



Measures of Insulin Resistance as a Screening Tool for Dysglycemia in Patients With Coronary Artery Disease: A Report From the EUROASPIRE V Population

Diabetes Care 2022;45:2111–2117 | <https://doi.org/10.2337/dc22-0272>

Giulia Ferrannini,¹ Dirk De Bacquer,² Iris Erlund,³ Viveca Gyberg,¹ Kornelia Kotseva,^{4,5} Linda Mellbin,^{1,6} Anna Norhammar,^{1,7} Oliver Schnell,⁸ Jaakko Tuomilehto,^{9,10,11,12} Terhi Vihervaara,³ David Wood,⁴ and Lars Rydén¹

OBJECTIVE

The optimal screening strategy for dysglycemia (including type 2 diabetes and impaired glucose tolerance) in patients with coronary artery disease (CAD) is debated. We tested the hypothesis that measures of insulin resistance by HOMA indexes may constitute good screening methods.

RESEARCH DESIGN AND METHODS

Insulin, C-peptide, glycated hemoglobin A_{1c}, and an oral glucose tolerance test (OGTT) were centrally assessed in 3,534 patients with CAD without known dysglycemia from the fifth European Survey of Cardiovascular Disease Prevention and Diabetes (EUROASPIRE V). Three different HOMA indexes were calculated: HOMA of insulin resistance (HOMA-IR), HOMA2 based on insulin (HOMA2-ins), and HOMA2 based on C-peptide (HOMA2-Cpep). Dysglycemia was diagnosed based on the 2-h postload glucose value obtained from the OGTT. Information on study participants was obtained by standardized interviews. The optimal thresholds of the three HOMA indexes for dysglycemia diagnosis were obtained by the maximum value of Youden's J statistic on receiver operator characteristic curves. Their correlation with clinical parameters was assessed by Spearman coefficients.

RESULTS

Of 3,534 patients with CAD (mean age 63 years; 25% women), 41% had dysglycemia. Mean insulin, C-peptide, and HOMA indexes were significantly higher in patients with versus without newly detected dysglycemia (all $P < 0.0001$). Sensitivity and specificity of the three HOMA indexes for the diagnosis of dysglycemia were low, but their correlation with BMI and waist circumference was strong.

CONCLUSIONS

Screening for dysglycemia in patients with CAD by HOMA-IR, HOMA2-ins, and HOMA2-Cpep had insufficient diagnostic performance to detect dysglycemia with reference to the yield of an OGTT, which should still be prioritized despite its practical drawbacks.

Dysglycemia, defined as either impaired glucose tolerance (IGT) or type 2 diabetes mellitus (T2DM), increases the risk of cardiovascular (CV) events (1,2). According to

¹Cardiology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

²Department of Public Health and Primary Care, Ghent University, Ghent, Belgium

³Department of Government Services, Finnish Institute for Health and Welfare, Helsinki, Finland

⁴National Institute for Prevention and Cardiovascular Health, National University of Ireland-Galway, Galway, Republic of Ireland

⁵St Mary's Hospital, Imperial College Healthcare NHS Trust, London, U.K.

⁶Heart & Vascular and Neuro Theme, Karolinska University Hospital, Stockholm, Sweden

⁷Capio St Görans Hospital, Stockholm, Sweden

⁸Forschergruppe Diabetes e.V., Munich, Germany

⁹Department of Public Health and Welfare, Finnish Institute for Health and Welfare, Helsinki, Finland

¹⁰Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi Arabia

¹¹Department of Public Health, University of Helsinki, Helsinki, Finland

¹²Department of International Health, National School of Public Health, Instituto de Salud Carlos III, Madrid, Spain

Corresponding author: Giulia Ferrannini, giulia.ferrannini@ki.se

Received 8 February 2022 and accepted 13 May 2022

This article contains supplementary material online at <https://doi.org/10.2337/figshare.20032724>.

