14%)	471 (15%)	945 (14%)
South and southwest	654 (20%)	634 (20%)	1288 (20%)
West and east	1125 (34%)	1124 (35%)	2249 (34%)
Northeast	485 (15%)	483 (15%)	968 (15%)
Hong Kong	18 (1%)	17 (1%)	35 (1%)
Clinical characteristics			
Bodyweight, 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)
BMI, kg/m²	25·3 (3·1)	25·5 (3·1)	25·4 (3·1)
<25	1543 (47%)	1473 (45%)	3016 (46%)
25–30	1514(46%)	1517 (47%)	3031 (46%)
≥30	211 (6%)	257 (8%)	468 (7%)
Waist circumference, cm	91·0 (8·8)	91·5 (8·9)	91·2 (8·9)
Systolic blood pressure, mm Hg	130 (14·2)	129 (14·1)	130 (14·2)
Number with systolic blood pressure <140 mm Hg	2399 (73%)	2344 (72%)	4743 (73%)
Diastolic blood pressure, mm Hg	78 (9·2)	78 (9·2)	78 (9·2)
Smoking			
Never	1321 (40%)	1312 (41%)	2640 (40%)
Ex	1551 (47%)	1506 (46%)	3057 (47%)
Current	398 (12%)	425 (13%)	823 (13%)
Consuming alcohol			
Yes	309 (9%)	299 (9%)	608 (9%)
No	2961 (91%)	2951 (91%)	5912 (91%)

(Table 1 continues on next page)

	Acarbose group (n=3272)	Placebo group (n=3250)	All participants (n=6522)
(Continued from previous page)			
Biochemical characteristics			
Fasting plasma glucose, mmol/L	5·5 (0·86)	5·5 (0·78)	5·5 (0·82)
2 h 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 (8)
HbA_{1c}, %	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, $\times 10^9$ per L	6·3 (1·6)	6·4 (1·7)	6·4 (1·7)
Platelet count, $\times 10^9$ per 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)
Median eGFR, mL/min per 1·73 m^2	88 (75–103)	89 (75–103)	88 (75–103)
Number with eGFR <60 mL/min per 1·73 m^2	234 (7%)	249 (8%)	438 (7%)
Cholesterol			
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)
Median triglycerides, mmol/L	1·37 (1·00–1·91)	1·36 (0·99–1·91)	1·36 (1·00–1·91)
Coronary heart disease inclusion criteria			
Previous myocardial infarction	1350 (41%)	1362 (42%)	2712 (42%)
Previous unstable angina	1352 (41%)	1363 (42%)	2715 (42%)
Current stable angina	727 (22%)	690 (21%)	1417 (22%)
Cardiovascular treatments			
Lipid-lowering therapy			
Statins	3038 (93%)	3028 (93%)	6066 (93%)
Fibrate	35 (1%)	32 (1%)	67 (1%)
Niacin	13 (<1%)	9 (<1%)	22 (<1%)
Antiplatelet therapy			
Any	3198 (98%)	3186 (98%)	6384 (98%)
Aspirin	3063 (94%)	3063 (94%)	6126 (94%)
Clopidrogel	2000 (61%)	1983 (61%)	3983 (61%)
Other	40 (1%)	38 (1%)	78 (1%)
Other cardiovascular therapy			
β blocker	2141 (66%)	2160 (66%)	4301 (66%)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	1930 (59%)	1909 (59%)	3839 (59%)
Calcium channel blocker	967 (30%)	938 (29%)	1905 (29%)
Nitrates	1191 (36%)	1217 (37%)	2408 (37%)

Data are n (%), mean (SD), or median (IQR). eGFR=estimated glomerular filtration rate.

Table 1: **Baseline characteristics**

mmol/L for 2 h plasma glucose (–0·16 to –0·32), –0·09 mmol/L for triglycerides (–0·07 to –0·12), and –0·64 kg for bodyweight (95% CI –0·53 to –0·75; appendix).

At 1 year after the start of the study, no significant differences were seen between treatment groups for systolic blood pressure (130·3 mm Hg [SD 15·4] in the acarbose group *vs* 130·4 mm Hg [14·9] in the placebo group, p=0·53), diastolic blood pressure (78·2 mm Hg [9·5] *vs* 78·5 [9·6] p=0·93) or LDL cholesterol (2·4 mmol/L [0·9] *vs* 2·4 mmol/L [0·9], 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 mm Hg, –0·57 to –0·07), but not systolic blood pressure (–0·27 mm Hg, –0·67 to 0·13) in the acarbose group compared with the placebo group.

