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

3
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22 Text: 3640 words (Max 4500)

23 Tables & Figures: 3 Tables, 2 Figures (Max 5)

24 References: 26 (Max 30)

25

1 **Background**

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

4 **Methods**

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

11 **Findings**

12 Of 6526 patients randomised, 6522 were followed for median 5.0 years. The primary composite
13 outcome occurred in 470 acarbose group participants (14.4%; 3.33 *per* 100 person-years) and in
14 479 placebo group participants (14.7%; 3.41 *per* 100 person-years). Acarbose was not superior to
15 placebo for the primary outcome (hazard ratio 0.98; 95% Confidence Interval [CI] 0.86 to 1.11;
16 $P=0.73$), with no significant subgroup interactions. No significant differences were seen between
17 treatment groups for the secondary composite outcome (cardiovascular death, nonfatal myocardial
18 infarction, nonfatal stroke), death from any cause, cardiovascular death, fatal or nonfatal myocardial
19 infarction, fatal or nonfatal stroke, hospitalisation for unstable angina, or hospitalisation for heart
20 failure. Diabetes developed less frequently in the acarbose group (N=436, 13.3%; 3.17 *per* 100
21 person-years) compared with the placebo group (N=513, 15.8%; 3.84 *per* 100 person-years) (rate
22 ratio 0.82; 95% CI 0.71 to 0.94; $P=0.005$). Gastrointestinal disorders were numerically more frequent
23 with acarbose but adverse event rates did not differ significantly between groups.

24 **Interpretation**

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

27 **Funding**

28 Bayer AG.

1 **Introduction**

2 People with coronary heart disease and impaired glucose tolerance are at increased risk of future
3 cardiovascular events^{1,2,3} and developing type 2 diabetes.⁴ In 2006, the prevalence of impaired
4 glucose regulation in Chinese adults hospitalised for coronary artery disease was 37.3%.⁵
5 After the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) reported that
6 acarbose, an alpha-glucosidase inhibitor, reduced the incidence of type 2 diabetes by 25% in people
7 with impaired glucose tolerance,⁶ it was approved for treating this condition in China and elsewhere.
8 A subsequent pre-specified STOP-NIDDM secondary analysis suggested a decreased risk of a
9 cardiovascular composite outcome⁷, although only 47 participants experienced such an event in the
10 low cardiovascular risk population enrolled. Acarbose has also been shown to slow progression of
11 carotid artery intima-media thickness in people with impaired glucose tolerance.⁸ A meta-analysis of
12 seven trials showed that acarbose reduced cardiovascular events by one third in patients with type
13 2 diabetes, although none were specifically designed to test this hypothesis.⁹ These and other data
14 support a possible cardiovascular disease prevention role for acarbose.¹⁰
15 The Acarbose Cardiovascular Evaluation (ACE) trial examined whether acarbose could reduce
16 cardiovascular events in Chinese patients with established coronary heart disease and impaired
17 glucose tolerance, and whether the incidence of type 2 diabetes could be reduced.^{11,12}

18

19 **Methods**

20 *Study Design*

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

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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 $\geq 80\%$ 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

1 medication had been dispensed. Up until database lock, the assignment of “A” or “B” to active or
2 placebo was known only to the Bayer study medication packaging group and the Data Safety and
3 Monitoring Board.

4

5 *Procedures*

6 Follow-up visits were performed at one, two, four, and then every four months to provide study
7 medication, measure fasting plasma glucose, blood pressure and weight, and to ascertain clinical
8 outcomes, monitor study medication adherence and collect serious adverse events that were not
9 prespecified as study endpoints. At annual visits, oral glucose tolerance tests were conducted,
10 glycated haemoglobin (HbA_{1c}) measured and serum creatinine measurements performed with
11 estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease
12 study equation, adapted for a Chinese population.¹⁵ Whenever a four-monthly fasting plasma
13 glucose value was ≥ 7.0 mmol/L an additional oral glucose tolerance test was scheduled to confirm
14 the diagnosis of diabetes. Those who developed diabetes remained on blinded study medication
15 with the addition of metformin or other glucose-lowering agents (except alphaglucoSIDase inhibitors),
16 if required to maintain acceptable glycaemic control.