© 2022 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <https://www.diabetesjournals.org/journals/pages/license>.

recent estimates by the International Diabetes Federation, about half of people with T2DM are unaware of their condition (3), and previously unrecognized dysglycemia among people with atherosclerotic CV disease (CVD) is common (4–6). Therefore, accurate and clinically feasible screening tests for dysglycemia are important to enable the institution of measures to prevent subsequent complications. A recent risk model based on the European Survey of Cardiovascular Disease Prevention and Diabetes (EUROASPIRE) experiences indicated that uncontrolled diabetes is an independent risk factor for future cardiovascular events (7). Moreover, the origin of novel cardioprotective glucose-lowering agents, glucagon-like peptide 1 receptor agonists and sodium–glucose cotransporter 2 inhibitors, offers excellent possibilities to lower this risk (8).

There is an ongoing debate on the optimal screening strategy in terms of precision, prognostic information, cost-effectiveness, and feasibility (9,10). The most commonly used tests are glycated hemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose (FPG), and oral glucose tolerance test (OGTT) that includes both FPG and a 2-h postload glucose (2hPG) (11). Although more time-consuming, the OGTT is more informative not only because it is the only diagnostic test for IGT (12), but also because it discloses more people with T2DM than FPG and HbA_{1c} and provides superior prognostic information beyond that of FPG or HbA_{1c} (2,13–15). Still, the European Society of Cardiology (ESC)/European Association for the Study of Diabetes European guidelines on diabetes, prediabetes, and CVD recommend the use of FPG and HbA_{1c} as the first diagnostic tests in people at increased CV risk, restricting the role of OGTT to uncertain cases (16).

The Insulin Resistance Intervention after Stroke (IRIS) trial showed that pioglitazone, a potent insulin-sensitizing drug, decreased the risk of stroke or myocardial infarction in people without established T2DM but with insulin resistance and a recent stroke or transitory ischemic attack (17,18). The possibility to use insulin resistance to detect patients with significant glucometabolic derangement is appealing (19). In epidemiological studies, insulin resistance is usually expressed through HOMA, which can be calculated by fasting blood values of insulin, glucose, and C-peptide (20–22).

The objective of the current study was to test the hypothesis that a HOMA index may constitute a novel, simplified screening method for glucose perturbations in people at high CV risk by comparing different expressions of HOMA with the outcome of an OGTT in patients with coronary artery disease (CAD) in the fifth EUROASPIRE (EUROASPIRE V [EAV]) cohort.

RESEARCH DESIGN AND METHODS

Study Design

The EAV cross-sectional survey was conducted from 2016 to 2017 in 131 centers across 27 countries under the auspices of the European Society of Cardiology–EURObservational Research Programme (EORP). Patients, <80 years old, with a first or recurrent clinical diagnosis or treatment of: 1) elective or emergency coronary artery bypass graft; 2) elective or emergency percutaneous coronary intervention; 3) acute myocardial infarction (ICD-10 I21); and 4) acute myocardial ischemia (ICD-10 I20) 6 months to 2 years prior to the date of the present investigation were selected for the study. The median time between the index event and the present investigation was 1.1 years (interquartile range 0.8–1.6).

A comprehensive description of the study protocol and glycemic status assessment has been given elsewhere (23,24). At baseline, 4,440 of the 8,261 patients in the survey did not have a history of diabetes and underwent screening for dysglycemia with an OGTT comprising an FPG and a 2hPG, as well as measurement of HbA_{1c} (24).

Research personnel trained for the study procedures conducted a standardized interview, including personal and demographic details, lifestyle habits, and medical history, and performed a physical examination (23).

Definitions

Dysglycemia

The reference values for dysglycemia were those recommended by the World Health Organization (i.e., a 2hPG value ≥ 11.1 mmol/L [200 mg/dL] for T2DM and a 2hPG ≥ 7.8 –11.0 mmol/L [140–200 mg/L] for IGT) (25).

Smoking

Smoking was defined as self-reported smoking habits and/or a breath carbon monoxide >10 ppm by means of

Smokerlyzer (Model Micro+; Bedfont Scientific Limited) at the time of interview.

Height and Weight

Height and weight were measured in indoor clothes without shoes (SECA scales 701 and measuring stick model 220).

Obesity

Obesity was defined as a BMI ≥ 30 kg/m².