The primary outcome of five-point MACE occurred in 470 (14·4%) of 3272 participants in the acarbose group (3·33 per 100 person-years) and 479 (14·7%) of 3250 in the placebo group (3·41 per 100 person-years; HR 0·98, 95% CI 0·86–1·11, p=0·73; table 2, figure 2). The results did not differ when primary outcomes adjudicated as probable (19 in the acarbose group and 15 in the placebo group) were excluded (HR 0·97, 0·85–1·10, p=0·61), and results of the prespecified on-treatment analysis were similar (HR 1·07, 0·92–1·24, p=0·41). HRs for the components of the primary composite outcome did not differ between treatment groups and no significant interactions were identified in the prespecified subgroup analyses (appendix).

We identified no significant differences between the acarbose and placebo groups for the three-point MACE outcome, death from any cause, cardiovascular death, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, hospital admission for unstable angina, or hospital admission for heart failure (table 2).

The incidence of new-onset diabetes was 18% lower in the acarbose group than in the placebo group during a median of 4·4 years of follow-up. Incidental impaired renal function did not differ between the acarbose group and the placebo group.

The number of participants reporting mild and severe hypoglycaemic episodes did not differ between the acarbose and placebo groups (mild: 367 [11%] of 3272 *vs* 364 [11%] of 3250; severe: 54 [2%] of 3272 *vs* 52 [2%] of 3250). There were no clinically relevant differences in the incidence of events of clinical interest, serious adverse events, or adverse events other than gastrointestinal disorders (table 3), although haemorrhagic events were more common with acarbose in participants when taking dual antiplatelet therapy in a post-hoc analysis (appendix). Gastrointestinal disorders occurred with similar frequency in the acarbose group compared with the placebo group for serious adverse events (76 [2%] of 3263 *vs* 59 [2%] of 3241, p=0·16) but adverse events associated with drug discontinuation or dose changes occurred more frequently with acarbose than with placebo (215 [7%] of 3263 *vs* 150 [5%] of 3241, p=0·0007). Numbers of deaths from any cause (216 [7%] of 3272 *vs* 219 [7%] of 3250; p=0·85), non-cardiovascular deaths (71 [2%] of 3272 *vs* 56 [2%] of 3250, p=0·19) and cancer deaths (ten [<1%] of 3272 *vs* 12 [<1%] of 3250, p=0·08) did not differ between the groups in the intention-to-treat population.

	Acarbose group (n=3272)		Placebo group (n=3250)		Hazard ratio (95% CI)	p value
	n (%)	Number per 100 person-years	n (%)	Number per 100 person-years		
Primary outcome						
Five-point MACE*	470 (14·4%)	3·33	479 (14·7%)	3·41	0·98 (0·86–1·11)	0·73
Secondary outcomes						
Three-point MACE†	285 (8·7%)	1·93	299 (9·2%)	2·04	0·95 (0·81–1·11)	0·51
Death from any cause	216 (6·6%)	1·42	219 (6·7%)	1·45	0·98 (0·81–1·19)	0·85
Cardiovascular death	145 (4·4%)	0·96	163 (5·0%)	1·03	0·89 (0·71–1·11)	0·29
Fatal or non-fatal myocardial infarction	122 (3·7%)	0·82	108 (3·3%)	0·73	1·12 (0·87–1·46)	0·38
Fatal or non-fatal stroke	75 (2·3%)	0·50	77 (2·4%)	0·52	0·97 (0·70–1·33)	0·83
Hospital admission for unstable angina	174 (5·3%)	1·19	170 (5·2%)	1·17	1·02 (0·82–1·26)	0·87
Hospital admission for heart failure	65 (2·0%)	0·43	73 (2·2%)	0·49	0·89 (0·63–1·24)	0·48
Developed diabetes	436 (13·3%)	3·17	513 (15·8%)	3·84	0·82 (0·71–0·94)‡	0·005
Developed impaired kidney function§	41 (1·3%)	0·33	50 (1·5%)	0·41	0·81 (0·54–1·23)‡	0·33

Data are from the intention-to-treat population. MACE=major cardiovascular adverse event. eGFR=estimated glomerular filtration rate. *Five-point MACE consists of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospital admission for unstable angina, or hospital admission for heart failure. †Three-point MACE consists of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. ‡Rate ratios are reported. §Impaired kidney function was defined as eGFR <30 mL/min per 1·73 m^2, doubling of baseline serum creatinine level, or halving of baseline eGFR.