17 Non-serious adverse events were not collected unless related to the cessation or change in dose of
18 study medication, as acarbose is licensed in China for treatment of impaired glucose tolerance.
19 Adverse events were coded using the Medical Dictionary for Regulatory Activities Dictionary version
20 14.1.

21

22 *Outcomes*

23 During the trial, slow recruitment and lower than anticipated event rates required the Steering
24 Committee to amend the protocol ahead of database lock.¹⁴ This was done in a blinded manner with
25 no involvement of the Data Safety and Monitoring Board. The primary composite cardiovascular
26 outcome, a 3-point major cardiovascular adverse event [MACE] outcome (first occurrence of
27 cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) was expanded to a 5-point
28 MACE to include hospitalisation for unstable angina and hospitalisation for heart failure. Heart failure
29 was included in the composite as a cardiovascular outcome that can no longer be ignored,¹⁶ and

1 given evidence that glucagon-like peptide-1, which is elevated by acarbose,¹⁷ can improve left
2 ventricular function.¹⁸ The 3-point MACE became a secondary outcome.¹⁴ In addition, the sample
3 size was reduced from 7500 to 6500, and the power to detect a 20% reduction in the primary
4 composite outcome was reduced from 90% to 85%, requiring ≥ 728 rather than ≥ 904 participants to
5 have had a confirmed event.

6 The other secondary outcomes were all-cause death; cardiovascular death; nonfatal myocardial
7 infarction; nonfatal stroke; hospitalisation for unstable angina; hospitalisation for heart failure; as well
8 as the proportion of participants developing diabetes confirmed by two successive diagnostic plasma
9 glucose values (defined as fasting plasma glucose ≥ 126 mg/dl [≥ 7.0 mmol/L] and/or two-hour plasma
10 glucose ≥ 200 mg/dl [≥ 11.1 mmol/L]), with no intervening non-diagnostic values, or diagnosed
11 outside of the study, and the proportion of participants developing impaired renal function (defined
12 as ≥ 1 of eGFR < 30 ml/min/1.73m², doubling of baseline serum creatinine level, or halving of baseline
13 eGFR). To avoid confounding by competing mortality risks, we have chosen to report fatal or nonfatal
14 myocardial infarction and fatal or nonfatal stroke as post hoc secondary endpoints, rather than
15 nonfatal myocardial infarction and nonfatal stroke. The final secondary outcome is resource use,
16 costs and cost effectiveness. These health economic outcomes are beyond the scope of this
17 manuscript and will be reported elsewhere.

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

23 *Event Adjudication*

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

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

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

7

8 *Statistical Methods*

9 We estimated that ≥ 728 participants with a confirmed composite primary outcome were required for
10 the trial to have at least 85% power to detect a 20% risk reduction for acarbose, compared with
11 placebo (two-sided $\alpha=0.05$). For time-to event analyses, Kaplan-Meier curves were plotted and
12 compared using log-rank tests according to randomised assignment. A Cox regression model with
13 treatment arm as a predictor was used to derive the hazard ratio and 95% confidence interval (CI).
14 As development of diabetes and impaired kidney function events are interval censored, they were
15 analysed using discrete time proportional odds regression models. The analysis of the primary
16 composite outcome was based only on events that were adjudicated as definite or probable, with a
17 sensitivity analysis limited only to definite events. Sensitivity analyses for key endpoints were also
18 performed in the on-treatment population, a subset of the intent-to-treat population that censored
19 participants when they discontinued study medication.