Waist Circumference

Waist circumference was measured in the standing position by a metal tape placed horizontally in the midaxillary line midway between the lowest rim of the rib cage and the superior iliac crest (26).

Central Obesity

Central obesity was defined as a waist circumference ≥ 102 cm for men or ≥ 88 cm for women.

The physical activity target was defined by the following question: “Do you take regular physical activity of at least 30-min duration on average 5 times a week?”

Low educational level was defined as having attended primary school only or less.

Blood pressure was measured twice on the right upper arm with the participant in the sitting position using an automatic digital sphygmomanometer (Omron M6).

HOMA of insulin resistance (HOMA-IR) was calculated according to the formula

$$\text{HOMA-IR} = \frac{\text{glucose (mmol/L)} \times \text{insulin } (\mu\text{U/mL})}{22.5}$$

HOMA2 based on insulin (HOMA2-ins) and HOMA2 based on C-peptide (HOMA2-Cpep) were obtained by the calculator at <https://www.dtu.ox.ac.uk/homacalculator/>. The HOMA2 model is an updated version of the HOMA model that accounts for variations in hepatic and peripheral glucose resistance and the contribution of circulating proinsulin (27). In both cases, low HOMA values indicate high insulin sensitivity, whereas high HOMA-IR values indicate low insulin sensitivity (i.e., insulin resistance).

Laboratory Measurements

Venous blood specimen was drawn for a lipid assessment and HbA_{1c} carried out at the central laboratory in Helsinki (Biomarkers Team, Finnish Institute for Health and Welfare, Helsinki, Finland, accredited

by the Finnish Accreditation Service and fulfilling requirements of the standard SFS-EN ISO/IEC 17025:2017). The scope of accreditation covers all analyses, except for C-peptide. Specific assays used have been previously reported (23). Plasma glucose obtained from the OGTT in the fasting state and after 2 h was analyzed with the validated point-of-care technique HemoCue (Glucose 201RT; HemoCue, Ängelholm, Sweden) (28,29).

Fasting serum insulin and C-peptide were measured on frozen plasma samples, obtained during the OGTT, and stored at the central laboratory in Helsinki at -70°C . Both insulin and C-peptide were measured using chemiluminescent micro-particle immunoassay (Abbott Laboratories, Abbott Park, IL) on a clinical immunochemistry analyzer (Architect ci8200; Abbott Laboratories). Sample quality was assessed based on visual evaluation and internal controls. To ensure standardization of measurements, the laboratory took part in External Quality Assessment Schemes organized by Lab-quality (Helsinki, Finland). The coefficient of variation (mean \pm SD) and systematic error (bias) (mean \pm SD) were $2.2 \pm 0.4\%$ and $1.1 \pm 0.2\%$ for insulin and $4.0 \pm 0.7\%$ and $-10.2 \pm 0.5\%$ for C-peptide, respectively.

Statistical Analysis

Descriptive statistics (means, SD, and proportions) were used to present patient characteristics. Patients with and without newly diagnosed dysglycemia were compared according to the Mann-Whitney U test. Since there are no established reference values for HOMA indexes, their optimal thresholds (i.e., the values with the best balance between sensitivity and specificity) were obtained by the maximum value of Youden's J statistic on receiver operator characteristic (ROC) curves. The diagnostic performance of such thresholds was tested for both T2DM (2hPG value ≥ 11 mmol/L) and dysglycemia (2hPG value ≥ 7.8 mmol/L). The associations between 2hPG and the other screening parameters, as well as between HOMA indexes and clinical features, were characterized by Spearman correlation coefficients. All statistical analyses were undertaken using SAS statistical software release V.9.3 (SAS Institute, Cary, NC).

Ethics

Data from the participating centers were collected via an eCRF developed by the ESC-EORP department (European Heart House, Sophia Antipolis, France). They were checked for completeness, internal consistency, and accuracy and stored under the provisions of the National Data Protection Regulations.

Local ethics committees' approvals were obtained by national coordinators. Each participant provided written informed consent that was stored in the patient file.