Table 2: **Primary and secondary outcomes**

Discussion

In Chinese patients with coronary heart disease and impaired glucose tolerance, acarbose did not reduce the primary composite outcome of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospital admission for unstable angina, or hospital admission for heart failure compared with placebo. No significant effect was seen with acarbose on the risk of all-cause death, three-point MACE, or its individual components. However, acarbose reduced the risk of incidental diabetes by 18% compared with placebo, with a number-needed-to-treat to prevent one case of diabetes developing over 5 years of 41. There is no reason to suggest that these findings cannot be extrapolated to similar 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 at least one outcome event, this could have been a chance finding.[18] However, the absence of benefit on cardiovascular events in the ACE trial compared with STOP-NIDDM might reflect the lower dose of acarbose used (50 mg *vs* 100 mg three times per day), the younger population (median 54·5 years *vs* 64·3 years), the difference in ethnic group, or the more aggressive secondary cardiovascular prevention measures being recommended when the ACE trial took place compared with the 1990s.

Few large-scale studies have examined the effect of antihyperglycaemic drugs targeting postprandial glucose excursions, with none showing cardiovascular benefit. In the UK Prospective Diabetes Study, 1946 people with type 2 diabetes were randomly assigned to acarbose 100 mg three times per day or matched placebo for 3 years.[19] Participants allocated to acarbose had a lower mean HbA_{1c} but no difference in the primary outcome (any diabetes-related aggregate endpoint; HR 1·00, 95% CI 0·81–1·23) or microvascular disease (HR 0·91, 95% CI 0·61–1·35). The ABC study assessing whether the α-glucosidase inhibitor voglibose could reduce the recurrence of myocardial infarction in patients with a previous myocardial infarction and impaired glucose tolerance was terminated early because an interim analysis of the first 870 participants suggested a low probability of a positive outcome.[20] Nateglinide, a rapid-acting insulin secretagogue that reduces postprandial hyperglycaemia by increasing circulating insulin concentrations, was assessed in the NAVIGATOR trial.[21] In 9309 patients at high risk for cardiovascular disease and with impaired glucose tolerance followed up for a median of 5·0 years, nateglinide 120 mg once per day showed no effect on the risk of cardiovascular events and suggested an increased risk for new-onset diabetes by 7% (HR 1·07, 95% CI, 1·00–1·15, p=0·05).

Although no direct effect of acarbose was seen on cardiovascular outcomes in the ACE trial, a possible indirect effect should not be dismissed. Development of diabetes doubles the risk for major adverse cardiovascular events[22] and it might be that acarbose reduces cardiovascular risk in the longer term by delaying or preventing diabetes in people with coronary heart disease. A similar link was reported during the long-term passive follow-up of participants in the Da Qing diabetes prevention trial in which individuals allocated to lifestyle modification who developed diabetes at a slower rate had a lower 23-year mortality than those allocated to the control group.[23]

The significantly reduced risk of incidental diabetes of 18% with acarbose compared with placebo seen in the