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

27 Continuous measures are summarised using descriptive statistics, mean, standard deviation,
28 median and interquartile range as appropriate. For categorical variables, counts and percentage per
29 treatment group are presented. All analyses were performed on the intention-to-treat (ITT)

1 population unless specified otherwise, with two-sided tests at the 0.05 level of significance using
2 SAS software, version 9.2 or higher (SAS Institute). Interaction P values were not adjusted for
3 multiple testing.

4

5 *Role of the Funding Source*

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

13

14 **Results**

15 *Study Participants*

16 Of 6526 patients randomised between March 20th 2009 and October 23rd 2015, 6522 were included
17 in the intent-to-treat population as written consent for four patients could not be located (N=3272 for
18 acarbose, N=3250 for placebo). Planned closeout of participant follow-up was from 1 December
19 2016 to 18 April 2017. Vital status was ascertained for 94.4% of participants (Figure 1).

20 Median follow up was 5.0 years (interquartile range [IQR] 3.4 to 6.0, maximum 7.9 years) in the
21 acarbose group and 5.0 years (IQR 3.4 to 6.0, maximum 7.7 years) in the placebo group. The
22 percentage of observed versus expected participant-years of follow-up for the primary composite
23 outcome was 96.7% and 96.6% respectively. The mean percentage of time that participants
24 received study drug was 77.5% and 76.4%, respectively, with premature study drug discontinuation
25 primarily a participant decision (Appendix Figure S2). Overall, 29.8% and 31.4% respectively
26 permanently discontinued study medication before completing the study with median treatment
27 durations of 3.0 (1.3 to 5.0) and 3.0 (1.1 to 4.9) years.

28 Baseline characteristics and use of cardiovascular medications did not differ between treatment
29 groups (Table 1). All participants had prior coronary heart disease, categorised overall as myocardial

1 infarction (2712 of 6522, 41.6%), unstable angina (2715 of 6522, 41.7%) or stable angina (1417 of
2 6522, 21.7%) (not mutually exclusive). They were predominately male (4760 of 6522, 73.0%), of
3 Han ethnicity (6327 of 6522, 97.0%), with mean (standard deviation [SD]) age 64.2 (8.1) years and
4 body mass index 25.4 (3.1) kg/m². Their cardiovascular risk factors were well managed, with mean
5 systolic blood pressure 130 (14) mmHg (73% of participants <140 mmHg), LDL-cholesterol 87 (31)
6 mg/dl (2.3 (0.8) mmol/L), eGFR 91 (43) ml/min/1.73m² (6084 of 6522, 92.6% of participants ≥60
7 ml/min/1.73m²), and 5697 of 6522 (87.3%) were non- or ex-smokers. Atrial fibrillation and prior heart
8 failure were reported by the investigator in 274 of 6522 (4.2%) and 262 of 6522 (4.0%) of participants
9 respectively.

10

11 *Risk factor changes over time*

12 At one year, mean (SD) HbA_{1c} was lower in the acarbose group compared with the placebo group
13 (5.88 (0.65) versus 5.94 (0.65) %, P<0.0001), as were the 2-hour plasma glucose (8.4 (2.4) versus
14 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
15 body weight (69.9 (10.9) versus 70.8 (11.0) kg, P<0.0001). These values remained lower in the
16 acarbose group, compared with the placebo group, during the study with overall least-squares mean
17 differences of -0.07% (95% confidence interval [CI] -0.04 to -0.10), -0.24% (95% CI -0.16 to
18 -0.32), -0.09% (95% CI -0.07 to -0.12), and -0.64% (95% CI -0.53 to -0.75) respectively
19 (Appendix Figure S1).

20 At one year, no significant differences were seen between treatment groups for systolic blood
21 pressure (130.3 (15.4) versus 130.4 (14.9) mmHg, P=0.53), diastolic blood pressure (78.2 (9.5)
22 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).
23 During the study, overall least-squares mean differences showed lower LDL-cholesterol (-0.03
24 mmol/L, 95% CI -0.05 to -0.01) and diastolic blood pressure (-0.32 mmHg, 95%CI -0.57 to -0.07)
25 but not systolic blood pressure (-0.27 mmHg, 95%CI -0.67 to 0.13) in the acarbose group compared
26 with the placebo group.

