Impact of Acarbose on Incident Diabetes and Regression to Normoglycemia in People With Coronary Heart Disease and Impaired Glucose Tolerance: Insights From the ACE Trial

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https://doi.org/10.2337/dc19-2046

OBJECTIVE

We examined the impact of acarbose, an α-glucosidase inhibitor, on incident diabetes and regression to normoglycemia in 6,522 Acarbose Cardiovascular Evaluation trial participants in China who had impaired glucose tolerance (IGT) and coronary heart disease (CHD).

RESEARCH DESIGN AND METHODS

Participants were randomly assigned to acarbose or placebo and followed with four monthly fasting plasma glucose (FPG) tests and annual oral glucose tolerance tests. Incident diabetes was defined as two successive diagnostic FPG levels ≥7 mmol/L or 2-h plasma glucose (PG) levels ≥11.1 mmol/L while taking study medication or a masked adjudicated confirmation of this diagnosis. Regression to normoglycemia was defined as FPG <6.1 mmol/L and 2-h PG <7.8 mmol/L. Intention-to-treat and on-treatment analyses were conducted using Poisson regression models, overall and for subgroups (age, sex, coronary heart disease [CHD] type, HbA_{1c}, FPG, 2-h PG, BMI, estimated glomerular filtration rate, for IGT alone, IGT + impaired fasting glucose, and use of thiazides, ACE inhibitors [ACEis]/angiotensin receptor blockers [ARBs], β-blockers, calcium channel blockers, or statins).

RESULTS

Incident diabetes was less frequent with acarbose compared with placebo (3.2 and 3.8 per 100 person-years, respectively; rate ratio 0.82 [95% CI 0.71, 0.94]; $P = 0.005$), with no evidence of differential effects within the predefined subgroups after accounting for multiple testing. Regression to normoglycemia occurred more frequently in those randomized to acarbose compared with placebo (16.3 and 14.1 per 100 person-years, respectively; 1.16 [1.08, 1.25], $P < 0.0001$). This effect was greater in participants not taking an ACEi or ARB (1.36 [1.21, 1.53], $P_{interaction} = 0.0006$). The likelihood of remaining in normoglycemic regression did not differ between the acarbose and placebo groups ($P = 0.41$).

CONCLUSIONS

Acarbose reduced the incidence of diabetes and promoted regression to normoglycemia in Chinese people with IGT and CHD.

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Received 14 October 2019 and accepted 8 June 2020

Clinical trial reg. nos. ISRCTN91899513, www.isrctn.org, and NCT00829660, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.12466562.

Impaired glucose tolerance (IGT) is a risk factor for future diabetes (1). It is also a modifiable risk factor, and a large variety of interventions, including lifestyle changes and various glucose-lowering drugs, have been shown to reduce the incidence of diabetes in randomized controlled trials (1,2). Several of these interventions have also promoted regression from IGT to normoglycemia (1). None of these trials were done exclusively in people with proven heart disease.

IGT is also a risk factor for cardiovascular disease (3,4). Evidence that acarbose reduces the risk of diabetes in people with IGT (5), as well as several analyses suggesting that it is cardioprotective (6–9), provided the basis for the Acarbose Cardiovascular Evaluation (ACE) trial (10,11). The ACE trial, which was conducted entirely within China, randomized 6,522 people with established coronary heart disease (CHD) and IGT to the addition of either acarbose (50 mg) or matching placebo orally three times daily (10,11). Although no effect was seen on cardiovascular outcomes, this trial did report an 18% relative risk reduction in the incidence of diabetes, with a number needed to treat to prevent one case of diabetes over 5 years of 41.

The ACE trial is unique in that it is the only long-term trial to assess the effect of a drug on diabetes prevention in people with proven CHD. This feature, as well as the availability of periodic glucose values, regular glucose tolerance tests, and high use of cardioprotective therapies, provide an opportunity to further explore the effect of the acarbose intervention on both progression of IGT to diabetes and regression to normoglycemia and to determine whether the effect on progression or regression differs within subgroups.

RESEARCH DESIGN AND METHODS

The design, primary results, and baseline characteristics of ACE trial participants have been reported previously (10,11). Before randomization to acarbose or placebo, cardiovascular therapy was optimized, and appropriate advice for smoking, diet, and physical activity was provided. Participants were followed for a median of 5.0 years for the occurrence of cardiovascular outcomes, incident diabetes, and other outcomes. Medical care was provided by the participants' usual physicians. The ACE trial was approved by the relevant ethics committees, and all participants provided written informed consent.