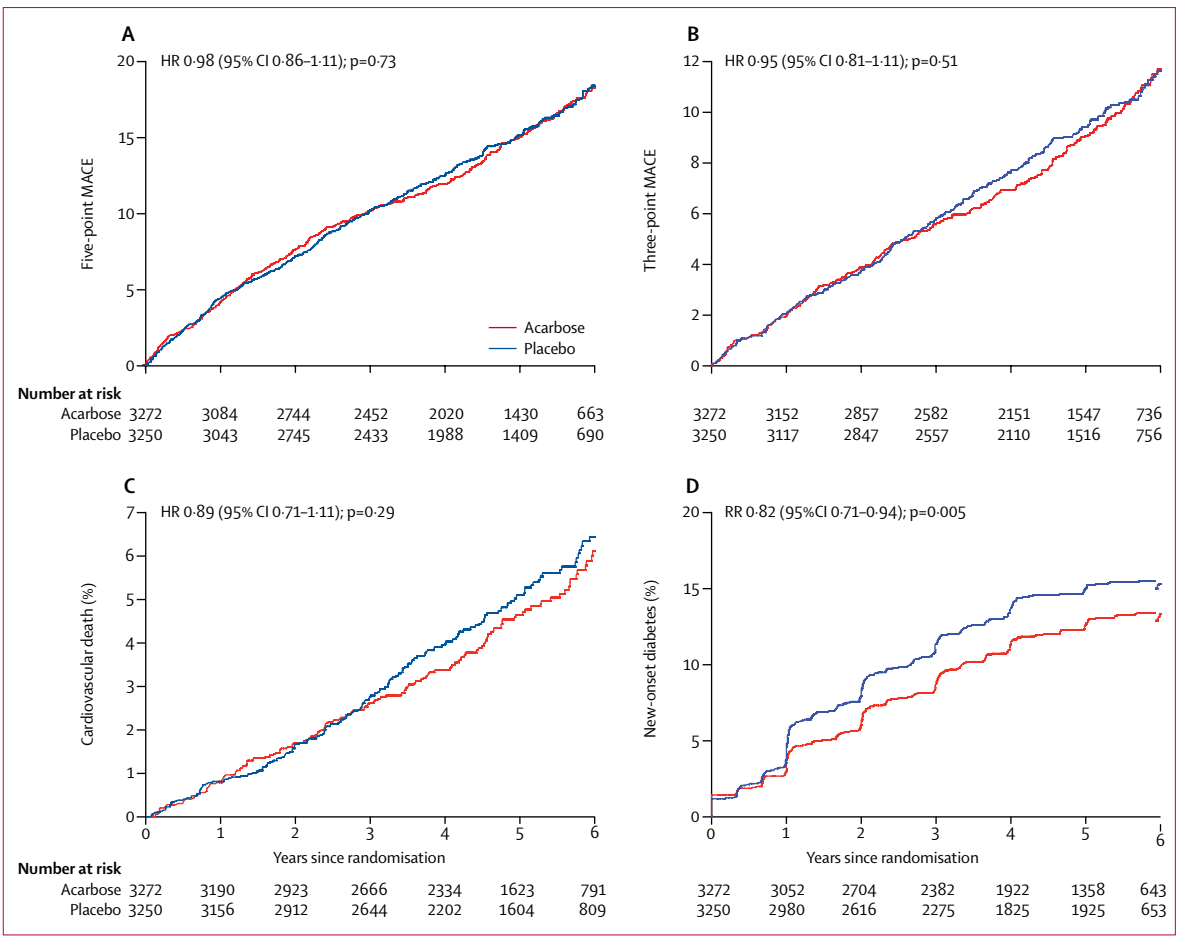

Figure 2: **Kaplan-Meier curves for composite cardiovascular outcomes, cardiovascular death, and new-onset diabetes**
Kaplan-Meier curves for five-point MACE (primary outcome; composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospital admission for unstable angina, or hospital admission for heart failure; A), three-point MACE (composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke; B), cardiovascular death (C), and new-onset diabetes (D) in the acarbose and placebo groups. MACE=major adverse cardiovascular events. HR=hazard ratio. RR=rate ratio.

	Acarbose group (n=3263)		Placebo group (n=3241)	
	Patients	Events	Patients	Events
Serious adverse events*				
Benign, malignant, and unspecified neoplasms	85 (3%)	109	88 (2%)	101
Infections and infestations	70 (2%)	87	74 (2%)	86
Gastrointestinal disorders	76 (2%)	94	59 (2%)	71
Vascular disorders	47 (1%)	52	36 (1%)	43
Nervous system disorders	37 (1%)	41	26 (1%)	62
Musculoskeletal and connective tissue disorders	30 (1%)	34	21 (1%)	23
Adverse events†				
Gastrointestinal disorders	215 (7%)	266	150 (5%)	175

Events are reported by Medical Dictionary for Regulatory Activities Dictionary (version 14.1) system organ class. All data are from the safety population. *Serious adverse events are reported if they occurred in ≥1% of participants in either treatment group. †Adverse events associated with drug discontinuation or dose changes are reported if they occurred in ≥5% in either treatment group.