27

1 *Outcomes*

2 The primary outcome occurred in 470 of 3272 participants in the acarbose group (14.4%; 3.33 per
3 100 person-years) and 479 of 3250 in the placebo group (14.7%; 3.41 per 100 person-years) (hazard
4 ratio 0.98; 95% CI 0.8 to 1.11; P=0.73) (Table 2, Figure 2). The results did not differ when primary
5 outcomes adjudicated as probable (19 acarbose, 15 placebo) were excluded (hazard ratio 0.97, 95%
6 CI 0.85 to 1.10, P=0.61), and the on-treatment analysis was similar (hazard ratio 1.07, 95% CI 0.92
7 to 1.24, P=0.41). Hazard rates for the components of the primary composite outcome did not differ
8 by treatment group (Appendix Figure S3) and no significant interactions were seen in the
9 prespecified subgroup analyses (Appendix Figure S4).

10 No statistically significant differences were seen between the acarbose and placebo groups for the
11 3-point MACE outcome (hazard ratio 0.95, 95% CI 0.81 to 1.11, P=0.51), death from any cause,
12 cardiovascular death, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, hospitalisation
13 for unstable angina, or hospitalisation for heart failure (Table 2).

14 Incident diabetes was lower in the acarbose group (N=436 of 3272, 13.3%; 3.17 per 100 person-
15 years) compared with the placebo group (N=513 of 3250, 15.8%; 3.84 per 100 person-years) (rate
16 ratio 0.82; 95% CI 0.71 to 0.94; p=0.005) during median 4.4 years' follow-up. Incident impaired
17 kidney function did not differ between acarbose (N=41 of 3272, 1.3%, 0.33 per 100 person-years)
18 and placebo (N=50 of 3250, 1.5%, 0.41 per 100 person-years) groups (rate ratio 0.81, 95% CI 0.54–
19 1.23, P=0.33).

20

21 *Safety outcomes*

22 The number of participants reporting mild and severe hypoglycaemic episodes did not differ between
23 acarbose and placebo groups (719 of 3272 [22.0%] versus 664 of 3250 [20.4%], and 65 of 3272
24 [2.0%] versus 63 of 3250 [1.9%] respectively). There were no clinically relevant differences in the
25 incidence of events of clinical interest, serious adverse events or adverse events (Table 3), although
26 bleeding events were more common with acarbose in participants whilst taking dual antiplatelet
27 therapy (Appendix Table S1). Gastrointestinal disorders were numerically more frequent in the
28 acarbose group compared with the placebo group for serious adverse events (92 of 3272 [2.8%]
29 versus 65 of 3250 [2.0%] respectively, P=0.057) and adverse events associated with drug

1 discontinuation or dose changes (252 of 3272 [7.7%] versus 179 of 3272 [5.5%] respectively,
2 P=0.19). Neither non-cardiovascular death rates (71 of 3272 [2.2%] versus 56 of 3250 [1.7%],
3 P=0.19) nor the incidence of cancer deaths (10 of 3272 [0.3%] versus 12 of 3250 [0.4%], P=0.08)
4 differed between groups.