Assessment of the Effect of Acarbose on Dysglycemia

Fasting plasma glucose (FPG) was measured at randomization and then four monthly thereafter. HbA_{1c} levels were measured and oral glucose tolerance tests (OGTTs) conducted annually. An additional OGTT was scheduled if any FPG was $\geq$7 mmol/L. Diabetes was diagnosed after two successive diagnostic plasma glucose (PG) levels (i.e., FPG $\geq$7.0 mmol/L or 2-h PG $\geq$11.1 mmol/L) were recorded during study visits or after a diagnosis made by a nonstudy physician was confirmed by masked adjudicators on the basis of available information. HbA_{1c} levels were not used to diagnose diabetes.

A participant was classified as having experienced regression to normoglycemia if at least one OGTT yielded an FPG $<$6.1 mmol/L and a 2-h PG $<$7.8 mmol/L. Regression using these World Health Organization (WHO) definitions of normoglycemia was also assessed using American Diabetes Association (ADA) definitions (i.e., an FPG $<$5.6 mmol/L and a 2-h PG $<$7.8 mmol/L) in a sensitivity analysis. If any subsequent FPG or 2-h PG value exceeded these thresholds, the regression was classified as transient, whereas if all subsequent glucose measurements remained below these thresholds, participants were classified as having experienced persistent regression to normoglycemia.

Subgroups

The effect of the double-blind acarbose intervention on incident diabetes and regression to normoglycemia was analyzed within predefined subgroups on the basis of sex, CHD inclusion criteria (myocardial infarction, unstable angina, or stable angina), median age ($\leq$63.5 or $>$63.5 years), HbA_{1c} ($\leq$5.9 or $>$5.9%), FPG ($\leq$5.47 or $>$5.47 mmol/L), 2-h PG ($\leq$9.12 or $>$9.12 mmol/L), BMI ($\leq$25 or $>$25 kg/m^2), estimated glomerular filtration rate ($\leq$88.5 or $>$88.5 mL/min/1.73 m^2), dysglycemic category (IGT only or IGT + impaired fasting glucose [IFG] [defined as an FPG 6.1–6.99 mmol/L]), and the use of thiazides, ACE inhibitors (ACEis) or angiotensin receptor blockers (ARBs), β-blockers, calcium channel blockers (CCBs), or statins at randomization.

Statistical Analysis

Continuous data were summarized as means and SDs or medians and interquartile ranges, and categorical data as numbers and percentages. The effect of acarbose on incident diabetes and on regression of IGT to normoglycemia was estimated using Poisson regression models. Possible differential effects within the 14 predefined subgroups for either progression from IGT to diabetes or remission from IGT to normoglycemia were assessed by including the subgroup and interaction term within the regression model. The main and subgroup analyses were conducted according to participants' assigned groups (i.e., intention to treat). A supplemental analysis of the effect of the intervention on incident diabetes and dysglycemia regression that was restricted to participants who remained on study drug during the trial (i.e., on-treatment analysis) was also conducted. All statistical analyses were performed using SAS 9.4 software.

RESULTS

As previously published, participants' mean age was 64 years, 27% were female, and 97% were of Han ethnicity, with balance across randomized groups (Table 1). There were 82% with IGT only (i.e., with a normal fasting glucose) and 18% with IGT + IFG. At baseline, the mean HbA_{1c} was 5.9%, FPG 5.5 mmol/L, 2-h PG 9.3 mmol/L, and BMI 25.4 kg/m^2. Overall, 93% of participants were taking a statin, 66% a β-blocker, and 59% either an ACEi or an ARB. Median follow-up for the primary outcome was 5 years, and median treatment duration was 3 years as a result of premature discontinuation of study drug. Study drug discontinuation or dose changes occurred more frequently with acarbose than with placebo (7% vs. 5%, respectively, $P = 0.0007$).

