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

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

Design: The Effect of Aleglitazar on Cardiovascular Outcomes after Acute Coronary Syndrome in Patients with Type 2 Diabetes Mellitus trial compared the peroxisome proliferator-activated receptor-α/γ agonist aleglitazar with placebo in patients with type 2 diabetes 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 (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, twofold higher baseline HOMA-IR was associated with lower risk of death [hazard ratio (HR): 0.79, 95% CI: 0.68 to 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 to 1.19, $P = 0.94$). Baseline HOMA-IR was not associated with major adverse cardiovascular events, nor was the change in HOMA-IR on study treatment associated with death or major adverse cardiovascular events.

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Abbreviations: ACS, acute coronary syndrome; AleCardio, Effect of Aleglitazar on Cardiovascular Outcomes after Acute Coronary Syndrome in Patients with Type 2 Diabetes Mellitus; eGFR, estimated glomerular filtration rate; HOMA2-B, updated homeostasis model assessment of β cell function; HOMA2-IR, updated homeostasis model assessment of insulin resistance; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PPAR, peroxisome proliferator-activated receptor.

Conclusions: After accounting for levels of NT-proBNP, insulin resistance assessed by HOMA-IR is not related to the risk of death or major adverse cardiovascular events in patients with type 2 diabetes and ACS. (*J Clin Endocrinol Metab* 103: 2522–2533, 2018)

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 nondiabetic 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 Effect of Aleglitazar on Cardiovascular Outcomes after Acute Coronary Syndrome in Patients with Type 2 Diabetes Mellitus (AleCardio) trial compared aleglitazar, a dual agonist of PPAR-α and -γ, with placebo in patients with type 2 diabetes and recent ACS. Aleglitazar 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 (ClinicalTrials.gov no. 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 aleglitazar (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 m^2, 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/d) 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):

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

The updated homeostasis model assessment of insulin resistance (HOMA2-IR) and updated homeostasis model assessment of β cell function (HOMA2-B) were also calculated using the online HOMA calculator version 2.2.3 for specific insulin available at 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 to 25 mmol/L and fasting insulin: 20 to 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), with an intra-assay precision of 0.8% to 1.1% coefficient of variation and an interassay precision of 1.1% to 1.3% coefficient of variation. Insulin was measured by the immunoenzymatic Access Ultrasensitive Insulin Assay (Beckman Coulter Inc., Brea, CA), with an intra-assay precision of 2.0% to 4.2% coefficient of variation and an interassay precision of ≤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 ± SD 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 analysis of variance or the Kruskal-Wallis test for continuous variables, and with χ^2 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 predefined 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 hemoglobin, $\log_2$ high-sensitivity C-reactive protein (hs-CRP), $\log_2$ eGFR using the Modification of Diet in Renal Disease 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 3 (difference between $\log_2$-transformed baseline and $\log_2$-transformed month 3 values) with each of the same endpoints occurring after 3 months.

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

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 antiplatelet 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 agonists or dipeptidyl peptidase-4 antagonists, and none were treated with sodium-glucose cotransporter 2 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. Mean NT-proBNP in quartile 1 of HOMA1-IR was 2.36 times higher than in quartile 4 of HOMA1-IR (Table 1).

In the placebo group, HOMA1-IR increased slightly from baseline to month 3 by 0.13 (–0.77, 1.14) [median (IQR); $P < 0.001$ vs 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) ($P < 0.001$ vs 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 Fig. 1. In unadjusted analysis, a twofold higher baseline level of HOMA1-IR was associated with a lower risk of all-cause death [hazard ratio (HR): 0.79, 95% CI: 0.68 to 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 to 0.87, $P = 0.0004$), without an association of $\log_2$ glucose with death (HR: 0.98, 95% CI: 0.68 to 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 to 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 to 1.19, $P = 0.94$).

Cardiovascular death occurred in 110 patients (2.6%). A twofold 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 to 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 to 0.92, $P < 0.001$) without association with $\log_2$ glucose (HR: 1.09, 95% CI: 0.72 to 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 to 1.02, $P = 0.07$) and neutralized after additional adjustment for NT-proBNP in model 2 (adjusted HR: 1.05, 95% CI: 0.85 to 1.29, $P = 0.66$). There was no interaction of baseline HOMA1-IR and treatment assignment on all-cause death ($p_{int} = 0.54$) or cardiovascular death ($p_{int} = 0.45$).

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

Hospitalization for heart failure occurred in 109 patients (2.5%). A twofold 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 to 0.90, $P = 0.002$) and when adjusted for the variables in model 1 (adjusted HR: 0.72, 95% CI: 0.59 to 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 to 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 (Supplemental Table 1). When analyzing the placebo and aleglitazar groups separately, neither HOMA1-IR nor HOMA2-IR was related with endpoints in adjusted analysis (Supplemental Table 2).

Associations of NT-proBNP with endpoints

In unadjusted analysis, a twofold higher baseline level of NT-proBNP was significantly associated with a higher risk of all-cause death (HR: 1.65, 95% CI: 1.51 to 1.81, $P < 0.001$), cardiovascular death (HR: 1.76, 95% CI: 1.58 to 1.95, $P < 0.001$), nonfatal myocardial infarction (HR: 1.17, 95% CI: 1.09 to 1.26, $P < 0.001$), nonfatal stroke (HR: 1.24, 95% CI: 1.06 to 1.46, $P = 0.008$), and major cardiovascular events (HR: 1.31, 95% CI: 1.24 to 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

Table 1. Baseline Clinical and Laboratory Characteristics According to HOMA1-IR Quartiles

Variable	All	HOMA1-IR Quartile 1	HOMA1-IR Quartile 2	HOMA1-IR Quartile 3	HOMA1-IR Quartile 4	*P* Value
		<1.69	1.69–2.77	2.77–4.46	≥4.46	
	N = 4303	n = 1077	n = 1075	n = 1076	n =1075	
Demographics						
Age, y	60.9 ± 10.0	62.5 ± 10.1	61.2 ± 10.0	60.8 ± 9.9	59.1 ± 9.7	<0.001
Sex, 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, y	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, mm Hg	128 ± 17	127 ± 18	127 ± 18	128 ± 17	129 ± 17	0.04
Diastolic blood pressure, mm Hg	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
Time from ACS hospitalization to randomization, d	29 ± 14	30 ± 14	29 ± 14	30 ± 15	29 ± 15	0.57
Medications						
Aspirin	4120 (95.7)	1038 (96.4)	1033 (96.1)	1028 (95.5)	1021 (95.0)	0.38
Other antiplatelet 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

(*Continued*)

Table 1. Baseline Clinical and Laboratory Characteristics According to HOMA1-IR Quartiles (Continued)

Variable	All	HOMA1-IR Quartile 1	HOMA1-IR Quartile 2	HOMA1-IR Quartile 3	HOMA1-IR Quartile 4	*P* Value
		<1.69	1.69–2.77	2.77–4.46	≥4.46	
	N = 4303	n = 1077	n = 1075	n = 1076	n =1075	
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). Renin-angiotensin system inhibitors include angiotensin converting enzyme inhibitors and receptor blockers.

Abbreviations: BMI, body mass index; HDL high-density lipoprotein; HOMA-B, homeostasis model assessment of β cell function; LDL low-density lipoprotein; MDRD, Modification of Diet in Renal Disease; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; UA, unstable angina.

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 represents 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 prediabetes (10–13). In that context, HOMA-IR has been shown to have incremental predictive value above glucose or insulin measurements alone (14, 27).

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 to 4.34)	2.14 (1.26 to 3.62)	−0.42 (–1.53 to 0.52)[a]
Aleglitazar	2.75 (1.67 to 4.33)	1.61 (1.02 to 2.68)	−0.94 (–2.14 to –0.16)[a,b]
Placebo	2.69 (1.70 to 4.38)	2.86 (1.75 to 4.54)	0.13 (–0.77 to 1.14)[a]
HOMA2-IR			
All	1.40 (0.90 to 2.20)	1.20 (0.80 to 1.90)	−0.20 (–0.70 to 0.30)[a]
Aleglitazar	1.40 (0.90 to 2.20)	1.00 (0.60 to 1.50)	−0.40 (–0.90 to 0.10)[a,b]
Placebo	1.40 (0.90 to 2.20)	1.50 (1.00 to 2.30)	0.10 (–0.30 to 0.50)[a]

[a] $P < 0.001$ Wilcoxon Signed-Rank test for baseline vs month 3.

[b] $P < 0.001$ Wilcoxon Rank-Sum test (treatment vs placebo for change).

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
Baseline HOMA2-IR								
Death from any cause	4299	151 (3.5)	0.74 (0.62–0.87)	<0.001	0.77 (0.64–0.94)	0.01	0.96 (0.79–1.17)	0.69
Cardiovascular events (incident cardiovascular death, myocardial infarction, and stroke)	4299	364 (8.5)	0.91 (0.82–1.02)	0.09	0.92 (0.81–1.04)	0.16	1.01 (0.90–1.15)	0.82
Death from cardiovascular cause	4299	109 (2.5)	0.75 (0.62–0.91)	0.004	0.77 (0.61–0.96)	0.02	1.00 (0.79–1.25)	0.98
Nonfatal myocardial infarction	4299	232 (5.4)	0.97 (0.85–1.11)	0.21	0.97 (0.83–1.13)	0.70	1.02 (0.87–1.19)	0.81
Nonfatal stroke	4299	48 (1.1)	0.98 (0.73–1.31)	0.88	1.03 (0.74–1.44)	0.86	1.11 (0.79–1.55)	0.56
Baseline HOMA2-B					0.86 (0.70–1.05)			
Death from any cause	4299	151 (3.5)	0.85 (0.73–0.998)	0.047	0.047	0.14	0.97 (0.79–1.19)	0.77
Cardiovascular events (incident cardiovascular death, myocardial infarction, and stroke)	4299	364 (8.5)	0.92 (0.83–1.02)	0.12	0.98 (0.86–1.12)	0.75	1.03 (0.91–1.18)	0.61
Death from cardiovascular cause	4299	109 (2.5)	0.84 (0.70–1.01)	0.07	0.87 (0.69–1.10)	0.25	1.00 (0.79–1.26)	0.98
Nonfatal myocardial infarction	4299	232 (5.4)	0.99 (0.86–1.13)	0.83	1.08 (0.92–1.27)	0.37	1.11 (0.94–1.30)	0.23
Nonfatal stroke	4299	48 (1.1)	0.79 (0.60–1.04)	0.09	0.66 (0.45–0.96)	0.03	0.69 (0.47–0.998)	0.049
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
Change in HOMA2-IR								
Death from any cause	3564	97 (2.7)	0.92 (0.74–1.14)	0.44	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)	3564	225 (6.3)	1.03 (0.89–1.19)	0.69	1.02 (0.86–1.20)	0.83	1.00 (0.85–1.18)	0.99
Death from cardiovascular cause	3564	62 (1.7)	0.91 (0.69–1.19)	0.49	0.89 (0.66–1.21)	0.46	0.84 (0.63–1.11)	0.22
Nonfatal myocardial infarction	3564	147 (4.1)	1.04 (0.87–1.25)	0.66	1.02 (0.83–1.26)	0.83	1.01 (0.83–1.24)	0.90
Nonfatal stroke	3564	31 (0.9)	1.31 (0.89–1.92)	0.17	1.34 (0.87–2.05)	0.19	1.32 (0.86–2.01)	0.21
Change in HOMA2-B								
Death from any cause	3564	97 (2.7)	0.89 (0.69–1.15)	0.36	0.87 (0.67–1.14)	0.32	0.82 (0.63–1.06)	0.13
Cardiovascular events (incident cardiovascular death, myocardial infarction, and stroke)	3564	225 (6.3)	0.90 (0.76–1.08)	0.24	0.90 (0.76–1.07)	0.24	0.89 (0.75–1.05)	0.17

(*Continued*)

Table 3. Association Between Baseline HOMA-IR or Change in HOMA-IR From Baseline to Month 3 and Endpoints (Continued)

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
Death from cardiovascular cause	3564	62 (1.7)	0.85 (0.62–1.16)	0.31	0.82 (0.59–1.12)	0.21	0.77 (0.57–1.05)	0.10
Nonfatal myocardial infarction	3564	147 (4.1)	0.90 (0.73–1.12)	0.31	0.90 (0.72–1.12)	0.33	0.89 (0.72–1.10)	0.29
Nonfatal stroke	3564	31 (0.9)	1.22 (0.79–1.88)	0.36	1.39 (0.85–2.28)	0.18	1.38 (0.84–2.25)	0.20

Values are reported as numbers and percentages. Log_2 transformation was applied for HOMA1-IR, HOMA2-IR, and HOMA2-B. Therefore, HRs 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 ACS event to randomization, glycated hemoglobin, log_2-eGFR, log_2 hs-CRP, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, log_2 triglycerides, biguanides, sulfonylureas, incretins, statins, beta-blockers, renin angiotensin blockers, calcium channel blockers, and treatment assignment (aleglitazar vs placebo); they were stratified by ACS 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 log_2 NT-proBNP.

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.

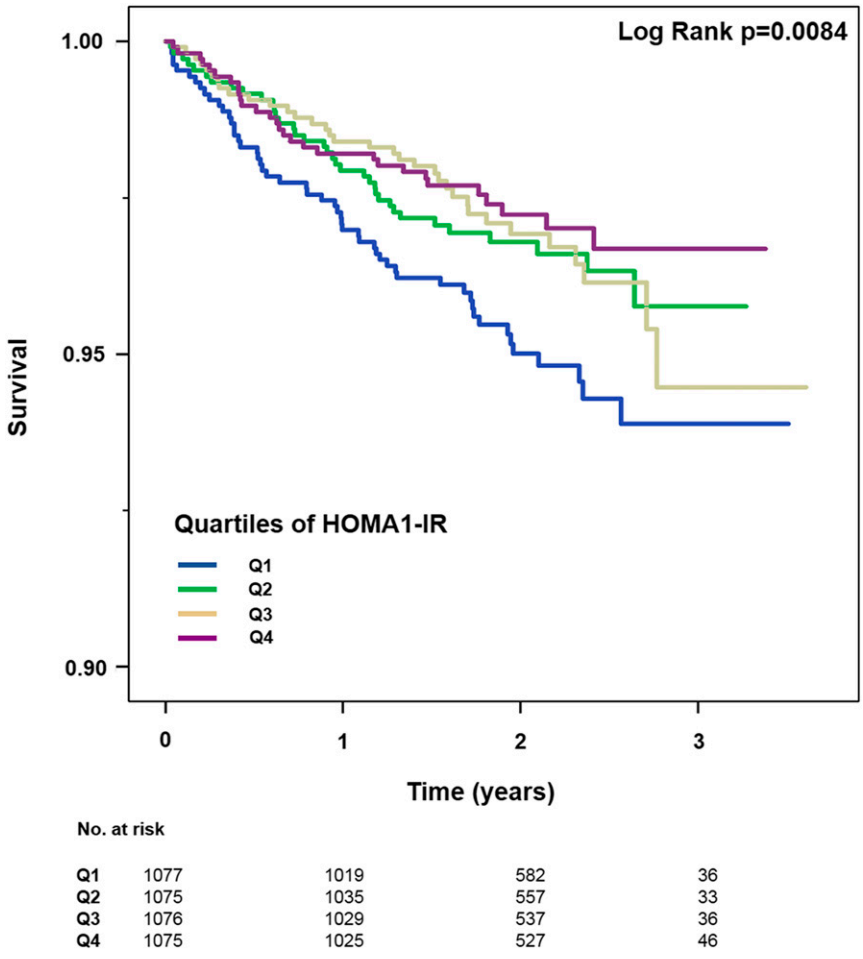

Figure 1. Kaplan-Meier estimates for all-cause mortality according to HOMA1-IR quartiles. Q, quartile.

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

HRs are for a doubling of baseline NT-proBNP.

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 to 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 most likely due to 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 β 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 and 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 nonfatal ischemic cardiovascular events. Despite a relatively large number of nonfatal 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 nonfatal 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 data set, 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 reflects not only 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 with 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 used 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 with an insulin-sensitizing agent is not related to outcomes. PPAR 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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References

1. Iguchi T, Hasegawa T, Otsuka K, Matsumoto K, Yamazaki T, Nishimura S, Nakata S, Ehara S, Kataoka T, Shimada K, Yoshiyama M. Insulin resistance is associated with coronary plaque vulnerability: insight from optical coherence tomography analysis. *Eur Heart J Cardiovasc Imaging*. 2014;**15**(3):284–291.
2. An X, Yu D, Zhang R, Zhu J, Du R, Shi Y, Xiong X. Insulin resistance predicts progression of de novo atherosclerotic plaques in patients with coronary heart disease: a one-year follow-up study. *Cardiovasc Diabetol*. 2012;**11**(1):71.
3. Nishimura M, Tokoro T, Nishida M, Hashimoto T, Kobayashi H, Yamazaki S, Imai R, Okino K, Takahashi H, Ono T. Association of insulin resistance with de novo coronary stenosis after percutaneous coronary artery intervention in hemodialysis patients. *Nephron Clin Pract*. 2008;**109**(1):c9–c17.
4. Uetani T, Amano T, Harada K, Kitagawa K, Kunimura A, Shimbo Y, Harada K, Yoshida T, Kato B, Kato M, Marui N, Nanki M, Hotta N, Ishii H, Matsubara T, Murohara T. Impact of insulin resistance on post-procedural myocardial injury and clinical outcomes in patients who underwent elective coronary interventions with drug-eluting stents. *JACC Cardiovasc Interv*. 2012;**5**(11):1159–1167.
5. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Steg PG, Gore JM, Budaj A, Avezum A, Flather MD, Fox KA; GRACE Investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA*. 2004;**291**(22):2727–2733.
6. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;**357**(20):2001–2015.
7. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;**372**(25):2387–2397.
8. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;**28**(7):412–419.
9. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care*. 2000;**23**(1):57–63.
10. Tenenbaum A, Adler Y, Boyko V, Tenenbaum H, Fisman EZ, Tanne D, Lapidot M, Schwammenthal E, Feinberg MS, Matas Z, Motro M, Behar S. Insulin resistance is associated with increased risk of major cardiovascular events in patients with preexisting coronary artery disease. *Am Heart J*. 2007;**153**(4):559–565.
11. Robins SJ, Rubins HB, Faas FH, Schaefer EJ, Elam MB, Anderson JW, Collins D, Veterans Affairs HDLIT; Veterans Affairs HDL Intervention Trial (VA-HIT). Insulin resistance and cardiovascular events with low HDL cholesterol: the Veterans Affairs HDL Intervention Trial (VA-HIT). *Diabetes Care*. 2003;**26**(5):1513–1517.
12. Yanase M, Takatsu F, Tagawa T, Kato T, Arai K, Koyasu M, Horibe H, Nomoto S, Takemoto K, Shimizu S, Watarai M. Insulin resistance and fasting hyperinsulinemia are risk factors for new cardiovascular events in patients with prior coronary artery disease and normal glucose tolerance. *Circ J*. 2004;**68**(1):47–52.
13. Hedblad B, Nilsson P, Engström G, Berglund G, Janzon L. Insulin resistance in non-diabetic subjects is associated with increased incidence of myocardial infarction and death. *Diabet Med*. 2002;**19**(6):470–475.
14. Bonora E, Formentini G, Calcaterra F, Lombardi S, Marini F, Zenari L, Saggiani F, Poli M, Perbellini S, Raffaelli A, Cacciatori V, Santi L, Targher G, Bonadonna R, Muggeo M. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. *Diabetes Care*. 2002;**25**(7):1135–1141.
15. Adler AI, Levy JC, Matthews DR, Stratton IM, Hines G, Holman RR. Insulin sensitivity at diagnosis of type 2 diabetes is not associated with subsequent cardiovascular disease (UKPDS 67). *Diabet Med*. 2005;**22**(3):306–311.
16. Chang HR, Hsieh JC, Hsu BG, Wang LY, Chen MY, Wang JH. Inverse association of N-terminal pro-B-type natriuretic peptide with metabolic syndrome in patients with congestive heart failure. *PLoS One*. 2013;**8**(11):e79096.
17. Inoue Y, Kawai M, Minai K, Ogawa K, Nagoshi T, Ogawa T, Yoshimura M. The impact of an inverse correlation between plasma B-type natriuretic peptide levels and insulin resistance on the diabetic condition in patients with heart failure. *Metabolism*. 2016;**65**(3):38–47.
18. Kim F, Biggs ML, Kizer JR, Brutsaert EF, de Filippi C, Newman AB, Kronmal RA, Tracy RP, Gottdiener JS, Djoussé L, de Boer IH, Psaty BM, Siscovick DS, Mukamal KJ. Brain natriuretic peptide and insulin resistance in older adults. *Diabet Med*. 2017;**34**(2):235–238.
19. Heeschen C, Hamm CW, Mitrovic V, Lantelme NH, White HD; Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Investigators. N-terminal pro-B-type natriuretic peptide levels for dynamic risk stratification of patients with acute coronary syndromes. *Circulation*. 2004;**110**(20):3206–3212.
20. Omland T, Persson A, Ng L, O'Brien R, Karlsson T, Herlitz J, Hartford M, Caidahl K. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. *Circulation*. 2002;**106**(23):2913–2918.
21. Lincoff AM, Tardif JC, Schwartz GG, Nicholls SJ, Rydén L, Neal B, Malmberg K, Wedel H, Buse JB, Henry RR, Weichert A, Cannata R, Svensson A, Volz D, Grobbee DE; AleCardio Investigators. Effect of aleglitazar on cardiovascular outcomes after acute coronary syndrome in patients with type 2 diabetes mellitus: the AleCardio randomized clinical trial. *JAMA*. 2014;**311**(15):1515–1525.
22. Lincoff AM, Tardif JC, Neal B, Nicholls SJ, Rydén L, Schwartz GG, Malmberg K, Buse JB, Henry RR, Wedel H, Weichert A, Cannata R, Grobbee DE. Evaluation of the dual peroxisome proliferator-activated receptor α/γ agonist aleglitazar to reduce cardiovascular events in patients with acute coronary syndrome and type 2 diabetes mellitus: rationale and design of the AleCardio trial. *Am Heart J*. 2013;**166**(3):429–434.
23. Ghasemi A, Tohidi M, Derakhshan A, Hasheminia M, Azizi F, Hadaegh F. Cut-off points of homeostasis model assessment of insulin resistance, beta-cell function, and fasting serum insulin to identify future type 2 diabetes: Tehran Lipid and Glucose Study. *Acta Diabetol*. 2015;**52**(5):905–915.
24. Ader M, Stefanovski D, Richey JM, Kim SP, Kolka CM, Ionut V, Kabir M, Bergman RN. Failure of homeostatic model assessment of insulin resistance to detect marked diet-induced insulin resistance in dogs. *Diabetes*. 2014;**63**(6):1914–1919.
25. Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR. Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow-up study. *Lancet*. 1992;**340**(8825):925–929.
26. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, Allen K, Lopes M, Savoye M, Morrison J, Sherwin RS, Caprio S. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med*. 2004;**350**(23):2362–2374.
27. Gast KB, Tjeerdema N, Stijnen T, Smit JW, Dekkers OM. Insulin resistance and risk of incident cardiovascular events in adults without diabetes: meta-analysis. *PLoS One*. 2012;**7**(12):e52036.

28. Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, MacGregor JM, Orchard TJ, Chaitman BR, Genuth SM, Goldberg SH, Hlatky MA, Jones TL, Molitch ME, Nesto RW, Sako EY, Sobel BE; BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009;**360**(24):2503–2515.
29. Wallander M, Malmberg K, Norhammar A, Rydén L, Tenerz A. Oral glucose tolerance test: a reliable tool for early detection of glucose abnormalities in patients with acute myocardial infarction in clinical practice: a report on repeated oral glucose tolerance tests from the GAMI study. *Diabetes Care*. 2008;**31**(1):36–38.
30. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet*. 2000;**355**(9206):773–778.
31. Norhammar A, Tenerz A, Nilsson G, Hamsten A, Efendíc S, Rydén L, Malmberg K. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet*. 2002;**359**(9324):2140–2144.
32. Wang TJ, Larson MG, Keyes MJ, Levy D, Benjamin EJ, Vasan RS. Association of plasma natriuretic peptide levels with metabolic risk factors in ambulatory individuals. *Circulation*. 2007;**115**(11):1345–1353.
33. Sanchez OA, Duprez DA, Bahrami H, Daniels LB, Folsom AR, Lima JA, Maisel A, Peralta CA, Jacobs DR Jr. The associations between metabolic variables and NT-proBNP are blunted at pathological ranges: the Multi-Ethnic Study of Atherosclerosis. *Metabolism*. 2014;**63**(4):475–483.
34. Neeland IJ, Winders BR, Ayers CR, Das SR, Chang AY, Berry JD, Khera A, McGuire DK, Vega GL, de Lemos JA, Turer AT. Higher natriuretic peptide levels associate with a favorable adipose tissue distribution profile. *J Am Coll Cardiol*. 2013;**62**(8):752–760.
35. Gruden G, Landi A, Bruno G. Natriuretic peptides, heart, and adipose tissue: new findings and future developments for diabetes research. *Diabetes Care*. 2014;**37**(11):2899–2908.
36. Hippisley-Cox J, Coupland C. Development and validation of risk prediction equations to estimate future risk of heart failure in patients with diabetes: a prospective cohort study. *BMJ Open*. 2015;**5**(9):e008503.
37. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PW, Vasan RS. Impact of obesity on plasma natriuretic peptide levels. *Circulation*. 2004;**109**(5):594–600.
38. Mehra MR, Uber PA, Park MH, Scott RL, Ventura HO, Harris BC, Frohlich ED. Obesity and suppressed B-type natriuretic peptide levels in heart failure. *J Am Coll Cardiol*. 2004;**43**(9):1590–1595.