5

6 **Discussion**

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

15 Acarbose was reported to reduce cardiovascular events in a secondary analysis of the STOP-
16 NIDDM trial,⁷ but with only 47 participants having the outcome in question this could be a chance
17 finding.¹⁹ The lack of any substantial benefit on cardiovascular events in ACE compared with STOP-
18 NIDDM might reflect the lower dose of acarbose used (50 versus 100 mg three times daily), the
19 younger population (54.5 versus 64.3 years), the different ethnic group, or the less-stringent
20 cardiovascular risk targets in the 1990s. Few large-scale studies have examined the impact of
21 antihyperglycaemic agents targeting postprandial glucose excursions, with none showing
22 cardiovascular benefit. The UK Prospective Diabetes Study randomised 1946 people with type 2
23 diabetes double-blind to the addition of acarbose 100 mg three times daily or placebo for three
24 years.²⁰ Those allocated to acarbose had lower mean HbA_{1c} values but no difference in “any
25 diabetes-related end point” (hazard ratio 1.00, 95% CI 0.81 to 1.23) or microvascular disease
26 (hazard ratio 0.91, 95% CI 0.61 to 1.35). The Assessment of an Alpha-Glucosidase Inhibitor to Block
27 Cardiac Events in Patients With Myocardial Infarction and IGT (ABC) study with voglibose was
28 terminated early as an interim analysis of the first 870 participants suggested a low probability of a
29 positive outcome.²¹ Nateglinide, a rapid-acting insulin secretagogue which reduces postprandial

1 hyperglycemia by increasing circulating insulin levels, was evaluated in the Nateglinide And
2 Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial.²² In 9309
3 patients at high cardiovascular disease risk and with impaired glucose tolerance followed for median
4 5·0 years, nateglinide 120 mg once daily showed no effect on the risk of cardiovascular events and
5 a 7% significant increased risk for new-onset diabetes.

6 Whilst no direct effect of acarbose was seen on cardiovascular outcomes in our trial, a possible
7 indirect effect should not be dismissed. Development of diabetes doubles the risk for major adverse
8 cardiovascular events²³ and it may be that in the longer term acarbose, by delaying or preventing
9 diabetes in a people with coronary heart disease, could reduce their cardiovascular risk. Such a link
10 was reported during the long-term passive follow-up of participants in the Da Qing diabetes
11 prevention trial where individuals allocated to lifestyle modification who developed diabetes at a
12 slower rate had a lower 23-year mortality rate than those allocated to the control group.²⁴

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

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

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

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

29

1 **Contributors:**

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

7
8 **Declarations of interests:**

9 **RRH** reports grants from Bayer AG, during the conduct of the study; personal fees from Amgen,
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22

23 **Research in Context:**

24 *Evidence before this study*

25 The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) demonstrated that
26 acarbose, an alphagucosidase inhibitor, decreased the incidence of diabetes in a population with
27 impaired glucose tolerance and at low cardiovascular risk. A pre-specified analysis of this study
28 suggested a decreased risk of a cardiovascular composite outcome, but only 47 participants in
29 total experienced such an event. A meta-analysis of seven short term trials showed that acarbose

1 reduced cardiovascular events by one third in patients with type 2 diabetes, although none were
2 specifically designed to test this hypothesis. A Japanese trial, the Assessment of an Alpha-
3 Glucosidase Inhibitor to Block Cardiac Events in Patients With Myocardial Infarction and IGT
4 (ABC), using another alphagucosidase inhibitor (voglibose) was discontinued for futility. The only
5 large-scale trial to date that has examined the cardiovascular impact of targeting postprandial
6 glucose excursions with an antihyperglycaemic agent in a population at high cardiovascular risk
7 and with impaired glucose tolerance was the Nateglinide And Valsartan in Impaired Glucose
8 Tolerance Outcomes Research (NAVIGATOR) trial. This showed no effect on the risk of
9 cardiovascular events and an increased risk for new-onset diabetes.