Table 3: **Adverse events**

ACE trial population (who were at high cardiovascular risk) was less than the 25% reduction over a mean of 3·3 years in STOP-NIDDM, which was done in a population at low cardiovascular risk (4·8% of participants had a previous cardiovascular event).[7] Notably, STOP-NIDDM participants were required to have a fasting plasma glucose concentration of 5·6–7·7 mmol/L as well as impaired glucose tolerance, resulting in an increase in the risk of progression to 3·4 times more than having impaired fasting glucose alone.[24]

The strengths of the ACE study include the long follow-up period, accumulation of sufficient participants with a primary composite outcome to provide an actual power of 90%, the fact that participants were well treated with respect to traditional cardiovascular risk factors, independent adjudication of all outcomes, and high ascertainment of vital status. The study limitations include the decline in study medication adherence over time, which reduced the possible effect of acarbose (although

adherence did not differ between treatment groups), and the addition of hospital admission for unstable angina and hospital admission for heart failure components to the primary composite outcome, which might have masked more definitive cardiovascular events.[25]

In conclusion, the results of the ACE study show that, 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, J-LC, JG, HCG, JJM, LR, MT, JT, WY, DH, and CP contributed to the design of the study. RRH wrote the first draft of the report. RLC, RG, and DW did the statistical analyses. HF, YS, MJT, LT, and YW provided study leadership. All authors contributed to preparation of the final submitted version of the report, assume responsibility for the accuracy and completeness of the report, and vouch for its fidelity to the trial protocol. Other members of the ACE Study Group are listed in the appendix.

Declaration of interests

RRH reports grants from Bayer AG (related to the present study); personal fees from Amgen, Bayer AG (related to the present study), and Servier; grants from AstraZeneca; grants and personal fees from Boehringer Ingelheim and Merck Sharp & Dohme; and chaired or participated in independent data monitoring committees for Elcelyx, GlaxoSmithKline, Janssen, and Takeda. JCNC reports grants and personal fees from AstraZeneca, Bayer AG (unrelated to the present study), Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novo Nordisk, Pfizer, and Sanofi. HCG reports personal fees from the University of Oxford (related to the present study); grants and personal fees from Sanofi, Eli Lilly, AstraZeneca, Boehringer Ingelheim, Novo Nordisk, and Merck Sharp & Dohme; and personal fees from Abbott and Amgen. ZL reports being a Bayer AG employee. JJM reports payment to his university for time spent working on trial committees for Novartis, Cardiorentis, Amgen, Novartis, the University of Oxford/Bayer AG, GlaxoSmithKline, Theracos, AbbVie, DalCor, Pfizer, Merck Sharp & Dohme, AstraZeneca, Bristol-Myers Squibb, Kidney Research UK/King's College Hospital, and London/Vifor-Fresenius Pharma. LR reports grants from Swedish Heart Lung Foundation Swedish Diabetes Foundation, Family E Perssons Foundation, and Amgen; and grants and personal fees from Bayer AG (related to the present study), Boehringer Ingelheim, Merck Sharp & Dohme, and Novo Nordisk. SS is a Bayer AG employee. MT reports personal fees from the University of Oxford (related to the present study) and personal fees from Bayer AG (unrelated to the present study), Celyad, Kowa, Janssen, PERFUSE Group, and Servier. JT reports research grants and fees for consultancy, advisory board membership, or lectures from AstraZeneca, Bayer AG (related to the present study), Boehringer Ingelheim, Eli Lilly, Impeto Medical, Merck (Germany), Merck Sharp & Dohme, Sanofi Aventis, Novartis, Novo Nordisk, and Servier. WY reports personal fees from Bayer AG, Novo Nordisk, Sanofi Aventis, Merck Sharp & Dohme, Eli Lilly, Boehringer Ingelheim, Servier, and Merck Sharp & Dohme; and grants and personal fees from AstraZeneca. DW reports grants from the University of Oxford (related to the present study). CP reports lecture honoraria from Bayer AG (unrelated to the present study). RLC, J-LC, HF, JG, RG, YH, YS, MJT, LT, YW, and DH declare no competing interests.

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