Incidence of Diabetes

A total of 5,063 of the 6,522 ACE trial participants (77.6%) were either diagnosed with diabetes during follow-up or had glucose testing within the 12-month period before their last follow-up time. Among those free of diabetes during

Table 1—Participant baseline characteristics

	Acarbose	Placebo	All
N	3,272	3,250	6,522
Age (years)*	64.4 (8.2)	64.3 (8.0)	64.3 (8.1)
Females*	877 (26.8)	885 (27.2)	1,762 (27.0)
Weight (kg)*	70.1 (10.7)	70.3 (11.0)	70.2 (10.8)
BMI (kg/m^2)*	25.3 (3.1)	25.5 (3.1)	25.4 (3.1)
Systolic BP (mmHg)*	130 (14.2)	129 (14.1)	130 (4.2)
Diastolic BP (mmHg)*	78 (9.2)	78 (9.2)	78 (9.2)
FPG (mmol/L)*	5.5 (0.86)	5.5 (0.78)	5.5 (0.82)
2-h PG (mmol/L)*	9.3 (1.1)	9.3 (1.1)	9.3 (1.1)
HbA_{1c}*			
%	5.9 (0.8)	5.9 (0.7)	5.9 (0.7)
mmol/mol	41 (8)	41 (7)	41 (7)
IGT only	2,697 (82.4)	2,663 (81.9)	5,360 (82.2)
IGT + IFG	571 (17.5)	586 (18.0)	1,157 (17.7)
Thiazide diuretic	98 (3.0)	92 (2.8)	190 (2.9)
ACEi or ARB*	1,930 (59.0)	1,909 (58.7)	3,839 (58.9)
β-Blocker*	2,141 (65.4)	2,160 (66.5)	4,301 (66.0)
CCB*	967 (29.6)	938 (28.9)	1,905 (29.2)
Statin*	3,038 (92.8)	3,028 (93.2)	6,066 (93.0)

Data are mean (SD) or *n* (%) unless otherwise indicated. IFG is FPG 6.1–6.99 mmol/L. BP, blood pressure. *Data have been reported previously (10).

follow-up, 2,119 of 2,836 participants (74.7%) who were randomly assigned to acarbose and 1,995 of 2,737 participants (72.8%) who were randomly assigned to placebo had glucose testing within that same 12-month period (Supplementary Table 1).

As shown in Table 2, participants assigned to acarbose had an 18% relative risk reduction in the incidence of diabetes (rate ratio [RR] 0.82 [95% CI 0.71, 0.94], $P = 0.005$), with a clear benefit noted at the time the first OGTT was conducted at 1 year after randomization (Fig. 1*A*). When the effect of acarbose was examined within the 14 prespecified subgroups (Fig. 2*A* and *B*), a similar, homogenous effect was noted within 12 ($P_{interaction} > 0.08$). At a nominal $P < 0.05$, there was the possibility of an interaction between acarbose and BMI ($P_{interaction} = 0.013$) and between acarbose and the baseline use of CCBs ($P_{interaction} = 0.03$). However, these analyses made no adjustment for multiple testing.

When the analysis of the effect of acarbose on incident diabetes was repeated with censoring at the last known time of drug use (i.e., on-treatment analysis) (Table 2 and Supplementary Fig. 1*A*), there was a 22% relative risk reduction in the incidence of diabetes (RR 0.78 [95% CI 0.68, 0.89], $P = 0.0003$). Baseline characteristics of participants in this on-treatment analysis did not differ by treatment group (Supplementary Table 2).

Incidence of Regression to Normoglycemia

As noted in Table 2, participants assigned to acarbose compared with placebo had a 16% higher relative rate of regression to normoglycemia on at least one occasion after randomization (RR 1.16 [95% CI 1.08, 1.25], $P < 0.0001$), with a clear effect noted at the time of the first OGTT that was conducted 1 year after randomization (Fig. 1*B*). There was no significant increase in the rate of persistent regression (1.05 [0.94, 1.17], $P = 0.41$). As shown in Fig. 2*A* and *B*, a similar, homogenous effect was noted within the 14 subgroups ($P_{interaction} \geq 0.09$), whereas there was a clearly significant interaction between acarbose and the use of renin-angiotensin system drugs ($P_{interaction} = 0.0006$). When the analysis of the effect of acarbose, compared with placebo, on regression to normoglycemia was repeated with censoring at the last known time of drug use (Table 2 and Supplementary Fig. 1*B*), there was a 14% higher relative rate

Table 2—Impact of acarbose on incident diabetes and regression to normoglycemia

	Acarbose		Placebo			
	n (%)	*n*/100 PY	*n* (%)	*n*/100 PY	RR (95% CI)	*P* value
Intention-to-treat analysis (acarbose *n* = 3,272, placebo *n* = 3,250)						
Incident diabetes	436 (13.3)	3.2	513 (15.8)	3.8	0.82 (0.71, 0.94)	0.005
Regression to normoglycemia (WHO)[a]						
Persistent regression[b]	625 (19.1)	5.1	587 (18.1)	4.8	1.05 (0.94, 1.17)	0.41
Transient regression[c]	1,481 (45.3)	16.3	1,317 (40.5)	14.1	1.16 (1.08, 1.25)	<0.0001
Regression to normoglycemia (ADA)[d]						
Persistent regression[b]	469 (14.3)	3.6	445 (13.7)	3.5	1.03 (0.90, 1.17)	0.70
Transient regression[c]	754 (23.0)	5.9	666 (20.5)	5.3	1.13 (1.02, 1.25)	0.023
On-treatment analysis (acarbose *n* = 3,254, placebo *n* = 3,236)						
Incident diabetes	436 (13.4)	4.5	513 (15.8)	5.5	0.78 (0.68, 0.89)	0.0003
Regression to normoglycemia (WHO)[a]	1,480 (45.5)	24.2	1,316 (40.7)	21.1	1.14 (1.06, 1.23)	<0.0001
Regression to normoglycemia (ADA)[d]	1,143 (35.1)	15.0	1,040 (32.1)	13.4	1.11 (1.02, 1.21)	0.013

PY, person-years. [a]WHO criteria (FPG <6.1 mmol/L and 2-h PG <7.8 mmol/L). [b]Remained normal glucose tolerant until study end. [c]Returned to IGT before study end. [d]ADA criteria (FPG <5.6 mmol/L and 2-h PG <7.8 mmol/L).

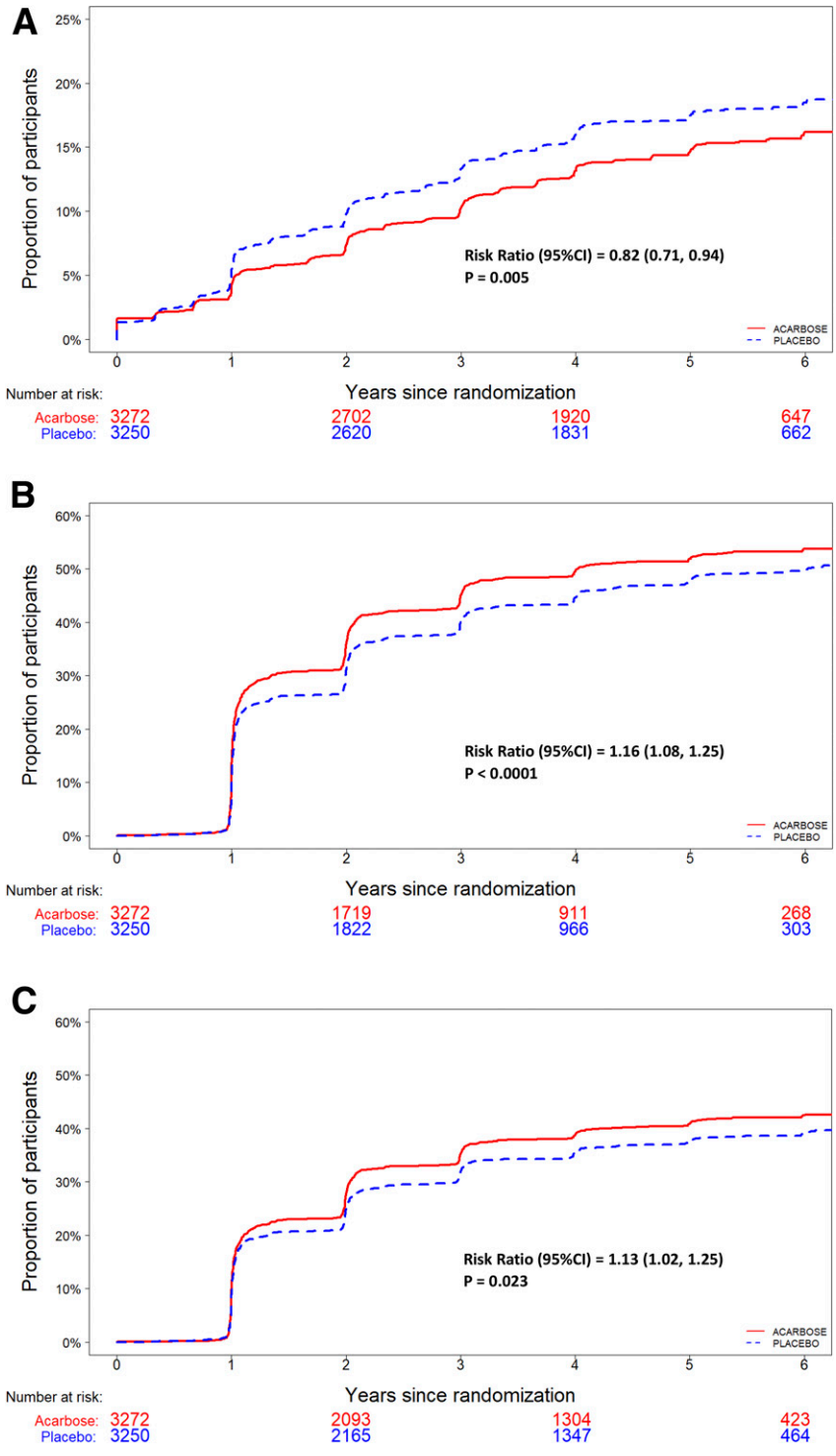


Figure 1—Kaplan-Meier plots of the time to incident diabetes (*A*) and first occurrence of regression to normoglycemia using WHO criteria (*B*) and ADA criteria (*C*). Glycemic status during follow-up was based on both the 4 monthly FPGs and the annual OGTTs.

of regression to normoglycemia (1.14 [1.06, 1.23], $P < 0.0001$). Similar findings were noted when the regression analyses were repeated using ADA definitions of normoglycemia (Table 2, Fig. 1*C*, and Supplementary Fig. 1*C*).

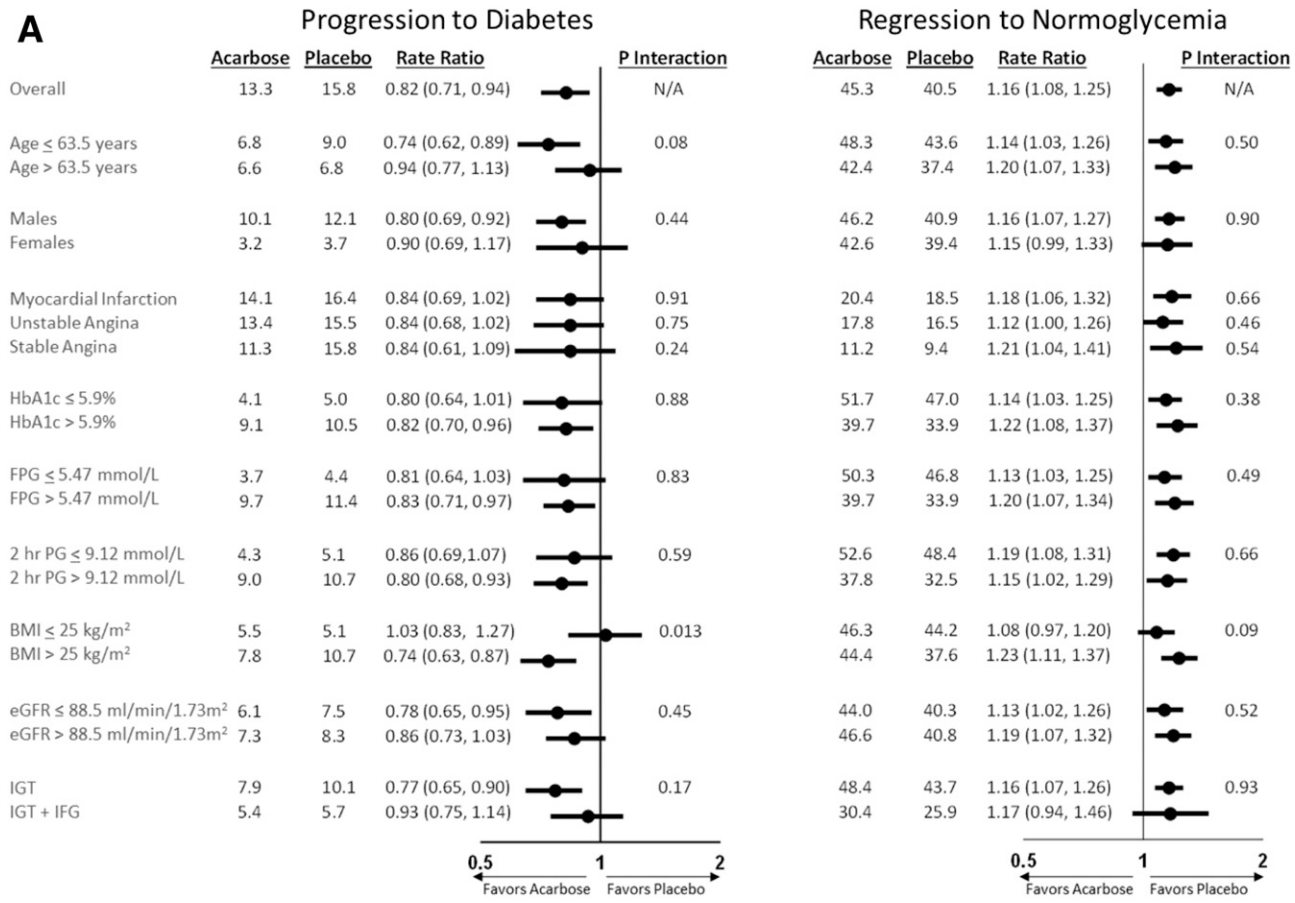
CONCLUSIONS

These analyses of data from the long-term, randomized, placebo-controlled ACE trial show that acarbose both reduces incident diabetes and promotes regression to normoglycemia in Chinese people with IGT and CHD. This effect is apparent within the first year of therapy and is unaffected by age, sex, degree of dysglycemia, and renal function. These findings also suggest that the effect may be greatest in heavier people who are not taking drugs that affect the renin-angiotensin system or CCBs. Notably, the consistent effects observed in the on-treatment analyses provide further support for the beneficial effect of acarbose on progression and regression of dysglycemia.

These findings add to previous diabetes prevention research. Both IGT (12) and cardiovascular disease (13,14) are well-established risk factors for diabetes. The observation that acarbose reduces incident diabetes in people with both of these risk factors adds acarbose to the list of other drugs that have been reported to reduce diabetes incidence in people with both IGT and a high risk for incident cardiovascular outcomes. These include insulin glargine (15) and valsartan (16). Notably, for these drugs, the relative reduction in diabetes was similar, ranging from 18 to 28%.

The observation that acarbose also promoted regression to normoglycemia is consistent with the known glucose-lowering effect of acarbose and the fact that the assessments were done while taking study medication. The absence of any persistent effect likely reflects progression of the underlying dysglycemic state with time, despite the use of acarbose. It is quite notable that acarbose had a highly significant different effect on regression to normoglycemia in people who were not taking an ACEi or ARB than those who were. This suggests that drugs that inhibit the renin-angiotensin system may modestly reduce the glucose-lowering effect of acarbose in people without diabetes.

Strengths of these analyses are the large sample size, the prospective conduct of regular OGTTs, the adjudication of all diabetes outcomes, the long-term duration of the trial, and the high follow-up rate. The absence of final glucose testing in 1,459 of 6,522 people (22.4%) within the year before being censored means that end-of-follow-up diabetes status is unknown. However, the finding of similar results with the intention-to-treat and on-treatment analyses, similar proportions of unascertained diabetes status in both treatment groups, and



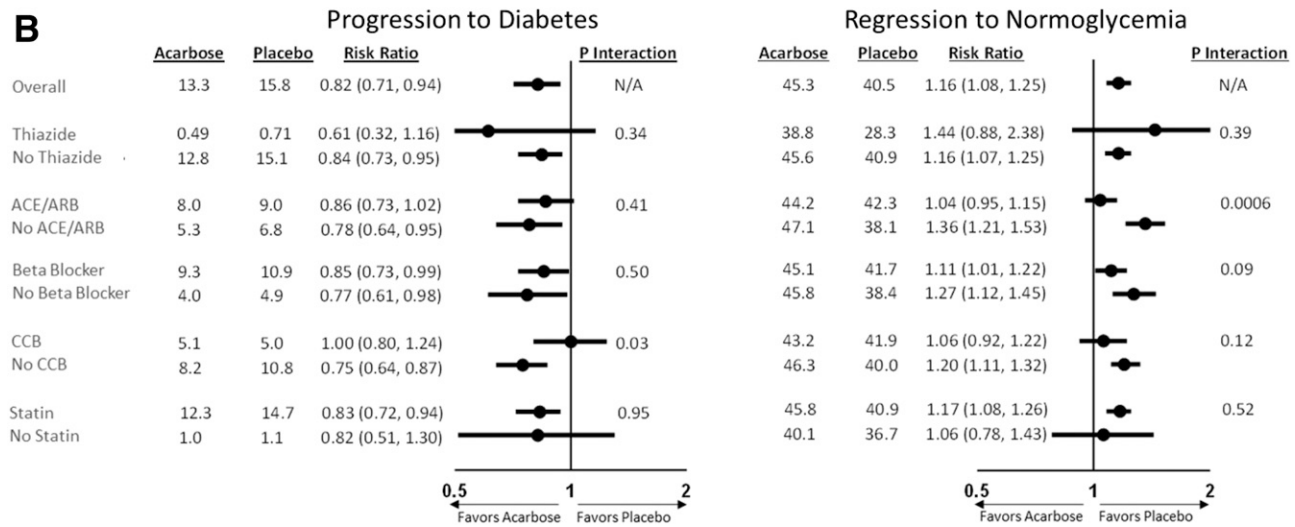


Figure 2—Impact of acarbose, compared with placebo, on incident diabetes and on regression to normoglycemia is shown for subgroups defined by clinical characteristics (*A*) and for use or nonuse of various drug classes (*B*). The numbers under acarbose and placebo denote the percentage of participants. eGFR, estimated glomerular filtration rate; N/A, not applicable.

similar effects on diabetes prevention in other acarbose trials (5) strongly support the observed findings.

In summary, acarbose slows progression of dysglycemia in Chinese people with IGT and CHD who are on statins and other therapies to prevent cardiovascular outcomes and should be included in the list of diabetes prevention therapies for similar patients. Although this improvement in glucose physiology did not reduce cardiovascular outcomes in ACE trial participants, its longer-term effect on other consequences of dysglycemia remain unknown.

Acknowledgments. The authors thank the patients, without whom this study and these analyses would not have been possible. R.R.H. is

an Emeritus National Institute for Health Research Senior Investigator.

Funding and Duality of Interest. The ACE trial was investigator sponsored and funded by Bayer AG. H.C.G. holds the McMaster-Sanofi Population Health Institute Chair in Diabetes Research and Care. He reports research grants from Eli Lilly, AstraZeneca, Merck, Novo Nordisk, and Sanofi; honoraria for speaking from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and Sanofi; and consulting fees from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, Janssen, Sanofi, Kowa, and Cirius. J.T. reports research grants from the European Commission, Bayer AG, Boehringer Ingelheim, and Merck and honoraria for lectures from Merck, MSD, and Novo Nordisk. He owns shares from Orion Pharma. L.R. reports research grants from the Swedish Heart Lung Foundation, Family Erling Perssons Foundation, and Stockholm County Council and honoraria for consultancies and lectures from Bayer AG, Boehringer Ingelheim, Eli Lilly, Merck, and Novo Nordisk. R.R.H. reports receiving grants from AstraZeneca, Bayer AG, and Merck Sharp & Dohme, and personal fees from Amgen, Bayer AG, Boehringer Ingelheim, Novo Nordisk, and SERVIER. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. H.C.G. designed the study and wrote the first draft of the manuscript. R.L.C. performed the statistical analyses and reviewed and edited the manuscript. C.A.B.S. performed the statistical analyses and reviewed and edited the manuscript. S.X. reviewed and edited the manuscript. J.T. contributed to study design and reviewed and edited the manuscript. L.R. contributed to the study design and editing of the manuscript. R.R.H. contributed to study design and data interpretation and reviewed and edited the manuscript. H.C.G. and R.R.H. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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