10 *Added value of this study*

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

15 *Implications of all the available evidence*

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

23

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- 17

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

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	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			
<i>Lipid-lowering therapy</i>			
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%)
<i>Antiplatelet therapy</i>			
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%)
<i>Other cardiovascular therapy</i>			
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/1.73m², doubling of baseline serum creatinine level, or halving of baseline eGFR

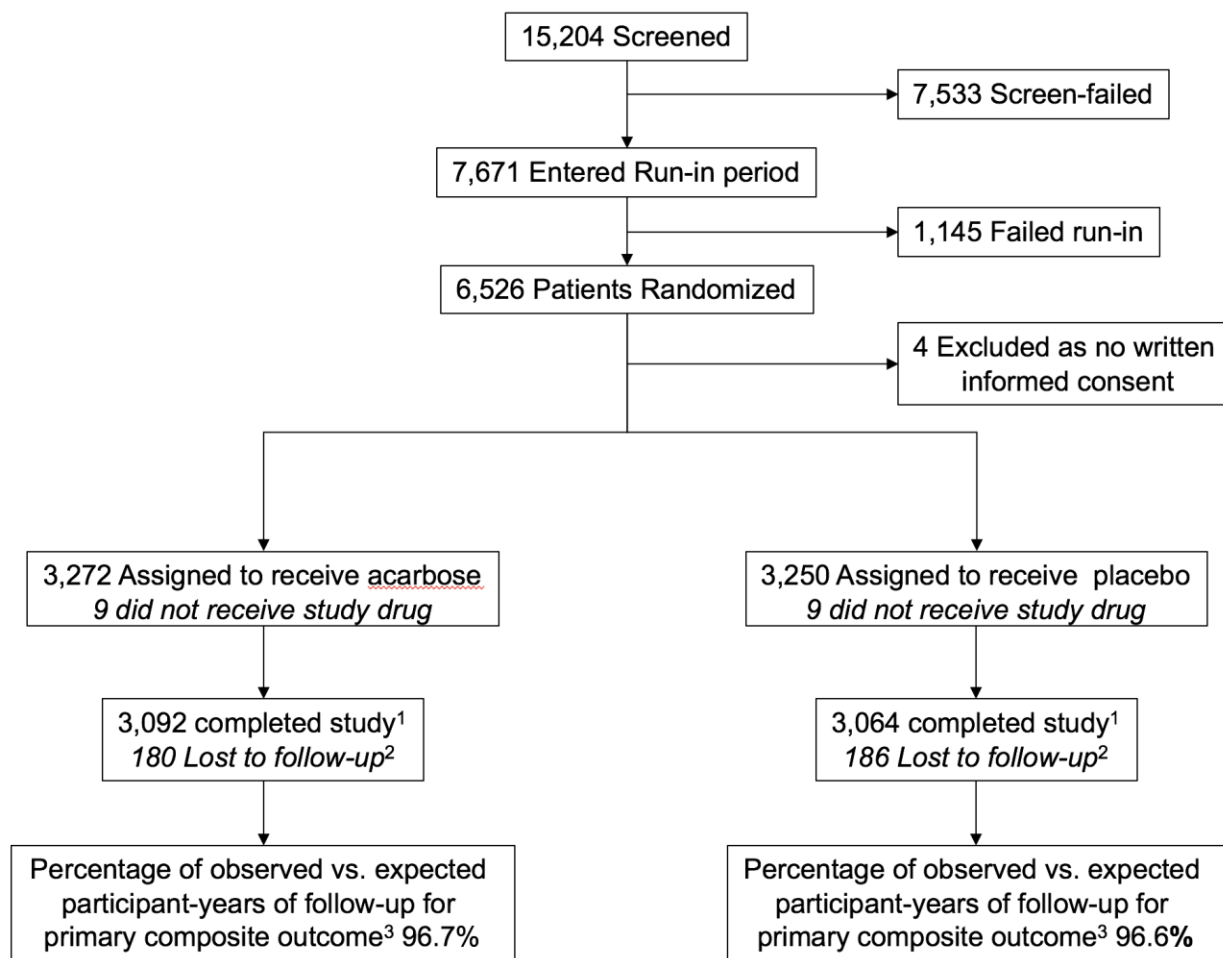
Table 3: Adverse Events Reported During the Trial According to System Organ Class

	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 $\geq 1\%$ of participants in either treatment group.

† Adverse events associated with drug discontinuation or dose changes were reported where they occur in $\geq 5\%$ 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:

