

Homeostasis Model Assessment of Insulin Resistance and Survival in Patients with Diabetes and Acute Coronary Syndrome

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ABSTRACT

Purpose: Insulin resistance has been linked to development and progression of atherosclerosis and is present in most patients with type 2 diabetes (T2D). Whether the degree of insulin resistance predicts adverse outcomes in patients with T2D and acute coronary syndrome (ACS) is uncertain.

Methods: The AleCardio trial compared the peroxisome proliferator-activated receptor- α/γ agonist aleglitazar with placebo in patients with T2D and recent ACS. In participants not treated with insulin, we determined whether baseline homeostasis model assessment of insulin resistance (HOMA-IR, $n=4303$) or the change in HOMA-IR on assigned study treatment ($n=3568$) was related to the risk of death or major adverse cardiovascular events (MACE: cardiovascular death, myocardial infarction, and stroke) in unadjusted and adjusted models. Because an inverse association of HOMA-IR with N-terminal pro-B-type natriuretic peptide (NT-proBNP) has been described, we specifically examined effects of adjustment for the latter.

Results: In unadjusted analysis, two-fold higher baseline HOMA-IR was associated with lower risk of death (HR 0.79, 95% CI 0.68-0.91, $p=0.002$). Adjustment for 24 standard demographic and clinical variables had minimal effect on this association. However, after further adjustment for NT-proBNP, the association of HOMA-IR with death was no longer present (adjusted HR 0.99, 95% CI 0.83-1.19, $p=0.94$). Baseline HOMA-IR was not associated with MACE, nor was the change in HOMA-IR on study treatment associated with death or MACE.

Conclusions: After accounting for levels of NT-proBNP, insulin resistance assessed by HOMA-IR is not related to the risk of death or MACE in patients with T2D and ACS.

KEY WORDS

88 Type 2 diabetes, insulin resistance, coronary artery disease, acute coronary
89 syndrome

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91 **PRÉCIS**

92 This study demonstrates that the homeostasis model assessment of insulin resistance
93 is not related with adverse cardiovascular events in patients with type 2 diabetes and
94 acute coronary syndromes.

INTRODUCTION

Insulin resistance is present in most patients with type 2 diabetes and has been related to the development and accelerated progression of atherosclerosis, the vulnerability of coronary plaques to rupture and thrombosis,^{1, 2} and the risk of adverse outcomes after coronary revascularization.^{3, 4} Patients with acute coronary syndrome (ACS) and type 2 diabetes are at particularly high risk for recurrent ischemic events.⁵⁻⁷ It is unknown whether the degree of insulin resistance predicts subsequent risk among patients with type 2 diabetes and ACS.

The homeostasis model assessment of insulin resistance (HOMA-IR) is a simple, although imperfect index of insulin resistance that is derived from measurements of fasting plasma glucose and insulin.^{8, 9} Elevated HOMA-IR has been associated with an increased risk of cardiovascular events in non-diabetic patients, both in primary and secondary prevention.¹⁰⁻¹³ However, there is conflicting evidence for a relation of HOMA-IR to cardiovascular risk among patients with established type 2 diabetes. In the Verona Diabetes Complications Study and the Veterans Affairs High-Density Lipoprotein Intervention Trial, HOMA-IR was related to an increased risk of future cardiovascular events.^{11, 14} Conversely, an association between HOMA-IR and cardiovascular risk was not observed in the UK Prospective Diabetes Study.¹⁵

Complicating the interpretation of these data, other studies have found an inverse association of HOMA-IR with levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP),¹⁶⁻¹⁸ and a direct association of NT-proBNP with mortality and cardiovascular events.^{19, 20} Thus, NT-proBNP levels could confound an association of HOMA-IR with outcomes.

Agonists of peroxisome proliferator-activated receptor (PPAR)- γ increase insulin sensitivity and therefore lower HOMA-IR in patients with insulin resistance. The

AleCardio (Effect of Aloglitazar on Cardiovascular Outcomes after Acute Coronary Syndrome in Patients with Type 2 Diabetes Mellitus) trial compared aloglitazar, a dual agonist of PPAR- α and - γ , with placebo in patients with type 2 diabetes and recent ACS. Aloglitazar did not affect the risk of cardiovascular events.²¹

To gain insight into the relationship between insulin resistance and outcomes after ACS in patients with type 2 diabetes, we examined data from the Alecardio trial to determine associations of baseline HOMA-IR, or the change in HOMA-IR on assigned study treatment, with death and major adverse cardiovascular events. Because an inverse relationship of HOMA-IR with levels of natriuretic peptides has been described,¹⁶⁻¹⁸ we specifically examined whether associations of HOMA-IR with outcomes were influenced by levels of NT-proBNP.

MATERIALS AND METHODS

Study design

The current report is a post-analysis of the AleCardio trial (NCT01042769). The design and principal results of the trial have been described previously.^{21, 22} The protocol was approved by institutional review boards, written informed consent was obtained from all participants, and the study was conducted in full conformance with the principles of the Declaration of Helsinki and in accordance with local law and regulations.

AleCardio compared the efficacy and safety of aloglitazar (F. Hoffmann-La Roche Ltd, Basel, Switzerland) with placebo in patients with established or newly diagnosed type 2 diabetes and recent ACS including unstable angina, non-ST segment elevation myocardial infarction, and ST segment elevation myocardial infarction. A total of 7226 patients at 720 sites in 26 countries on 5 continents were

enrolled. Patients with symptomatic heart failure or hospitalization with a primary diagnosis of heart failure within the previous 12 months were excluded. Other exclusion criteria included severe peripheral edema, an estimated glomerular filtration rate [eGFR] less than 45 mL/min/1.73 m², or treatment with another PPAR agonist. Evidence-based use of cardiovascular medications and coronary revascularization procedures was recommended for all participants. Patients were randomly assigned in a double-blind fashion to receive aleglitazar (150 µg per day) or matching placebo in a 1:1 ratio. Randomization occurred during an interval beginning at hospital discharge and extending until 12 weeks after the index ACS event. Fasting glucose and insulin were measured in all participants at randomization (baseline values). However, the use of exogenous insulin influences the value of HOMA-IR. Therefore, the present analysis included 4303 participants (2159 patients in the Aleglitazar group and 2144 patients in the placebo group) with a baseline measurement of fasting insulin and glucose who were not treated with insulin at that time. Analysis of the change in HOMA-IR from baseline to 3 months later was performed in a subset of 3568 patients (1801 patients in the Aleglitazar group and 1767 patients in the placebo group) who had paired measurements of fasting insulin and glucose at both time points and were not treated with exogenous insulin between those times.

HOMA-IR models

At baseline and 3 months later, blood samples were collected after an overnight fast of at least 8 hours. The original HOMA1-IR was calculated as ⁸

$$HOMA1-IR = \frac{\text{fasting plasma glucose [mmol/L]} \cdot \text{fasting plasma insulin [\mu U/mL]}}{22.5}$$

The updated HOMA2-IR and HOMA2-B were also calculated using the online HOMA calculator version 2.2.3 for specific insulin available at <http://www.dtu.ox.ac.uk/homacalculator>.²³ The HOMA2-IR and HOMA2-B models include fasting glucose and insulin levels in a defined steady-state condition (fasting glucose: 3-25 mmol/L and fasting insulin: 20-300 pmol/L), patients with levels outside these limits were excluded (baseline HOMA2-IR and HOMA2-B: n=3999, 99.9%; change in HOMA2-IR and HOMA2-B from baseline to Month 3 n=3564, 99.9%).²³

Plasma glucose was measured with the Roche Cobas Analyzer and GLUC3 reagent kit (Roche Diagnostics, Indianapolis, IN, USA), with an intra-assay precision of 0.8%-1.1% coefficient of variation and an inter-assay precision of 1.1%-1.3% coefficient of variation. Insulin was measured by the immuno-enzymatic Access Ultrasensitive Insulin assay (Beckman Coulter Inc., Brea, CA, USA), with an intra-assay precision of 2.0%-4.2% coefficient of variation and an inter-assay precision of $\leq 7\%$ coefficient of variation.

Endpoints

We examined relationships of baseline HOMA1-IR with all-cause death, cardiovascular death (a secondary outcome measure in the parent trial), and major cardiovascular events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; the primary outcome measure in the parent trial). We also examined the relationship of the change in HOMA1-IR from baseline to 3 months to the risk of the outcome events after 3 months. Sensitivity analyses were performed using HOMA2-IR, excluding patients on sulfonylureas, and assessing aleglitazar and placebo groups separately.

Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation or median with interquartile range (IQR), as appropriate. HOMA-IR was described as a continuous variable and by quartiles. The distribution of HOMA-IR was skewed, and therefore $\log_2$ transformation was applied for further analysis. Differences among quartiles of HOMA-IR were compared with ANOVA or the Kruskal-Wallis test for continuous variables, and with chi-square test for categorical variables.

We used Cox proportional hazard regression models stratified by ACS index event (unstable angina, non-ST segment elevation myocardial infarction/ST segment elevation myocardial infarction) and presence/absence of reperfusion therapy to evaluate the association of each doubling in HOMA-IR with the endpoints.

Unadjusted and two adjusted models were examined. Model 1 was adjusted for the following pre-defined variables: age, sex, race, body mass index, smoking, hypertension, prior coronary artery disease, prior congestive heart failure, duration of diabetes prior to randomization, time from ACS index event to randomization, glycated haemoglobin, $\log_2$ high-sensitivity C-reactive protein (hs-CRP), $\log_2$ eGFR using the Modification of Diet in Renal Disease (MDRD) equation, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, $\log_2$ triglycerides, and treatment with biguanides, sulfonylureas, incretins, statins, beta blockers, renin angiotensin blockers, calcium channel blockers, and either aleglitazar or placebo. Model 2 was adjusted for all of the above variables plus $\log_2$ NT-proBNP. Cox proportional hazards regression test of interaction (HOMA-IR by treatment assignment) was used to assess whether there was a differential effect of HOMA-IR by treatment assignment on the endpoints. In the same fashion, we used the Cox model to evaluate the association of the change in HOMA-IR from baseline to Month

221 3 (difference between $\log_2$ transformed baseline and $\log_2$ transformed Month 3
222 values) with each of the same endpoints occurring after 3 months.

223 All testing was two-sided and conducted at the 0.05 significance level. All
224 statistical analyses were performed using SAS (SAS Institute, Cary, NC, USA),
225 version 9.4.

226

RESULTS

Baseline characteristics

At baseline, HOMA1-IR was 2.8 [1.7, 4.5] (median [IQR]). Patient characteristics by quartile of HOMA1-IR are shown in **Table 1**. Compared with patients in the lower quartiles of HOMA1-IR, patients in the higher quartiles were younger, more likely to be white, and less likely to be Asian. They also had a shorter antecedent duration of diabetes, were more likely to have a history of hypertension, dyslipidemia, prior myocardial infarction or coronary revascularization, and were less likely to have presented with ST segment elevation myocardial infarction as the index ACS event.

Across quartiles of HOMA1-IR, most patients were treated with aspirin, other anti-platelet agents, statins, and biguanides. Patients in the higher quartiles of HOMA1-IR were somewhat more likely to be treated with renin-angiotensin system inhibitors, beta blockers, and diuretics. Very few patients in AleCardio were treated with glucagon-like peptide-1 (GLP-1) agonists or dipeptidyl peptidase-4 (DPP-4) antagonists and none were treated with sodium-glucose cotransporter 2 (SGLT2) antagonists.

As expected, patients in higher HOMA1-IR quartiles were characterized by higher levels of glucose, insulin, glycated hemoglobin, and triglycerides, and lower levels of high-density lipoprotein cholesterol. Progressive quartiles of HOMA1-IR were also associated with higher levels of hemoglobin and hs-CRP, but with lower levels of NT-proBNP.

In the placebo group, HOMA1-IR increased slightly from baseline to Month 3 by 0.13 [-0.77, 1.14] (median [IQR]; $p < 0.001$ versus baseline). In contrast, aleglitazar demonstrated the expected effects of a PPAR- γ activator by reducing HOMA1-IR during this period, by -0.94 [-2.14, -0.16] ($p < 0.001$ versus baseline, **Table 2**).

Associations of HOMA-IR with endpoints

Table 3 shows the unadjusted and adjusted risk of adverse events at the median [IQR] follow-up of 106 [82, 129] weeks. All-cause death occurred in 152 patients (3.5%). Kaplan-Meier estimates of survival by quartile of baseline HOMA1-IR are shown in **Figure 1**. In unadjusted analysis, a two-fold higher baseline level of HOMA1-IR was associated with a lower risk of all-cause death (HR 0.79, 95% CI 0.68-0.91, $p=0.002$). The inverse relation of baseline HOMA1-IR with death was due to an inverse association with $\log_2$ insulin with death (HR 0.74, 95% CI 0.62-0.87, $p=0.0004$), without an association of $\log_2$ glucose with death (HR 0.98, 95% CI 0.68-1.40, $p=0.90$). Adjustment for the variables in Model 1 had a minor effect on the association of HOMA1-IR with all-cause death (adjusted HR 0.82, 95% CI 0.69-0.98, $p=0.03$). However, additional adjustment for NT-proBNP in Model 2 neutralized the association of HOMA1-IR with all-cause death (adjusted HR 0.99, 95% CI 0.83-1.19, $p=0.94$).

Cardiovascular death occurred in 110 patients (2.6%). A two-fold higher baseline level of HOMA1-IR was associated with a lower risk of cardiovascular death in unadjusted analysis (HR 0.82, 95% CI 0.68-0.97, $p=0.02$). The relation of baseline HOMA1-IR with cardiovascular death was also driven by an inverse association with $\log_2$ insulin (HR 0.75, 95% CI 0.62-0.92, $p<0.001$) without association with $\log_2$ glucose (HR 1.09, 95% CI 0.72-1.65 $p=0.69$). The association of HOMA1-IR with cardiovascular death was attenuated after adjustment for the variables in Model 1 (adjusted HR 0.83, 95% CI 0.68-1.02, $p=0.07$) and neutralized after additional adjustment for NT-proBNP in Model 2 (adjusted HR 1.05, 95% CI 0.85-1.29, $p=0.66$). There was no interaction of baseline HOMA1-IR and treatment assignment on all-cause death ($p_{\text{int}}=0.54$) or cardiovascular death ($p_{\text{int}}=0.45$).

Major cardiovascular events occurred in 365 patients (8.5%). A two-fold higher level of baseline HOMA1-IR was not associated with major cardiovascular events, either in unadjusted analysis (HR 0.95, 95% CI 0.86-1.04, $p=0.26$), or in analyses adjusted for the variables in Model 1 (adjusted HR 0.94, 95% CI 0.84-1.05, $p=0.29$) and Model 2 (adjusted HR 1.03, 95% CI 0.92-1.15, $p=0.59$). There was no interaction of baseline HOMA1-IR and treatment assignment on major cardiovascular events ($p_{\text{int}}=0.67$).

Hospitalization for heart failure occurred in 109 patients (2.5%). A two-fold higher level of baseline HOMA1-IR was associated with a lower risk of hospitalization for heart failure in unadjusted analysis (HR 0.76, 95% CI 0.63-0.90, $p=0.002$) and when adjusted for the variables in Model 1 (adjusted HR 0.72, 95% CI 0.59-0.89, $p=0.002$). Additional adjustment for NT-proBNP in Model 2 neutralized the association of HOMA1-IR with hospitalization for heart failure (adjusted HR 0.93, 95% CI 0.75-1.15, $p=0.49$).

Hypoglycemia and serious hypoglycemia occurred in 425 (9.9%) and 26 (0.6%) patients. Hypoglycemia did not differ among HOMA1-IR quartiles (Q1: 97 [9.0%] patients, Q2: 105 [9.8%] patients, Q3: 107 [9.9%] patients, and Q4: 116 [10.8%] patients, $p=0.58$). Similar results were observed for serious hypoglycemia (Q1: 8 [0.7%] patients, Q2: 8 [0.7%] patients, Q3: 5 [0.5%] patients, and Q4: 5 [0.5%] patients, $p=0.71$).

Changes in HOMA1-IR from baseline to Month 3 were not related to outcomes (**Table 3**). There was no interaction of treatment assignment and the change in HOMA1-IR from baseline to Month 3 on the risk of any of the clinical outcomes.

In a sensitivity analysis, associations between HOMA2-IR and outcomes were analyzed. The results were similar to those obtained with HOMA1-IR. In unadjusted

analysis, HOMA2-IR was significantly related with all-cause and cardiovascular death; however, relations were attenuated after adjustment for the variables in Model 1 and neutralized after adjustment for the variables in Model 2 (**Table 3**). In unadjusted analysis, HOMA2-B was significantly associated with all-cause death, with trends observed for cardiovascular death. Associations with all-cause death were mitigated after multivariable adjustment (**Table 3**). Findings were further confirmed in a sensitivity analysis that excluded patients treated with sulfonylureas at baseline (**Supplementary Table 1**). When analyzing the placebo and aleglitazar groups separately, neither HOMA1-IR nor HOMA2-IR was related with endpoints in adjusted analysis (**Supplementary Table 2**).

Associations of NT-proBNP with endpoints

In unadjusted analysis, a two-fold higher baseline level of NT-proBNP was significantly associated with a higher risk of all-cause death (HR 1.65, 95% CI 1.51-1.81, $p<0.001$), cardiovascular death (HR 1.76, 95% CI 1.58-1.95, $p<0.001$), nonfatal myocardial infarction (HR 1.17, 95% CI 1.09-1.26, $p<0.001$), nonfatal stroke (1.24, 95% CI 1.06-1.46, $p=0.008$), and major cardiovascular events (HR 1.31, 95% CI 1.24-1.39, $p<0.001$). All associations remained significant after multivariable adjustments. Changes in NT-proBNP from baseline to Month 3 were independently related to all-cause death, cardiovascular death, and major adverse cardiovascular events (**Table 4**).

DISCUSSION

This study shows that the degree of insulin resistance, as reflected by HOMA-IR, does not independently determine the prognosis of patients with type 2 diabetes and ACS who are not treated with exogenous insulin. Neither the baseline level of HOMA-IR, nor the change in HOMA-IR from baseline to Month 3 under treatment with aleglitazar or placebo, was related to clinical outcomes in fully adjusted models.

HOMA-IR has been established as an easily measurable surrogate marker of insulin resistance. Although the glucose clamp technique or the IV glucose tolerance test represent gold standard measures of insulin sensitivity, measurements of fasting glucose and insulin levels may be particularly useful in broad clinical applications.^{8, 9,}
²⁴ Moreover, HOMA-IR has been recognized as an independent predictor for the development of type 2 diabetes, for the progression of the metabolic syndrome,^{25, 26} and for the risk of cardiovascular events among patients with pre-diabetes.¹⁰⁻¹³ In that context, HOMA-IR has been shown to have incremental predictive value above glucose or insulin measurements alone.^{14, 27}

However, the literature provides no consensus on whether the degree of insulin resistance predicts cardiovascular events among patients with established type 2 diabetes, with or without established cardiovascular disease,^{11, 14, 15} and there has been no prior data on this question regarding patients with type 2 diabetes and ACS. The present analysis indicates no direct association of insulin resistance with prognosis in such patients. Moreover, the findings were consistent in the placebo and the aleglitazar group of the trial, and there was no significant interaction of treatment assignment and baseline HOMA-IR on outcomes.

Similarly, the change in HOMA-IR from baseline to Month 3 had no association with subsequent outcomes. On average, HOMA-IR increased slightly in the placebo

group and declined substantially in the aleglitazar group, with a large range of response in each group. Association of change in HOMA-IR with outcomes was absent in both groups. This may explain, at least in part, the failure of aleglitazar to reduce cardiovascular events in diabetic patients with established cardiovascular disease despite a substantial reduction in HOMA-IR.^{21, 28}

The immediate period following ACS may be characterized by stress hyperglycemia that can transiently perturb measurements of glucose and HOMA-IR without reflecting the steady-state level of insulin resistance. Stress hyperglycemia ordinarily resolves within 3-4 days following ACS.²⁹⁻³¹ In the AleCardio trial, patients were randomized no sooner than hospital discharge and as late as 12 weeks following ACS. We found no association of baseline HOMA-IR with the time from ACS to randomization; therefore, the baseline measurement of HOMA-IR in the present analysis is presumed to reflect a stable glucometabolic state.

Surprisingly, our unadjusted analysis showed that HOMA-IR was inversely related to all-cause mortality, cardiovascular mortality, and hospitalization for heart failure at a median follow-up of 2.0 years. Adjustment for 24 baseline variables had only a minor effect on this association. However, after additional adjustment for NT-proBNP all association of HOMA-IR with death, cardiovascular death, or hospitalization for heart failure was nullified. We explored the potential reasons why adjustment for NT-proBNP influenced the relationship of HOMA-IR with these outcomes.

An inverse relation between HOMA-IR and levels of natriuretic peptides has been observed previously in patients with diabetes and heart failure,^{16, 17} in Framingham Offspring study participants without overt heart failure,³² in elderly adults,¹⁸ and in subjects free of cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis.³³

Similarly, we found that increasing quartiles of HOMA-IR were associated with decreasing levels of NT-proBNP. This inverse relationship is based upon an interplay between adipose tissue and natriuretic peptides. Natriuretic peptides promote lipolysis, leading to decreased body weight and consecutively decreased insulin resistance.^{17, 34, 35} Thus, patients with lower HOMA-IR may have been more likely to have mild or subclinical heart failure, reflected by higher levels of NT-proBNP and accompanied by an increased risk of death or hospitalization due to heart failure. Moreover, patients in the lowest quartile of HOMA-IR had the longest duration of diabetes and the lowest percentage of newly diagnosed diabetes. Long-standing diabetes is more likely to lead to beta cell failure and lower fasting insulin levels, finally resulting in lower HOMA-IR. At the same time, long-standing diabetes is more likely to be accompanied by subclinical heart failure, reflected by higher levels of NT-proBNP, associated with higher morbidity and mortality.³⁶

Conversely, adipose tissue promotes catabolism of natriuretic peptides.^{37, 38} Across increasing quartiles of HOMA-IR we observed a progressive increase in body mass index and thus adipose tissue mass, decreasing levels of NT-proBNP, but an increasing prevalence of traditional coronary risk factors such as hypertension and dyslipidemia, and of prior myocardial infarction or coronary revascularization. Thus, patients with higher HOMA-IR may have had increased atherosclerotic risk despite lower levels of NT-proBNP. In aggregate, these mechanisms may explain the inverse relationship of HOMA-IR and NT-proBNP, and the overall neutral relationship of HOMA-IR to mortality and heart failure hospitalization after accounting for levels of NT-proBNP.

We found no association of HOMA-IR with the risk of non-fatal ischemic cardiovascular events. Despite a relatively large number of non-fatal myocardial

infarctions (n=232), there was no association of HOMA-IR with these events in either unadjusted or adjusted analysis. This suggests that once patients have established type 2 diabetes and coronary heart disease, the degree of insulin resistance may not determine the risk of future myocardial infarction. Inferences regarding non-fatal stroke are more difficult to draw because of the smaller number of events (n=48).

Strengths of the current analysis include the use of a large, global dataset; high utilization of contemporary, evidence-based pharmacologic and procedural treatments for ACS; and a broad range of baseline HOMA-IR values and the change in HOMA-IR with treatment, allowing robust analyses of the relationships of baseline and on-treatment HOMA-IR with outcomes. In addition, principal findings were confirmed in sensitivity analyses using HOMA2-IR, excluding patients on sulfonylureas, and investigating treatment groups separately.

Several limitations also warrant consideration. First, this study is a post-hoc analysis of the AleCardio trial with the limitations inherent to such a design. Second, AleCardio was not conceived as a heart failure trial, and measures of left ventricular ejection fraction were not available systematically in this patient cohort. Third, fasting insulin incorporated into the HOMA-IR model not only reflects insulin resistance, but also insulin secretion and clearance, and as a proxy for fasting insulin, HOMA-IR cannot distinguish between insulin resistance and circulating insulin itself. Fourth, the predictive value of the HOMA-IR was investigated in diabetic patients not treated with insulin, as exogenous insulin would have influenced the value of HOMA-IR. Therefore, the present findings may not apply to patients treated with insulin. Further, in comparison to some other studies,¹⁴ HOMA-IR in the present cohort is lower; the differences may be due to a shorter duration of diabetes among patients in AleCardio and the inclusion of patients with newly diagnosed diabetes at the time of ACS. In

addition, although we employed a comprehensive group of adjustment variables, we cannot exclude the possibility of residual confounding by factors not incorporated into the multivariate models.

In conclusion, insulin resistance as estimated by the HOMA-IR is not an independent predictor of mortality and cardiovascular events in patients with type 2 diabetes and recent ACS. Our study adds to the literature that measurements of glucose and insulin, tests that are available in nearly all laboratories, are not independent predictors of prognosis in these patients, and that the change in HOMA-IR under treatment is not related to outcomes. Peroxisome proliferator-activated receptor agonists exert a multitude of effects, among which insulin sensitization is only one. Nonetheless, the findings of the current analysis and other investigations ²¹, ²⁸ raise some doubt whether insulin resistance or hyperinsulinemia will prove to be a valid target of therapy in patients with established type 2 diabetes and coronary heart disease.

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Table 1. Baseline clinical and laboratory characteristics according to HOMA-IR quartiles.

Variable	All n=4303	HOMA-IR Quartile 1 <1.69 n=1077	HOMA-IR Quartile 2 1.69 – 2.77 n=1075	HOMA-IR Quartile 3 2.77 – 4.46 n=1076	HOMA-IR Quartile 4 ≥4.46 n=1075	P-value
Demographics						
Age, years	60.9±10.0	62.5±10.1	61.2±10.0	60.8±9.9	59.1±9.7	<0.001
Gender, female	1080 (25.1)	242 (22.5)	266 (24.7)	275 (25.6)	297 (27.6)	0.05
Race						<0.001
White	2831 (65.8)	580 (53.9)	674 (62.8)	781 (72.6)	796 (74.1)	
Asian	1179 (27.4)	429 (39.8)	330 (30.7)	223 (20.7)	197 (18.3)	
Black	118 (2.7)	25 (2.3)	28 (2.6)	27 (2.5)	38 (3.5)	
Other	174 (4.0)	43 (4.0)	42 (3.9)	45 (4.2)	44 (4.1)	
Geographic region						<0.001
Europe	1370 (31.9)	283 (26.3)	320 (29.8)	368 (34.2)	399 (37.2)	
North America	1226 (28.5)	235 (21.8)	283 (26.4)	344 (32.0)	364 (33.9)	
Asia/Pacific	1217 (28.3)	433 (40.2)	334 (31.1)	239 (22.2)	211 (19.7)	
Latin America	485 (11.3)	125 (11.6)	137 (12.8)	124 (11.5)	99 (9.2)	
Medical history						
Duration of type 2 diabetes, years	4.3 [1.1-9.6]	4.8 [1.3-10.3]	3.9 [0.9-9.3]	4.0 [1.1-9.0]	4.1 [1.0-8.7]	0.003
Newly diagnosed type 2 diabetes	531 (12.3)	120 (11.1)	147 (13.7)	132 (12.3)	132 (12.3)	0.36
Hypertension	3329 (77.4)	789 (73.3)	820 (76.3)	837 (77.8)	883 (82.1)	<0.001
Dyslipidemia	2684 (62.4)	583 (54.1)	683 (63.5)	697 (64.8)	721 (67.1)	<0.001
History of smoking						0.11
Current	912 (21.2)	236 (21.9)	220 (20.5)	205 (19.1)	251 (23.4)	

Former	1770 (41.2)	434 (40.3)	426 (39.6)	470 (43.8)	440 (40.9)	
Never	1618 (37.6)	406 (37.8)	429 (39.9)	399 (37.1)	384 (35.7)	
Myocardial infarction	916 (21.3)	199 (18.5)	193 (18.0)	240 (22.3)	284 (26.4)	<0.001
Coronary artery bypass grafting	285 (6.6)	60 (5.6)	48 (4.5)	86 (8.0)	91 (8.5)	<0.001
Percutaneous coronary intervention	747 (17.4)	145 (13.5)	157 (14.6)	209 (19.4)	236 (22.0)	<0.001
Stroke	200 (4.6)	47 (4.4)	52 (4.8)	45 (4.2)	56 (5.2)	0.67
Peripheral vascular disease	345 (8.0)	85 (7.9)	72 (6.7)	89 (8.3)	99 (9.2)	0.19
Congestive heart failure	407 (9.5)	94 (8.7)	92 (8.6)	93 (8.6)	128 (11.9)	0.02
Clinical findings						
BMI, kg/m ²	28.4 [25.4-31.9]	25.9 [23.4-28.8]	27.8 [25.4-30.8]	29.2 [26.6-32.4]	31.1 [27.8-34.9]	<0.001
Systolic blood pressure, mmHg	128±17	127±18	127±18	128±17	129±17	0.04
Diastolic blood pressure, mmHg	76±10	75±10	76±10	77±10	77±10	<0.001
Heart rate, bpm	70±11	70±11	70±11	70±11	72±11	<0.001
ACS index event						<0.001
STEMI	1708 (39.7)	463 (43.0)	456 (42.4)	421 (39.1)	368 (34.3)	
NSTEMI	1591 (37.0)	389 (36.1)	394 (36.7)	384 (35.7)	424 (39.5)	
UA	1003 (23.3)	225 (20.9)	225 (20.9)	271 (25.2)	282 (36.3)	
Coronary revascularization during index hospitalization	3333 (77.5)	829 (70.1)	825 (76.7)	845 (78.5)	834 (77.7)	0.77
Percutaneous coronary intervention	3116 (72.5)	767 (71.4)	768 (71.4)	790 (73.4)	791 (73.7)	0.46
Coronary bypass surgery	217 (5.0)	62 (5.8)	57 (5.3)	55 (5.1)	43 (4.0)	0.29
<u>Time from ACS hospitalization to randomization, days</u>	<u>29±14</u>	<u>30±14</u>	<u>29±14</u>	<u>30±15</u>	<u>29±15</u>	<u>0.57</u>
Medications						
Aspirin	4120 (95.7)	1038 (96.4)	1033 (96.1)	1028 (95.5)	1021 (95.0)	0.38
Other anti-platelet agents	3836 (89.1)	959 (89.0)	967 (90.0)	960 (89.2)	950 (88.4)	0.70
Statins	4030 (93.7)	991 (92.0)	1013 (94.2)	1020 (94.8)	1006 (93.6)	0.049

Beta blockers	3603 (83.7)	882 (81.9)	892 (83.0)	892 (82.9)	937 (87.2)	0.005
Renin-angiotensin system inhibitors	3555 (82.6)	846 (78.6)	898 (83.5)	910 (84.6)	901 (83.8)	<0.001
Diuretics	1215 (28.2)	258 (24.0)	303 (28.2)	324 (30.1)	330 (30.7)	0.002
Biguanides	3178 (73.9)	793 (73.6)	806 (75.0)	755 (70.2)	824 (76.7)	0.005
Sulfonylureas	1855 (43.1)	477 (44.3)	454 (42.2)	445 (41.4)	479 (44.6)	0.36
Laboratory values						
Fasting plasma glucose, mmol/l	7.2 [6.1-8.8]	6.3 [5.4-7.3]	6.9 [6.0-8.1]	7.5 [6.4-9.0]	8.7 [7.2-11.0]	-
Fasting plasma insulin, pmol/L	59.9 [39.0-91.2]	29.1 [22.0-36.9]	51.2 [42.6-60.2]	73.9 [60.6-87.1]	127.1 [97.2-174.5]	-
HOMA2-IR	1.5 [0.9-2.2]	0.7 [0.5-0.8]	1.2 [1.1-1.4]	1.8 [1.6-2.0]	3.2 [2.6-4.2]	-
HOMA-B	45.5 [25.7-77.6]	28.5 [17.7-46.7]	42.1 [26.8-64.5]	52.8 [31.5-80.2]	73.3 [40.1-122.1]	-
HOMA2-B	56.9 [35.6-84.7]	43.5 [29.8-63.3]	54.9 [36.6-77.6]	62.3 [38.9-88.2]	74.1 [44.0-115.4]	-
Glycated hemoglobin, %	7.5±1.5	7.2±1.4	7.4±1.5	7.5±1.5	7.9±1.6	<0.001
Hemoglobin, g/L	13.8±1.5	13.5±1.5	13.7±1.4	13.9±1.5	14.0±1.5	<0.001
eGFR (MDRD), ml/min/1.73m ²	78 [65-90]	77 [65-90]	77 [64-90]	78 [65-91]	78 [64-91]	0.77
LDL cholesterol, mmol/L	2.05±0.80	2.05±0.81	2.04±0.78	2.04±0.80	2.07±0.79	0.80
HDL cholesterol, mmol/L	1.09±0.28	1.14±0.31	1.08±0.28	1.07±0.26	1.05±0.25	<0.001
Triglycerides, mmol/L	1.49 [1.13-2.00]	1.31 [0.97-1.65]	1.43 [1.10-1.91]	1.56 [1.19-2.07]	1.74 [1.31-2.34]	<0.001
Creatine kinase, U/L	70 [49-102]	68 [48-98]	70 [50-99]	70 [49-102]	74 [51-113]	<0.001
hs-CRP, nmol/L	21.4 [9.1-55.5]	16.9 [7.3-48.5]	18.4 [8.5-47.5]	22.7 [10.3-58.8]	27.9 [11.6-65.5]	<0.001
NT-proBNP, pg/mL	359 [136-887]	542 [206-1274]	396 [158-945]	350 [120-803]	230 [94-594]	<0.001

Values are reported as mean±SD, median (IQR), or frequencies (percentages). ACS denotes acute coronary syndrome, BMI body mass index, eGFR estimated glomerular filtration rate, HDL high-density lipoprotein, HOMA-B homeostasis model assessment of beta cell function,

HOMA-IR homeostasis model assessment of insulin resistance, HOMA2-IR updated homeostasis model assessment of insulin resistance, and HOMA2-B updated homeostasis model assessment of beta cell function, hs-CRP high-sensitivity C-reactive protein, LDL low-density lipoprotein, MDRD Modification of Diet in Renal Disease, NSTEMI non-ST segment elevation myocardial infarction, NT-proBNP N-terminal pro-B-type natriuretic peptide, STEMI ST segment elevation myocardial infarction, and UA unstable angina. Renin-angiotensin system inhibitors include angiotensin converting enzyme inhibitors and receptor blockers.

Table 2. HOMA-IR at baseline and Month 3, and change in HOMA-IR from baseline to Month 3.

		Baseline	Month 3	Change (from baseline to Month 3)
		Median (IQR)	Median (IQR)	Median (IQR)
HOMA1-IR	All	2.72 (1.68 – 4.34)	2.14 (1.26 – 3.62)	-0.42 (-1.53 – 0.52)*
	Aleglitazar	2.75 (1.67 – 4.33)	1.61 (1.02 – 2.68)	-0.94 (-2.14 – -0.16)*†
	Placebo	2.69 (1.70 – 4.38)	2.86 (1.75 – 4.54)	0.13 (-0.77 – 1.14)*
HOMA2-IR	All	1.40 (0.90 – 2.20)	1.20 (0.80 – 1.90)	-0.20 (-0.70 – 0.30)*
	Aleglitazar	1.40 (0.90 – 2.20)	1.00 (0.60 – 1.50)	-0.40 (-0.90 – 0.10)*†
	Placebo	1.40 (0.90 – 2.20)	1.50 (1.00 – 2.30)	0.10 (-0.30 – 0.50)*

*P<0.001 Wilcoxon Signed-Rank test for baseline versus Month 3. †P<0.001 Wilcoxon Rank-Sum test (treatment versus placebo for change). HOMA-IR denotes homeostasis model assessment of insulin resistance.

Table 3. Association between baseline HOMA-IR or change in HOMA-IR from baseline to Month 3 and endpoints.

	Outcome variables	Number of patients	Events	Unadjusted Model HR (95% CI)	P-value	Adjusted Model 1 HR (95% CI)	P-value	Adjusted Model 2 HR (95% CI)	P-value
Baseline HOMA1-IR	Death from any cause	4303	152 (3.5)	0.79 (0.68-0.91)	0.002	0.82 (0.69-0.98)	0.03	0.99 (0.83-1.19)	0.94
	Cardiovascular events (incident cardiovascular death, myocardial infarction, and stroke)	4303	365 (8.5)	0.95 (0.86-1.04)	0.26	0.94 (0.84-1.05)	0.29	1.03 (0.92-1.15)	0.59
	Death from cardiovascular cause	4303	110 (2.6)	0.82 (0.68-0.97)	0.02	0.83 (0.68-1.02)	0.07	1.05 (0.85-1.29)	0.66
	Nonfatal myocardial infarction	4303	232 (5.4)	0.98 (0.87-1.10)	0.74	0.97 (0.84-1.11)	0.64	1.01 (0.88-1.16)	0.89
	Nonfatal stroke	4303	48 (1.1)	1.06 (0.82-1.38)	0.66	1.14 (0.85-1.53)	0.39	1.22 (0.90-1.64)	0.20
<u>Baseline HOMA2-IR</u>	<u>Death from any cause</u>	<u>4299</u>	<u>151 (3.5)</u>	<u>0.74 (0.62-0.87)</u>	<u><0.001</u>	<u>0.77 (0.64-0.94)</u>	<u>0.01</u>	<u>0.96 (0.79-1.17)</u>	<u>0.69</u>
	<u>Cardiovascular events (incident cardiovascular death, myocardial infarction, and stroke)</u>	<u>4299</u>	<u>364 (8.5)</u>	0.91 (0.82-1.02)	0.09	0.92 (0.81-1.04)	0.16	<u>1.01 (0.90-1.15)</u>	<u>0.82</u>
	<u>Death from cardiovascular cause</u>	<u>4299</u>	<u>109 (2.5)</u>	<u>0.75 (0.62-0.91)</u>	<u>0.004</u>	<u>0.77 (0.61-0.96)</u>	<u>0.02</u>	<u>1.00 (0.79-1.25)</u>	<u>0.98</u>
	<u>Nonfatal myocardial infarction</u>	<u>4299</u>	<u>232 (5.4)</u>	0.97 (0.85-1.11)	0.21	0.97 (0.83-1.13)	0.70	<u>1.02 (0.87-1.19)</u>	<u>0.81</u>
	<u>Nonfatal stroke</u>	<u>4299</u>	<u>48 (1.1)</u>	0.98 (0.73-1.31)	0.88	1.03 (0.74-1.44)	0.86	<u>1.11 (0.79-1.55)</u>	<u>0.56</u>
<u>Baseline HOMA2-B</u>	<u>Death from any cause</u>	<u>4299</u>	<u>151 (3.5)</u>	0.85 (0.73-0.998)	0.047	0.86 (0.70-1.05)	0.14	<u>0.97 (0.79-1.19)</u>	<u>0.77</u>
	<u>Cardiovascular events (incident cardiovascular death, myocardial infarction, and stroke)</u>	<u>4299</u>	<u>364 (8.5)</u>	0.92 (0.83-1.02)	0.12	0.98 (0.86-1.12)	0.75	<u>1.03 (0.91-1.18)</u>	<u>0.61</u>
	<u>Death from cardiovascular cause</u>	<u>4299</u>	<u>109 (2.5)</u>	0.84 (0.70-1.01)	0.07	0.87 (0.69-1.10)	0.25	<u>1.00 (0.79-1.26)</u>	<u>0.98</u>
	<u>Nonfatal myocardial infarction</u>	<u>4299</u>	<u>232 (5.4)</u>	0.99 (0.86-1.13)	0.83	1.08 (0.92-1.27)	0.37	<u>1.11 (0.94-1.30)</u>	<u>0.23</u>
	<u>Nonfatal stroke</u>	<u>4299</u>	<u>48 (1.1)</u>	0.79 (0.60-1.04)	0.09	0.66 (0.45-0.96)	0.03	<u>0.69 (0.47-0.998)</u>	<u>0.049</u>

Change in HOMA1-IR	Death from any cause	3568	98 (2.8)	0.94 (0.78-1.13)	0.50	0.94 (0.76-1.16)	0.54	0.88 (0.71-1.08)	0.22
	Cardiovascular events (incident cardiovascular death, myocardial infarction, and stroke)	3568	229 (6.4)	1.05 (0.93-1.19)	0.42	1.04 (0.91-1.20)	0.55	1.03 (0.89-1.18)	0.72
	Death from cardiovascular cause	3568	62 (1.7)	0.91 (0.72-1.14)	0.40	0.87 (0.67-1.14)	0.32	0.82 (0.64-1.07)	0.14
	Nonfatal myocardial infarction	3568	150 (4.2)	1.09 (0.93-1.26)	0.29	1.08 (0.90-1.28)	0.41	1.07 (0.90-1.27)	0.47
	Nonfatal stroke	3568	31 (0.9)	1.23 (0.88-1.70)	0.23	1.24 (0.85-1.80)	0.27	1.22 (0.84-1.77)	0.29
<u>Change in HOMA2-IR</u>	<u>Death from any cause</u>	<u>3564</u>	<u>97 (2.7)</u>	<u>0.92 (0.74-1.14)</u>	<u>0.44</u>	<u>0.94 (0.76-1.16)</u>	<u>0.54</u>	<u>0.88 (0.71-1.08)</u>	<u>0.22</u>
	<u>Cardiovascular events (incident cardiovascular death, myocardial infarction, and stroke)</u>	<u>3564</u>	<u>225 (6.3)</u>	<u>1.03 (0.89-1.19)</u>	<u>0.69</u>	<u>1.02 (0.86-1.20)</u>	<u>0.83</u>	<u>1.00 (0.85-1.18)</u>	<u>0.99</u>
	<u>Death from cardiovascular cause</u>	<u>3564</u>	<u>62 (1.7)</u>	<u>0.91 (0.69-1.19)</u>	<u>0.49</u>	<u>0.89 (0.66-1.21)</u>	<u>0.46</u>	<u>0.84 (0.63-1.11)</u>	<u>0.22</u>
	<u>Nonfatal myocardial infarction</u>	<u>3564</u>	<u>147 (4.1)</u>	<u>1.04 (0.87-1.25)</u>	<u>0.66</u>	<u>1.02 (0.83-1.26)</u>	<u>0.83</u>	<u>1.01 (0.83-1.24)</u>	<u>0.90</u>
	<u>Nonfatal stroke</u>	<u>3564</u>	<u>31 (0.9)</u>	<u>1.31 (0.89-1.92)</u>	<u>0.17</u>	<u>1.34 (0.87-2.05)</u>	<u>0.19</u>	<u>1.32 (0.86-2.01)</u>	<u>0.21</u>
<u>Change in HOMA2-B</u>	<u>Death from any cause</u>	<u>3564</u>	<u>97 (2.7)</u>	<u>0.89 (0.69-1.15)</u>	<u>0.36</u>	<u>0.87 (0.67-1.14)</u>	<u>0.32</u>	<u>0.82 (0.63-1.06)</u>	<u>0.13</u>
	<u>Cardiovascular events (incident cardiovascular death, myocardial infarction, and stroke)</u>	<u>3564</u>	<u>225 (6.3)</u>	<u>0.90 (0.76-1.08)</u>	<u>0.24</u>	<u>0.90 (0.76-1.07)</u>	<u>0.24</u>	<u>0.89 (0.75-1.05)</u>	<u>0.17</u>
	<u>Death from cardiovascular cause</u>	<u>3564</u>	<u>62 (1.7)</u>	<u>0.85 (0.62-1.16)</u>	<u>0.31</u>	<u>0.82 (0.59-1.12)</u>	<u>0.21</u>	<u>0.77 (0.57-1.05)</u>	<u>0.10</u>
	<u>Nonfatal myocardial infarction</u>	<u>3564</u>	<u>147 (4.1)</u>	<u>0.90 (0.73-1.12)</u>	<u>0.31</u>	<u>0.90 (0.72-1.12)</u>	<u>0.33</u>	<u>0.89 (0.72-1.10)</u>	<u>0.29</u>
	<u>Nonfatal stroke</u>	<u>3564</u>	<u>31 (0.9)</u>	<u>1.22 (0.79-1.88)</u>	<u>0.36</u>	<u>1.39 (0.85-2.28)</u>	<u>0.18</u>	<u>1.38 (0.84-2.25)</u>	<u>0.20</u>

Values are reported as numbers and percentages. HOMA-IR denotes homeostasis model assessment of insulin resistance, HOMA2-IR updated homeostasis model assessment of insulin resistance, and HOMA2-B updated homeostasis model assessment of beta cell function. Log₂ transformation was applied for HOMA-IR, HOMA2-IR, and HOMA2-B. Therefore, hazard ratios (HR) are for a doubling of the variable in question. The following variables were included in Cox regression Model 1: age, sex, race, body mass index, smoking, hypertension, prior coronary artery disease, prior congestive heart failure, diabetes duration prior to randomization, time from acute coronary syndrome event to randomization, glycated haemoglobin, log₂ estimated glomerular filtration rate, log₂ high-sensitivity C-reactive protein, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, log₂ triglycerides, biguanides, sulfonylureas, incretins, statins, beta blockers, renin angiotensin blockers, calcium channel blockers, and treatment assignment (aleglitazar versus placebo); and stratified by acute coronary syndrome index event and presence or absence of reperfusion therapy. The following variables were included in Cox regression Model 2: variables of Model 1 with addition of log₂ NT-proBNP

Table 4. Association between baseline NT-proBNP or change in NT-proBNP from baseline to Month 3 and endpoints.

Outcome variables		Unadjusted Model HR (95% CI)	P-value	Adjusted Model 2 HR (95% CI)	P-value
Baseline NT-proBNP	Death from any cause	1.65 (1.51-1.81)	<0.001	1.57 (1.41-1.76)	<0.001
	Cardiovascular events (incident cardiovascular death, myocardial infarction, and stroke)	1.31 (1.24-1.39)	<0.001	1.29 (1.20-1.39)	<0.001
	Death from cardiovascular cause	1.76 (1.58-1.95)	<0.001	1.80 (1.57-2.07)	<0.001
	Nonfatal myocardial infarction	1.17 (1.09-1.26)	<0.001	1.13 (1.03-1.23)	0.008
	Nonfatal stroke	1.24 (1.06-1.46)	0.008	1.22 (1.00-1.48)	0.045
Change in NT-proBNP	Death from any cause	1.38 (1.16-1.65)	<0.001	1.50 (1.30-1.72)	<0.001
	Cardiovascular events (incident cardiovascular death, myocardial infarction, and stroke)	1.27 (1.13-1.43)	<0.001	1.23 (1.12-1.35)	<0.001
	Death from cardiovascular cause	1.47 (1.18-1.83)	<0.001	1.77 (1.47-2.12)	<0.001
	Nonfatal myocardial infarction	1.23 (1.06-1.43)	0.008	1.11 (1.00-1.24)	0.08
	Nonfatal stroke	1.01 (0.72-1.42)	0.97	1.14 (0.89-1.47)	0.30

NT-proBNP denotes N-terminal pro-brain natriuretic peptide. Hazard ratios (HR) are for a doubling of baseline NT-proBNP.

Figure 1.

