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Predicting Heart Failure Events in Patients with Coronary Heart Disease and Impaired Glucose Tolerance: Insights from the Acarbose Cardiovascular Evaluation (ACE) trial --Manuscript Draft--

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Corresponding Author:	Rury Holman Oxford, United Kingdom
First Author:	Malgorzata Wamil
Order of Authors:	Malgorzata Wamil John J. V. McMurray Charles A.B. Scott Ruth L. Coleman Yihong Sun Eberhard Standl Lars Rydén Rury R. Holman
Abstract:	<p>AIMS Heart failure is a fatal complication of type 2 diabetes but little is known about its incidence in people with impaired glucose tolerance (IGT). We used Acarbose Cardiovascular Evaluation (ACE) trial data to identify predictors of hospitalisation for heart failure (hHF) or cardiovascular (CV) death in patients with coronary heart disease (CHD) and IGT randomised to acarbose or placebo.</p> <p>METHODS Independent hHF/CV death risk factors were determined using Cox proportional hazards models, with participants censored at first hHF event, CV death, or end of follow-up.</p> <p>RESULTS During median 5-year follow-up, the composite outcome of hHF/CV death occurred in 393 (6.0%) participants. Significant hHF/CV death multivariate predictors were higher age and plasma creatinine, as and prior heart failure (HF), myocardial infarction (MI), atrial fibrillation (AF) and stroke. Acarbose, compared with placebo, did not reduce hHF/CV death (hazard ratio [HR] 0.89, 95% CI 0.64–1.24, P=0.48) or hHF (HR 0.90, 95% CI 0.74–1.10, P=0.32).</p> <p>CONCLUSIONS Patients with CHD and IGT at greater risk of hHF/CV death were older with higher plasma creatinine, prior HF, MI, AF or stroke. Addition of acarbose to optimised CV therapy to reduce post-prandial glucose excursions did not reduce the risk of hHF/CV death or hHF</p>
Suggested Reviewers:	<p>Bernard Zinman zinman@lunenfeld.ca Diabetologist with particular interest in acarbose</p> <p>Aldo Maggioni maggioni@anmco.it Cardiologist with particular interest in heart failure</p> <p>John Lachin jml@bsc.gwu.edu</p>

	Statistician with particular interests in impaired glucose tolerance and heart failure trials
Opposed Reviewers:	

3rd August 2020

Editor-in-Chief
Prof Antonio Ceriello

Dear Toni,

On behalf of my co-authors, I would be grateful if you would consider this secondary ACE trial manuscript entitled “Predicting Heart Failure Events in Patients with Coronary Heart Disease and Impaired Glucose Tolerance: Insights from the Acarbose Cardiovascular Evaluation (ACE) trial” for publication in *Diabetes Research and Clinical Practice*.

We used data from the 5-year Acarbose Cardiovascular Evaluation (ACE) trial of acarbose versus placebo, conducted in 6522 patients, to identify baseline variables that are predictive of first hospitalisation for heart failure or cardiovascular death in patients with coronary heart disease and impaired glucose tolerance.

We show that those at greater risk were older with higher plasma creatinine values, lower haemoglobin, prior heart failure, prior myocardial infarction and prior atrial fibrillation. In accord with the NAVIGATOR trial, our results also show that a therapy to lower post-prandial glucose excursions in patients with coronary heart disease and impaired glucose tolerance does not reduce their risk of hHF or hHF/CV death.

All authors have approved the submission of this version of the paper and take full responsibility for the manuscript. The paper is not under consideration elsewhere and will not be submitted to another journal while under consideration by *Diabetes Research and Clinical Practice*. Information regarding funding and potential conflicts of interest is reported in the paper.

We look forward to receiving your comments.



Prof. Rury R. Holman FRCP, FMedSci
ACE trial Chair, on behalf of the ACE Study Group

Predicting Heart Failure Events in Patients with Coronary Heart Disease and Impaired Glucose Tolerance: Insights from the Acarbose Cardiovascular Evaluation (ACE) trial- Wamil *et al.*

Highlights

1. Higher age and plasma creatinine, lower haemoglobin, and prior HF, MI and AF were all predictive of incident hHF
2. Higher age and creatinine values predicted case fatality
3. Allocation to acarbose in the ACE trial was not associated with risk reductions in incident hHF, recurrent hHF or hHF/CV death
4. Improved glycaemic control in patients with CHD and IGT does not reduce the risk of hHF/CV death
5. Our results emphasise the value of early screening for signs of HF in people with IGT

**Predicting Heart Failure Events in Patients with Coronary Heart Disease and Impaired
Glucose Tolerance: Insights from the Acarbose Cardiovascular Evaluation (ACE) trial**

Malgorzata Wamil,¹ John J. V. McMurray,² Charles A.B. Scott,¹ Ruth L. Coleman,¹ Yihong Sun,³
Eberhard Standl,⁴ Lars Rydén,⁵ Rury R. Holman¹

¹Diabetes Trials Unit, Radcliffe Department of Medicine, University of Oxford, Oxford, UK

²Institute of Cardiovascular & Medical Sciences, University of Glasgow, Glasgow, UK

³China-Japan Friendship Hospital, Beijing, China

⁴Diabetes Research Group eV at Munich Helmholtz Centre, Munich, Germany

⁵Department of Medicine K2, Karolinska Institute, Stockholm, Sweden

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Corresponding author

Rury R. Holman

Diabetes Trials Unit (OCDEM)

Churchill Hospital

Oxford OX3 7LJ UK

Email: rury.holman@dtu.ox.ac.uk

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24 **ABSTRACT**

25 **AIMS**

26 Heart failure is a fatal complication of type 2 diabetes but little is known about its incidence in
27 people with impaired glucose tolerance (IGT). We used Acarbose Cardiovascular Evaluation (ACE)
28 trial data to identify predictors of hospitalisation for heart failure (hHF) or cardiovascular (CV)
29 death in patients with coronary heart disease (CHD) and IGT randomised to acarbose or placebo.

30 **METHODS**

31 Independent hHF/CV death risk factors were determined using Cox proportional hazards models,
32 with participants censored at first hHF event, CV death, or end of follow-up.

33 **RESULTS**

34 During median 5-year follow-up, the composite outcome of hHF/CV death occurred in 393 (6.0%)
35 participants. Significant hHF/CV death multivariate predictors were higher age and plasma
36 creatinine, as and prior heart failure (HF), myocardial infarction (MI), atrial fibrillation (AF) and
37 stroke. Acarbose, compared with placebo, did not reduce hHF/CV death (hazard ratio [HR] 0.89,
38 95% CI 0.64–1.24, P=0.48) or hHF (HR 0.90, 95% CI 0.74–1.10, P=0.32).

39 **CONCLUSIONS**

40 Patients with CHD and IGT at greater risk of hHF/CV death were older with higher plasma
41 creatinine, prior HF, MI, AF or stroke. Addition of acarbose to optimised CV therapy to reduce
42 post-prandial glucose excursions did not reduce the risk of hHF/CV death or hHF.

43

44 **Clinical Trial Registration:** ClinicalTrials.gov, number NCT00829660, and the International
45 Standard Randomised Controlled Trial Number registry, number ISRCTN91899513.

46

47 **Keywords:** heart failure, coronary heart disease, impaired glucose tolerance (IGT), randomised
48 controlled trial, acarbose, diabetes

49

Introduction

It is well known that individuals with type 2 diabetes (T2D) have a higher incidence of heart failure than those without.(1) Less is known, however, about the relationship between impaired glucose tolerance (IGT) and heart failure incidence, and whether treating IGT to delay or prevent development of T2D might reduce the incidence of heart failure. China has one of the highest rates of IGT and new-onset T2D in the world.(2) In addition, the China Heart Survey showed that the prevalence of IGT is significantly higher in individuals with coronary heart disease (CHD), compared with those without CHD.(3) Thus, the combination of CHD and IGT potentially identifies individuals at a greatly increased risk of developing heart failure.

The Acarbose Cardiovascular Evaluation (ACE) trial was a randomised, double-blind, placebo-controlled, phase 4 cardiovascular outcome trial that randomised Chinese patients with CHD and IGT to acarbose or placebo designed primarily to assess whether acarbose could reduce the frequency of cardiovascular events and, secondarily, reduce the incidence of type 2 diabetes.(4-6) Acarbose is alpha-glucosidase inhibitor that reduces post-prandial hyperglycaemia by delaying carbohydrate digestion and absorption after meals.(7) In a meta-analysis of seven randomised controlled trials of acarbose, the incidence of heart failure was numerically but not significantly lower compared with placebo.(8)

Using ACE data, we aimed to identify independent baseline predictors for a composite endpoint of incident hospitalisation for heart failure (hHF), or incident hHF or cardiovascular (CV) death in this population, and to assess the impact of post-prandial glucose lowering with acarbose on this outcome, compared with placebo. We also investigated the cumulative risk of hHF, recurrent hHF (given the competing risk of death), and death following hHF, to determine the total burden of hHF in this population.

1. Methods

2.1 The ACE trial design

The design and results of the ACE trial have been published previously.(4, 6) In brief, it was a prospective, double blind, randomised, multi-centre, cardiovascular intervention trial that enrolled 6,522 patients aged 50 years or more with established CHD and IGT. CHD was defined as: acute myocardial infarction (MI), unstable angina (UA) or stable angina. IGT was diagnosed on a single 70g OGTT, defined as a 2-hour plasma glucose (2HPG) value ≥ 7.8 but < 11.1 mmol/l and a fasting plasma glucose (FPG) < 7.0 mmol/l within six months prior to enrolment. The primary ACE trial outcome was a five-point composite major adverse cardiovascular event (MACE5) outcome (defined as any of CV death, non-fatal MI, non-fatal stroke, hospitalisation for UA or hHF). Pre-specified secondary endpoints included a diagnosis of T2D, all-cause mortality and analysis of the individual MACE5 components.

2.2 Outcomes

The four pre-specified outcomes for this analysis were: i) Incident hHF; ii) A composite of hHF or CV death (to account for a portion of the competing risk of death); iii) Recurrent hHF; iv) Death following hHF. Incident hHF was defined by the ACE trial Cardiovascular Event Adjudication Committee (CVEAC) charter as an emergency/unplanned admission to the hospital setting that resulted in fulfilment of at least one of the following three criteria: i) Manifestation of new or worsening heart failure (HF); ii) New or additional therapy specifically for the treatment of HF; iii) That the CVEAC should be satisfied that HF was the primary reason for hospitalisation.

2.3 Statistical analysis

Continuous baseline variables were summarised using means and standard deviations, except where noted otherwise. Categorical variables were summarised as counts and percentages. We identified potential independent predictors using a Cox proportional hazards model by first testing pre-

100 specified variables for univariate associations with each of the four outcomes. Nominally
101 statistically significant variables ($P < 0.1$) were then tested in a multivariate model and required to
102 achieve $P < 0.05$ to be considered as independent predictors. Potential risk factors examined were:
103 age, sex, body mass index (BMI), race, waist circumference, smoking status, plasma creatinine,
104 systolic blood pressure (SBP), haemoglobin, FPG, 2-HPG, HbA_{1c}, allocation to acarbose or
105 placebo, and presence of prior CV events, atrial fibrillation (AF) or hypertension, as well as use of
106 statins, aspirin or anti-hypertensive medications. Recurrent hHF events were analysed using the
107 Andersen-Gill model, a generalisation of the Cox proportional hazards model.(9) This model is
108 appropriate as correlations among events for each individual are induced by measured covariates.
109 Thus, the dependence is captured by specifying time-dependent covariates such as number of
110 previous events. To identify predictors of death following hHF we used logistic regression analysis,
111 with $P < 0.1$ indicating a univariate association and $P < 0.05$ required for retention in a multivariable
112 model.

113

114 **2. Results**

115 **3.1 Patient Characteristics**

116 Mean (SD) age was 64.3 (8.1) years, BMI 25.4 (3.1) kg/m², median (IQR) eGFR 88.5
117 ml/min/1.73m² (74.8–103.3), and 73% of participants were male (**Table 1**). There were 243 (3.7%)
118 of ACE participants with a history of HF at baseline.

119

120 **3.2 Predictors of hHF**

121 During median 5.0 years follow-up, 138 (2.1%) participants experienced one or more hHF events
122 (0.46 first events *per* 100 person-years follow-up). Baseline characteristics for those who did, or did
123 not, experience hHF during the trial are listed in **Table 1**. Participants with, compared with those
124 without, incident hHF were older, had lower mean haemoglobin, higher mean plasma creatinine
125 values, and were more likely to have had a prior MI (54.4% *vs.* 41.3%, $p = 0.0021$), UA (26.8% *vs.*

126 42%, $p=0.0004$), HF (19.6% vs. 3.4%, $p<0.0001$) or AF (16.7% vs. 3.6%, $p<0.0001$). Participants
127 with incident hHF were also more likely at baseline to be taking ACE inhibitors/angiotensin
128 receptor blockers, diuretics, nitrates or digitalis.

129 Univariate associations of variables with hHF are listed in **Table 2**. Of these, only higher age,
130 higher plasma creatinine, lower haemoglobin, prior HF, prior MI and prior AF remained as
131 statistically significant independent risk factors in multivariate models (**Table 3**).

132

133 ***3.3 Predictors of hHF/CV death***

134 The composite hHF/CV death outcome occurred in 393 (6.0%) ACE participants during median 5.0
135 years follow-up, triggered by 138 hHF events and 255 CV deaths. Univariate hHF/CV death
136 predictors were: higher age, higher BMI, higher plasma creatinine, lower haemoglobin, prior HF,
137 prior MI, prior UA, prior AF, prior stroke/TIA and hypertension (**Table 2**). Of these, only age,
138 plasma creatinine, prior HF, prior MI, prior AF and prior stroke remained as statistically significant
139 independent risk factors in multivariate models (**Table 3**). Measures of glycemia (FPG, 2HPG,
140 HbA_{1c}), lipids, SBP, BMI and waist circumference were not associated independently with hHF/CV
141 death.

142

143 ***3.4 Recurrent hHF events***

144 A total of 232 hHF events occurred in 138 participants during the study, of whom 40 (29.0%)
145 experienced ≥ 2 events (94 recurrent events in total) with a median (IQR) of 3 (2–4) hHF events
146 during follow-up.

147

148 ***3.5 Mortality following incident hHF***

149 The proportion of participants who died following a first hHF event was similar in those with or
150 without prior HF (**Table 4**). A multivariate analysis of risk factors for case-fatality following a first
151 hHF event showed that significant predictors were higher age (Odds Ratio [OR] 1.08, 95% CI

(1.03–1.13), P=0.003) and higher plasma creatinine values (OR 1.02, 95% CI (1.00–1.03), P=0.040).

3.6 Effect of acarbose

Acarbose, compared with placebo, had no statistically significant effect on incident hHF (HR 0.89, 95% CI 0.64–1.24, P=0.48) or recurrent hHF (HR 1.19, 95% CI 0.92–1.55, P=0.19). Acarbose, compared with placebo, also had no effect on hHF/CV death (HR 0.90, 95% CI 0.74–1.10, P=0.32) (**Figure 1**) or death following hHF (OR 1.49, 95% CI 0.75–2.95, P=0.25).

3. Discussion

This is the first study describing incident hHF and associated mortality in a large Asian population with CHD and IGT. In Chinese patients with CHD and IGT, we show that higher age, higher plasma creatinine, lower haemoglobin, prior HF, prior MI and prior AF were all predictive of incident hHF, and that higher age, higher plasma creatinine, prior HF, prior MI, prior AF and prior stroke were predictive of hHF/CV death. Death following hHF was predicted by older age and higher plasma creatinine. Allocation to acarbose 50 mg TID, compared with placebo, in the ACE trial,(4, 6) showed no risk reductions for incident hHF, recurrent hHF or for hHF/CV death despite an 18% reduction in the risk of T2D.(5)

Our within trial observations are in accord with those seen in the NAVIGATOR trial, which also showed no reduction in hHF in patients with IGT and CHD despite the improved glycaemic control achieved with nateglinide, a short-acting insulin secretagogue.(10, 11) Lowering post-prandial glycemia has been suggested as a way to reduce HF risk,(12, 13) but neither increasing post-prandial insulin concentrations with nateglinide, nor using the insulin-sparing mode of action of acarbose to do so, reduced the risk of hHF in populations with IGT and CHD (**Figure 2**).

Similar findings have been reported consistently with other glucose-lowering therapies (DPP-4 inhibitors and insulin) in patients with established T2D (10, 14-16) suggesting that

therapeutic strategies focused on glycaemic control in T2D have a neutral effect on incident hHF or hHF-related death. Additionally, despite the reduced risk for new-onset diabetes seen with acarbose in the ACE trial, the within-trial risk of incident and recurrent hHF was unchanged. IGT is a precursor to T2D and has been shown to be a risk factor for cardiovascular morbidity. Thus, it is plausible that metabolic alterations leading to myocardial damage may start at an earlier stage, even before the formal diagnosis of T2D. In the ACE trial, 2.1% of participants experienced ≥ 1 episode of hHF, equating to 0.46 cases *per* 100 person-years of follow-up.(5) The hHF rate was similar in the NAVIGATOR trial (0.36 cases *per* 100 person-years of follow-up). For comparison, in the EXAMINE and the ELIXA trials, 3.6% and 8.3% of patients with acute coronary syndrome and established T2D experienced ≥ 1 episode of hHF respectively, equating to 1.09 and 1.94 cases *per* 100 person-years of follow-up.(17, 18) The higher hHF rates observed in T2D patients, compared with IGT subjects, likely reflects their more advanced CHD and myocardial damage, which could be secondary to longer duration of abnormal glycaemic exposure.

MI is a major predictor of HF, as confirmed in our study, but given no CV benefit was evident in the three ~5-year duration randomised controlled trials that have compared intensive with conventional glycaemic control in T2D patients (19-21), it may not be surprising that improving glycaemic control over a similar timescale in ACE subjects with CHF and IGT had little impact on incident hHF. In the longer term, the UKPDS has demonstrated a legacy effect of the benefits of earlier improved glycaemic control with sulfonylurea or insulin in people with newly-diagnosed T2D. The UKPDS showed a 15% lower risk of MI ($P = 0.01$) over a median follow-up of 16.8 years, but did not report HF rates. (22)

Considering the increasing burden of HF events observed in people with IGT or T2D, early screening for those factors contributing to an individual's heightened risk needs careful consideration. Several studies have shown that prior HF is a powerful independent predictor of readmission (23, 24). Our study is in accord with these observations, confirming that in a Chinese population with CHD and IGT a prior history of HF was the most significant predictor of hHF.

204 In our multivariable model, older age and increased plasma creatinine were also major predictors
205 for incident hHF and subsequent case fatality. Kidney dysfunction is common in elderly
206 populations and strongly associated with short-term and long-term outcomes in patients with HF
207 (25).

208 In the high-risk ACE trial population with CHD and IGT, previous MI but not angina was
209 independently associated with hHF. Of note, measures of glycaemic control, weight and blood
210 pressure showed no association with hHF. This may reflect the fact that ACE trial participants were
211 exceptionally well-managed with respect to administration of evidence-based secondary CV
212 prevention therapies, as there was a protocol-mandated 4-week CV risk factor optimisation run-in
213 period preceding randomisation.(4) Hence, additional HF risk factors such as age and plasma
214 creatinine may become more prominent with good control of traditional CV risk factors such as
215 hypertension, dyslipidaemia and smoking. However, an alternative interpretation of the ACE and
216 the NAVIGATOR trial findings might be that in populations with CHD and IGT already
217 established on maximum CV secondary prevention, those with kidney disease have a poorer
218 prognosis with a higher risk of hHF and CV death. In this context it is important to note novel
219 glucose-lowering treatments with SGLT-2 inhibitors with their promising beneficial renal profile
220 have been shown to be of particular value in reducing the risk of HF in people with or without T2D.
221 (26-30)

222 Of note, there were some differences between the major predictors for hHF reported by the
223 NAVIGATOR and the ACE trials. NAVIGATOR, which included 9,306 participants with IGT and
224 either CV disease or CV risk, confirmed waist circumference among three major predictors of hHF
225 (11). In the ACE trial by contrast, neither waist circumference nor BMI were independently
226 associated with an increased hHF rates, possibly due to phenotypic differences in those recruited.
227 Whilst NAVIGATOR recruited subjects with a mean BMI \geq 30 kg/m², the mean BMI of the ACE
228 Chinese participants was 25.4 kg/m². This could suggest that the mechanisms leading to the

229 development of HF in an Asian ‘lean’ cardiometabolic phenotype are distinct from those in Western
230 patients whose IGT is closely linked to obesity.

231 Epidemiological data strongly support the role of AF in the development of HF in people
232 with diabetes. The pathophysiology and risk factors for AF and HF are closely aligned, with
233 affected patients usually being elderly with multiple comorbidities (31, 32). In our study, we found
234 prior AF to be an independent predictor of incident hHF, as did NAVIGATOR. (11)

235 These analyses have several limitations. Firstly, of the entire spectrum of heart failure events
236 the ACE trial only examined hHF events. Restricting HF outcomes to hospitalised cases does not
237 reflect contemporary management of HF, with an on-going shift towards community and
238 ambulatory care. Secondly, left ventricular ejection fraction data was not collected so we do not
239 know whether participants with incident hHF had a reduced or preserved ejection fraction. While
240 T2D and IGT are associated with both types of HF, it is likely that adjudicated hHF events represent
241 ischaemic cardiomyopathy as the more predominant phenotype. Hence, more subtle changes
242 expected in HF with a preserved ejection fraction, which are frequently observed in the setting of
243 IGT and insulin resistance(33), have not been detected in this trial. Thirdly, any conclusions
244 regarding the predictive role of AF for HF in the ACE and NAVIGATOR populations need to
245 circumspect given the low number of hHF events recorded in both trials.

246 In conclusion, in Chinese patients with CHD and IGT established on optimal secondary CV
247 risk prevention, we identified higher age, increased plasma creatinine, lower haemoglobin, prior MI
248 and prior AF as independent predictors of hHF. Higher age and increased creatinine predicted case
249 fatality. Allocation to acarbose 50mg TID was not associated with reductions in hHF, hHF/CV
250 death, recurrent hHF or death following hHF. These findings will assist health care professionals to
251 risk stratify patients with CHD and IGT and help identify those that might benefit from early
252 screening for signs of HF. As this study focused on a Chinese population with a lower BMI
253 compared with similar Western cohorts studied to date, any extrapolation of our results should
254 consider the potential influence of phenotypic differences on HF risk.

255 **4. Abbreviations list:**

- 256 ACE: Acarbose Cardiovascular Evaluation (ACE)
- 257 AF: atrial fibrillation
- 258 CHD: coronary heart disease
- 259 CV death: cardiovascular death
- 260 IGT: impaired glucose tolerance
- 261 hHF: hospitalisation heart failure
- 262 HR: hazard ratio
- 263 MI: myocardial infarction
- 264 UA: unstable angina
- 265 TIA: transient ischaemic attack

266 **5. Ethics approval and consent to participate**

267 The UKPDS was performed according to the Helsinki guidelines. All patients gave written

268 informed consent to participate and the study protocol was approved by the ethics committees from

269 all 23 UKPDS clinical centres.

270

271 **6. Consent for publication**

272 Not applicable

273

274 **7. Availability of data and materials**

275 CABS, RLC and RRH had full access to the data.

276

277 **8. Competing interests**

278 The authors declare that they have no competing interests.

279

280 **9. Disclosures**

281 MW, CABS, RLC and YS report no disclosures.

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293

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295 **13. Authors' contributions**

296 MW analysed data and wrote the manuscript. CABS and RLC analysed the data and reviewed the
297 manuscript. JJM and RRH designed the study and reviewed the manuscript. ES, LR and YS
298 contributed to the discussion and reviewed the manuscript.

299

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301

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305

306

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16. Figure Legend

Figure 1: Kaplan-Meier plot of hospitalisation for heart failure (hHF)/CV death, split by participants allocated to acarbose or placebo.

Figure 2: Therapies that lower post-prandial glucose excursions examined in the ACE and NAVIGATOR trials had no impact on incident hospitalisation for heart failure (hHF) or hHF-related death.

421 **Table 1: Baseline characteristics of participants with or without incident hospitalisation for**
422 **heart failure (hHF) during the trial**

Variable	All participants (n=6522)	Incident hHF		P-value for those with vs. those without incident hHF
		Yes (n=138)	No (n=6384)	
Allocated to acarbose	3272 (50.2%)	65 (47.1%)	3207 (50.2%)	0.47
Age (years)	64.3 (8.1)	70.6 (8.8)	64.2 (8.0)	<.0001
Male	4760 (73.0%)	105 (76.1%)	4655 (72.9%)	0.41
BMI (kg/m ²)	25.4 (3.1)	25.2 (3.2)	25.4 (3.1)	0.45
Han ethnicity	6327 (97.0%)	135 (97.8%)	6192 (97.0%)	0.57
Current smoker	823 (12.6%)	17 (12.3%)	806 (12.6%)	0.55
SBP (mmHg)	130 (14.2)	128.6 (13.2)	129.5 (14.2)	0.41
HBA _{1c} (%)	5.9 (0.7)	5.9 (0.7)	5.9 (0.7)	0.91
HBA _{1c} (mmol/mol)	41 (8)	41 (8)	41 (8)	
FPG (mmol/L)	5.5 (0.8)	5.4 (0.7)	5.5 (0.7)	0.47
2HPG (mmol/L)	9.3 (1.1)	9.3 (0.9)	9.2 (1.0)	0.78
eGFR (mL/min/1.73 m ²)	88 (75, 103)	73 (59, 89)	89 (75, 103)	<.0001
Plasma creatinine (μmol/L)	78.9 (19.4)	93.0 (27.7)	78.6 (19.1)	<.0001
Haemoglobin (g/L)	141.5 (15.0)	134.5 (18.0)	141.6 (14.9)	<.0001
Waist circumference (cm)	91.2 (8.9)	91.0 (8.7)	91.2 (8.9)	0.76
Medical history				
Prior MI	2712 (41.6%)	75 (54.4%)	2637 (41.3%)	0.0021
Prior UA	2715 (41.7%)	37 (26.8%)	2678 (42.0%)	0.0004
Prior stable angina	1417 (21.7%)	38 (27.5%)	1379 (21.6%)	0.095
Prior AF	255 (3.9%)	23 (16.7%)	232 (3.6%)	<.0001
Prior stroke/TIA	428 (6.6%)	12 (8.7%)	416 (6.5%)	0.31
Prior hypertension	4274 (65.5%)	90 (65.2%)	4184 (65.5%)	0.058
Prior HF	243 (3.7%)	27 (19.6%)	216 (3.4%)	<.0001
Concomitant Medication				
Statins	6066 (93.2%)	128 (92.8%)	5938 (93.2%)	0.85
Aspirin	6126 (93.9%)	224 (93.0%)	5901 (94.1%)	0.50
Beta blockers	4301 (66.1%)	95 (68.8%)	4206 (66.0%)	0.49
Calcium channel blockers	1905 (29.3%)	39 (28.3%)	1866 (29.3%)	0.79
Thiazide diuretics	190 (2.9%)	10 (7.3%)	180 (2.8%)	0.0022
ACE inhibitors/ARB's	3839 (58.9%)	105 (58.5%)	3734 (76.1%)	<.0001
Non-thiazide diuretics	141 (2.2%)	18 (13.0%)	123 (1.9%)	<.0001
Digitalis	70 (1.1%)	11 (8.0%)	59 (0.9%)	<.0001
Antiarrhythmic	94 (1.4%)	4 (2.9%)	90 (1.4%)	0.15
Eplerenone	9 (0.1%)	1 (0.7%)	8 (0.1%)	0.061
Spironolactone	164 (2.5%)	18 (13.0%)	146 (2.3%)	<.0001
Renin Inhibitors	13 (0.2%)	1 (0.7%)	12 (0.2%)	0.16
Alpha blockers	53 (0.8%)	2 (1.5%)	51 (0.8%)	0.40
Clopidogrel	3983 (61.2%)	85 (61.6%)	3898 (61.2%)	0.92
Nitrates	2408 (37.0%)	63 (45.7%)	2345 (36.8%)	0.033
Nicotinic acid	22 (0.3%)	1 (0.7%)	21 (0.3%)	0.43

423 Data are N (%), Mean (SD) or Median (IQR); Abbreviations: ACE inhibitor- angiotensin converting enzyme, ARB-
424 angiotensin II receptor blocker, AF- atrial fibrillation, BMI- body mass index, eGFR-estimated glomerular filtration rate,
425 FPG- fasting plasma glucose, HBA_{1c} -haemoglobin A_{1c}, 2HPG- 2 hour plasma glucose, MI- myocardial infarction, SBP-
426 systolic blood pressure, TIA- transient ischaemic attack, UA- unstable angina
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428 **Table 2: Univariate analysis of risk factors for incident hospitalisation for heart failure (hHF)**
429 **or hHF/CV death. Statistically significant risk factors are highlighted in bold text.**

Variable	hHF 138 events			hHF/CV death 393 events		
	Hazard Ratio	95% Confidence Interval	P-value	Hazard Ratio	95% Confidence Interval	P-value
Acarbose (vs. placebo)	0.89	0.64–1.24	0.48	0.90	0.74–1.10	0.32
Age (years)	1.10	1.08–1.13	<0.0001	1.07	1.06–1.09	<0.0001
Sex: Female (vs. male)	0.86	0.58–1.27	0.44	0.71	0.56–0.91	0.0064
Ethnicity: Han (vs. not Han)	1.35	0.43–4.24	0.61	1.14	0.66–1.99	0.64
HBA _{1c} (%)	1.00	0.78–1.29	0.99	0.95	0.82–1.10	0.45
FPG (mmol/L)	0.92	0.74–1.15	0.45	0.92	0.81–1.05	0.20
2HPG (mmol/L)	1.03	0.89–1.20	0.70	1.00	0.91–1.09	0.91
BMI (kg/m ²)	0.98	0.92–1.03	0.36	0.96	0.92–0.99	0.0057
Waist Circumference (cm)	1.00	0.98–1.02	0.78	1.00	0.99–1.01	0.67
SBP (mmHg)	1.00	0.98–1.01	0.47	1.00	1.00–1.01	0.66
Plasma Creatinine (μmol/L)	1.03	1.02–1.03	<0.0001	1.02	1.02–1.03	<0.0001
Haemoglobin (g/dL)	0.97	0.96–0.98	<0.0001	0.99	0.98–0.99	0.0002
Smoking Status						
Ex vs. Never	0.82	0.58–1.17	0.28	1.15	0.93–1.43	0.20
Current vs. Never	0.88	0.51–1.50	0.64	1.20	0.87–1.63	0.26
Medical history						
Prior HF	6.57	4.31–10.01	<0.0001	3.81	2.82–5.15	<0.0001
Prior MI	1.64	1.17–2.30	0.0037	1.64	1.34–2.00	<0.0001
Prior UA	0.53	0.36–0.77	0.0009	0.64	0.52–0.80	<0.0001
Prior stable angina	1.30	0.90–1.89	0.17	0.97	0.76–1.23	0.80
Prior AF	4.92	3.14–7.70	<0.0001	2.63	1.88–3.68	<0.0001
Prior stroke/TIA	1.33	0.74–2.40	0.35	1.97	1.46–2.66	<0.0001
Prior hypertension	0.98	0.69–1.39	0.90	1.43	1.00–2.05	0.053

430 Abbreviations: AF- atrial fibrillation, BMI- body mass index, FPG- fasting plasma glucose, HBA_{1c}-haemoglobin A_{1c}, 2HPG-
431 2-hour plasma glucose, MI- myocardial infarction, SBP-systolic blood pressure, TIA- transient ischaemic attack, UA- unstable angina
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433 **Table 3: Significant risk factors in multivariate models for incident hospitalisation for heart**
 434 **failure (hHF) and for hHF/CV death**

	hHF 138 events			hHF/CV death 393 events		
Variable	Hazard Ratio	95% Confidence Interval	P value	Hazard Ratio	95% Confidence Interval	P value
Age (per 10 years)	1.89	1.52–1.36	<0.0001	1.81	1.59–2.04	<.0001
Plasma creatinine (per 10 µmol/L)	1.20	1.12–1.28	<0.0001	1.16	1.11–1.21	<.0001
Haemoglobin (g/dL)	0.98	0.97–0.99	0.0033
Prior HF	3.08	1.96–4.85	<0.0001	2.29	1.67–3.13	<.0001
Prior MI	1.74	1.24–2.44	0.0014	1.71	1.40–2.09	<.0001
Prior AF	2.53	1.58–4.04	0.0001	1.62	1.15–2.28	0.0059
Prior stroke/TIA	1.53	1.13–2.08	0.0041

435 Abbreviations: AF- atrial fibrillation, CV-cardiovascular, MI- myocardial infarction, TIA- transient ischaemic attack

436 **Table 4: Deaths following first hospitalisation for heart failure event, overall, and for those**
437 **with or without prior heart failure (HF)**

	CV Death		All-cause mortality	
	Deaths	Proportion	Deaths	Proportion
Overall (n=138)	53	38%	58	42%
Prior HF (n=27)	13	48%	14	52%
No prior HF (n=111)	40	36%	44	40%

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Figure 1

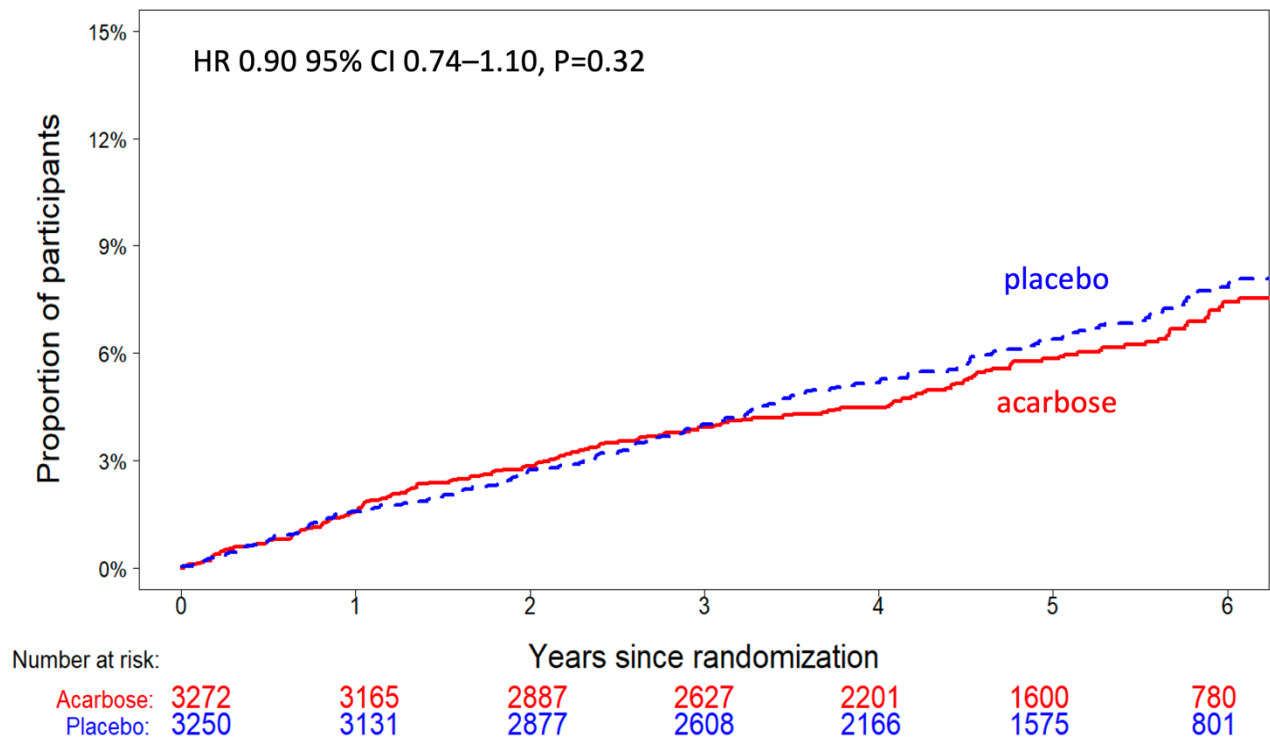


Figure 2