Role of the Funding Source

The sponsors and supporters had no role in the design, data collection, data analysis, data interpretation, decision to publish, or writing the manuscript.

Data and Resource Availability

The study protocol, statistical analysis plan, and results can be made available upon reasonable request to the authors who are guarantors of this work (G.F., D.D.B., and L.R.) via e-mail to the corresponding author, with no time limits. Deidentified individual patient data can be made available after approval of a proposal, with a signed agreement, with the European Society of Cardiology administrative headquarters: European Heart

House, Les Templiers, 2035 Route des Colles, CS 80179 Biot, 06903 Sophia Antipolis Cedex, France.

RESULTS

A total of 4,440 patients underwent an OGTT, from whom 4,036 samples were received and stored at the central laboratory. The present analysis was performed on samples from 3,534 of the study participants, as those from 502 patients were considered unreliable according to the quality assessments as detailed in Fig. 1.

Baseline characteristics of the study population are reported in Table 1. The mean age of the patients was 63 years, and 25% were women. As regards the CV risk factors, 54% of the patients had central obesity, 18% were current smokers, mean blood pressure was 133/80 mmHg, and mean LDL-cholesterol 2.4 mmol/L. The OGTT revealed that 1,439 (41%) of the 3,534 with available insulin and C-peptide values were dysglycemic (IGT, 24%; T2DM, 16%) (Fig. 1). The complete glycemic profile, including the FPG, 2hPG, HbA_{1c}, fasting serum insulin, and C-peptide and HOMA indexes, is reported in Table 1.

The mean values of all different screening tests were significantly higher in patients

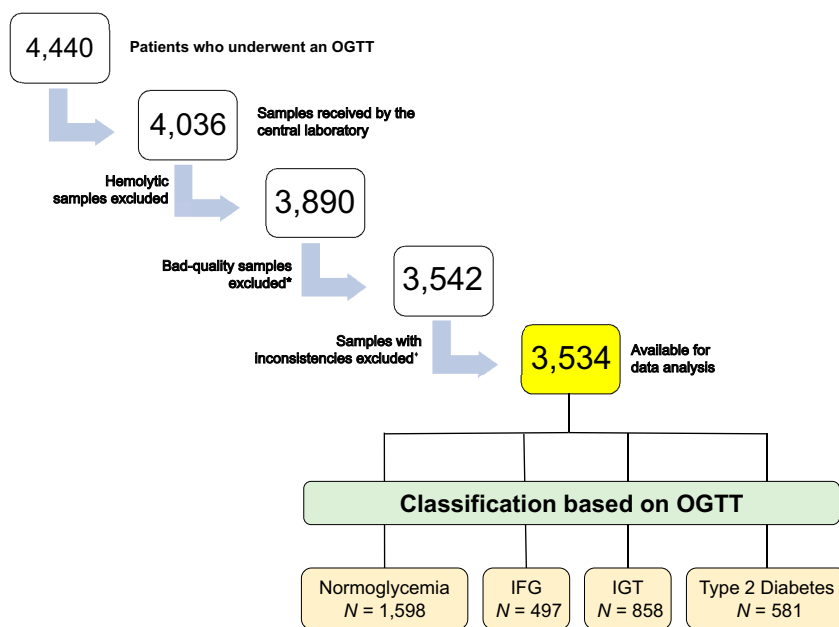


Figure 1—Sample selection. Flowchart describing the sample selection process and reasons for sample exclusion. In total, 3,534 samples were considered for the current analyses. The glycemic status of patients was classified based on the results of the OGTT. IFG, impaired fasting glucose. *Bad quality includes samples with extremely out-of-range insulin and/or C-peptide values and out-of-range calcium values and samples that arrived in poor condition at visual assessment. ♦Inconsistencies includes molar ratio of insulin to C-peptide > 1 .

Table 1—Baseline characteristics of the study population

Variable	All (n = 3,534)	Men (N = 2,667)	Women (N = 867)
Age (years)	63.4 (9.6)	62.8 (9.7)	65.4 (9.1)
Low educational level	11.9 (418)	11.2 (297)	14.0 (121)
Current smoking	18.1 (640)	19.1 (510)	15.0 (130)
Low physical activity	61.5 (1,977)	58.8 (1,433)	69.8 (544)
Cardiovascular medical history			
CABG	17.7 (624)	19.8 (528)	11.1 (96)
PCI	83.8 (2,960)	84.1 (2,244)	82.6 (716)
Stroke	3.4 (120)	3.0 (79)	4.7 (41)
Heart failure	4.4 (155)	3.9 (104)	5.9 (51)
Clinical assessment			
BMI (kg/m ²)	28.7 (4.6)	28.7 (4.4)	28.9 (5.4)
Obesity (BMI ≥30 kg/m ²)	34.4 (1,214)	33.2 (885)	38.2 (329)
Waist circumference (cm)	100.2 (12.5)	101.6 (11.9)	95.7 (13.4)
Central obesity	54.3 (1,851)	48.3 (1,249)	72.8 (602)
Systolic blood pressure (mmHg)	133 (18)	134 (18)	132 (19)
Diastolic blood pressure (mmHg)	80 (11)	81 (11)	79 (11)
Heart rate (bpm)	89 (139)	90 (144)	84 (122)
Laboratory assessment (serum)			
Total cholesterol (mmol/L)	4.3 (1.2)	4.2 (1.1)	4.7 (1.3)
LDL-cholesterol (mmol/L)	2.4 (1.0)	2.4 (0.9)	2.7 (1.1)
HDL-cholesterol (mmol/L)	1.2 (0.3)	1.1 (0.3)	1.4 (0.3)
Triglycerides (mmol/L)	1.5 (1.0)	1.5 (1.0)	1.5 (0.9)
Creatinine (mg/dL)	87.9 (27.8)	91.9 (28.9)	75.5 (19.6)
eGFR (mL/min/1.73 m ²)	83.9 (19.3)	79.9 (17.6)	96.3 (18.9)
Glycometabolic status			
FPG (mmol/L)	5.9 (0.9)	6.0 (0.9)	5.9 (0.9)
2hPG (mmol/L)	7.6 (2.5)	7.5 (2.5)	7.8 (2.5)
HbA _{1c} (%) [mmol/mol]	5.6 (0.4) [37]	5.6 (0.4) [37]	5.6 (0.4) [38]
Fasting serum insulin (μU/mL)	11.4 (6.6)	11.4 (6.5)	11.4 (6.9)
Fasting serum C-peptide (nmol/L)	0.74 (0.36)	0.75 (0.36)	0.73 (0.37)
HOMA-IR	3.1 (2.0)	3.1 (1.9)	3.0 (2.0)
HOMA2-ins	1.5 (0.9)	1.5 (0.9)	1.5 (0.9)
HOMA2-Cpep	1.7 (0.9)	1.7 (0.8)	1.7 (0.9)
Cardiovascular medical therapy			
RAAS blockers	74.6 (2,616)	74.6 (1,977)	74.5 (639)
β-Blockers	79.3 (2,785)	79.1 (2,098)	80.0 (687)
Antiaggregant	93.1 (3,270)	93.4 (2,476)	92.2 (794)
Lipid-lowering	84.7 (2,971)	85.4 (2,262)	82.5 (709)

Data are percent (n) or mean (SD) unless otherwise indicated. CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; RAAS, renin-angiotensin-aldosterone system.

with versus without newly diagnosed dysglycemia (all $P < 0.0001$) as reported in Table 2.

The optimal thresholds identified by the ROC analyses for different glycemic parameters are showed in Table 3 as regards their diagnostic performance for T2DM (2hPG value ≥ 11 mmol/L) and dysglycemia (2hPG value ≥ 7.8 mmol/L). Table 3 reports the diagnostic performances of HOMA-IR, HOMA2-ins, HOMA2-Cpep, fasting serum insulin, and fasting serum C-peptide for patients with newly detected T2DM, identified by a 2hPG value ≥ 11.1 mmol/L, and with newly detected dysglycemia (IGT and T2DM),

identified by a 2hPG value ≥ 7.8 mmol/L. The diagnostic performance of HOMA indexes in detecting dysglycemia was slightly worse than FPG or HbA_{1c}, but this difference was not significant (data not shown).

There were no differences in the diagnostic performance of HOMA indexes between men and women or in participants older and younger than 65 years of age.

The associations between 2hPG and the other parameters in the total sample were weak, with Spearman correlation coefficients of 0.15 for fasting insulin, 0.19 for C-peptide, 0.24 for HOMA-IR, 0.18 for HOMA2-ins, and 0.22 for HOMA2-Cpep.

HOMA-IR, HOMA2-ins, and C-peptide were strongly correlated with BMI (Spearman correlation coefficient 0.47 for all three parameters) and waist circumference (Spearman correlation coefficient 0.43, 0.44, and 0.44, respectively). In contrast, FPG, 2hPG, and HbA_{1c} did not have any strong correlation with either BMI (Spearman correlation coefficient 0.14, 0.15, and 0.21, respectively) or waist circumference (Spearman correlation coefficient 0.16, 0.15, and 0.19, respectively).

CONCLUSIONS

To the best of our knowledge, this is the first attempt to use expressions of

Table 2—Glycemic parameters in patients with CAD without vs. with newly diagnosed dysglycemia

	No dysglycemia (N = 2,095)	Newly diagnosed dysglycemia (N = 1,439)
FPG (mmol/L)	5.6 (0.7)	6.4 (1.0)
2hPG (mmol/L)	6.1 (1.1)	9.8 (2.3)
HbA _{1c} (%) [mmol/mol]	5.5 (0.3) [37]	5.7 (0.5) [39]
Fasting serum insulin (μU/mL)	10.7 (6.2)	12.4 (7.0)
Fasting serum C-peptide (nmol/L)	0.7 (0.3)	0.8 (0.37)
HOMA-IR	2.7 (1.6)	3.6 (2.2)
HOMA2-ins	1.4 (0.8)	1.7 (0.9)
HOMA2-Cpep	1.6 (0.8)	1.9 (0.9)

Data are mean (SD) unless otherwise indicated. Dysglycemia is defined as either IGT or T2DM according to the OGTT.

insulin resistance as screening tools for dysglycemia in a high-risk population of patients with CAD. However, the substitution of the OGTT with HOMA-IR, HOMA2-ins, and HOMA2-Cpep did not turn out to be reliable, still leaving OGTT as the best screening tool for dysglycemia. Overall, the sensitivity and specificity of HOMA indexes, fasting insulin, and C-peptide were low and poorly correlated with the result of the OGTT. Internationally recommended thresholds of FPG and HbA_{1c} for the screening of T2DM and IGT had a higher specificity than all of the other tests.

To detect T2DM, international guidelines put different emphasis on different tests: ESC/European Association for the Study of Diabetes European guidelines on diabetes, prediabetes, and CVD recommend to start with FPG or HbA_{1c} and to proceed to OGTT if the results are

uncertain (16); the American Diabetes Association guidelines equally recommend the use of HbA_{1c}, FPG, and 2hPG (30); the World Health Organization points out the discrepancies among the three tests, specifying that HbA_{1c} ≥48 mmol/mol may be superior for the prediction of retinopathy (31) and that its assessment is unreliable in common conditions, such as pregnancy, recent blood loss, transfusion, erythropoietin therapy, hemoglobinopathies, anemia, glucose-6-phosphate dehydrogenase deficiency, HIV, and hemodialysis. Since these conditions are more prevalent in countries where the cost of HbA_{1c} is a major issue, the World Health Organization advises policy-makers to ensure that accurate blood glucose measurement should be generally available before introducing HbA_{1c} measurement (31).

Several reasons led us to consider 2hPG as the “gold standard” in the present

work. IGT can only be diagnosed by a 2hPG during the OGTT, and accumulating evidence has established its association with adverse CV outcomes and death (2,14,15,32,33). Second, 2hPG reflects the pathophysiology behind glucose perturbations better than FPG and HbA_{1c}, since it mirrors the postprandial condition, when preserved β-cell function is essential for keeping glucose levels normal (34). Another reason is that the 2hPG by means of the OGTT is more sensitive (i.e., discloses more people with T2DM than FPG and HbA_{1c}). Compared with FPG ≥7 mmol/L or 2hPG ≥11 mmol/L, HbA_{1c} ≥6.5% (48 mmol/mol) has the lowest sensitivity for the diagnosis of T2DM according to the Noncommunicable Disease Risk Factor Collaboration (NCD-RisC) (35). The prevalence of diabetes based on FPG alone was 2–6% lower than that based on 2hPG, and HbA_{1c} seems to underdiagnose T2DM particularly in overweight and obese people (12). Results from the Diabetes Prevention Program highlight the lack of overlap between traditional screening methods among participants with newly diagnosed T2DM, in which only 26% of those diagnosed by FPG or 2hPG also had an HbA_{1c} ≥6.5% (48 mmol/mol), and 55% of those with an HbA_{1c} ≥6.5% (48 mmol/mol) had a current or previous diagnosis of T2DM by FPG or 2hPG (36). These results are confirmed by our previous investigation on EAV, in which only 3.4% of the 4,440 patients undergoing the OGTT had dysglycemia according to all three traditional screening methods (24). Finally, 2hPG is a stronger predictor

Table 3—Diagnostic performance for type 2 diabetes (according to 2hPG value ≥11.1 mmol/L) and dysglycemia (according to 2hPG value ≥7.8 mmol/L) of the optimal thresholds of different glycemic parameters obtained by Youden's J statistic on ROC curves

	Threshold	Sensitivity (%)	Specificity (%)	AUC
Patients with newly detected type 2 diabetes (N = 581)				
HOMA-IR	2.73	68.0	57.2	0.66
HOMA2-ins	1.32	65.0	51.8	0.61
HOMA2-Cpep	1.69	65.6	59.3	0.64
Fasting serum insulin (μU/mL)	7.9	79.2	35.2	0.59
Fasting serum C-peptide (nmol/L)	0.74	61.7	60.4	0.62
Patients with newly detected dysglycemia (N = 1,439)				
HOMA-IR	2.81	54.9	64.1	0.62
HOMA2-ins	1.32	58.2	55.3	0.59
HOMA2-Cpep	1.44	67.6	49.7	0.61
Fasting serum insulin (μU/mL)	7.9	50.3	61.7	0.57
Fasting serum C-peptide (nmol/L)	0.63	65.6	49.8	0.59

AUC, area under the curve.

of future CVD than FPG and HbA_{1c} in patients with CVD (2,15,33,37).

Unfortunately, an OGTT requires people to fast, it takes time, and it is more expensive than HbA_{1c} (9). Several of these drawbacks could be resolved by having a different test. The idea behind HOMA assessments is that they may be able to identify early glucometabolic disturbances, complying with the necessity of a screening test to be capable of detecting a high proportion of disease in its preclinical state (38). Moreover, insulin resistance measured by HOMA can be targeted by insulin-sensitizing interventions. This was the pathophysiological basis of the IRIS trial, which eventually proved the benefit of pioglitazone on major CV outcomes in a population without diabetes but insulin resistance and established CVD (18). In the IRIS trial, a cutoff value of 3 for HOMA-IR was chosen based on a single previous study in which it marked the highest quartile of insulin resistance in a small population sample without known diabetes (39). It must be kept in mind that, to date, no cutoff to define insulin resistance has been established, since data from large, high-risk populations are missing and no medications are specifically approved to treat insulin resistance. Thus, we calculated the optimal thresholds of HOMA-IR, HOMA2-ins, and HOMA2-Cpep by ROC curve analysis. Despite finding values quite close to 3 for HOMA-IR, none of these indexes performed well enough in terms of sensitivity and specificity for diagnosing dysglycemia based on the OGTT results. Indeed, the frequency of false positives was too high to consider HOMA indexes as good screening tests for dysglycemia. One possible explanation is that HOMA indexes mirror metabolic derangements beyond the glycemic status: accordingly, we found a strong correlation with BMI and waist circumference (i.e., markers of visceral fat). This positive correlation between visceral adiposity and insulin resistance has been extensively reported in adults with and without T2DM with varying CVD profiles (40,41). Results from the study by D'Agostino et al. (42) and from the ARIC study (43) reported that the classic risk factors for atherosclerotic CVD only explain ~70% of observed CV events, and it has been postulated that insulin resistance might be responsible for the remaining 30% (44). In conclusion, presently, the OGTT should be prioritized

to identify dysglycemia despite its practical drawbacks (24). Meanwhile, further studies are warranted to establish whether some measures of insulin resistance could be better markers of metabolic derangement and predictors of CV events in high-risk populations.

Strengths and Limitations

The main strength of our report is that in the EAV registry, all data were obtained from the standardized interviews and examinations, performed by specifically trained personnel, in a large cross-sectional population with CAD from 27 European countries. Serum insulin, C-peptide, and HbA_{1c} were measured at the central laboratory with the same assay, and careful sample selection and quality assessments were performed. Likewise, FPG and 2hPG were assessed by the HemoCue 201+ equipment for glucose determination with the appropriate quality control (28).

A possible limitation of this study is that screening for dysglycemia was only performed once, while current guidelines recommend at least two positive results to confirm the diagnosis of T2DM (25). However, in patients with an acute coronary event, a single OGTT at least 4 to 5 days after symptom onset correctly classified patients with dysglycemia by strongly correlating with subsequent tests at 3 and 12 months (45).

Conclusion

Screening for dysglycemia in patients with CAD by means of serum insulin, C-peptide, HOMA-IR, HOMA2-ins, and HOMA2-Cpep had a low sensitivity and specificity to detect glucometabolic abnormalities compared with the gold-standard 2hPG.

Acknowledgments. The EUROASPIRE Study Group thanks the administrative staff, physicians, nurses, and other personnel in the hospitals in which the survey was carried out and all patients who participated in the surveys. The EORP Oversight Committee, Registry Executive, and Steering Committees provided assistance. The study coordination was conducted by the EORP department from the ESC (Emanuela Fiorucci as Project Officer; Viviane Missiamenou, Gagan Chhabra, and Florian Larras as Data Managers; and Clara Berlé as Clinical Project Manager). A complete list of the investigators in EUROASPIRE V can be found in the supplementary material online.

Funding. EAV was carried out under the auspices of the European Society of Cardiology, EURObservational Research Programme. The survey was supported through research grants to the European Society of Cardiology from Amarin Corporation, Amgen, Daiichi Sankyo Company, Eli Lilly and Company, Grupo Ferrer Internacional, S.A., Novo Nordisk, Pfizer, and Sanofi. This investigation received financial support from Familjen Erling-Perssons Stiftelse and Irstadska Stiftelsen (grants to G.F. and L.R.).

The sponsors and supporters had no role in the design, data collection, data analysis, data interpretation, decision to publish, or writing the manuscript.

Duality of Interest. G.F. has received grant support from the Familjen Erling-Perssons Stiftelse for this work and speaker fees from the European Society of Cardiology, outside of the present work. V.G. has received research grants from the Swedish Heart-Lung Foundation and speaker fees outside this work from Novo Nordisk, MSD Sweden, and Boehringer Ingelheim. K.K. has received research grants from the European Society of Cardiology. L.M. reports personal fees from Novo Nordisk, Sanofi Aventis, AstraZeneca, Merck Sharp & Dohme, Boehringer Ingelheim, Novartis, and Amgen outside the submitted work. A.N. has received research grants from the Swedish Heart-Lung Foundation and Stockholm County Council and honorarium from advisory board meetings outside this work from AstraZeneca, Novo Nordisk, MSD Sweden, and Boehringer Ingelheim. J.T. has received research grants from Bayer and consultation fees from Eli Lilly and Company and owns stocks from Orion Corporation and Aktivolabs, outside the submitted work. L.R. has received research grants from the Swedish Heart-Lung Foundation, Stockholm County, Familjen Erling-Perssons Stiftelse, and Irstadska Stiftelsen. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. G.F., D.D.B., and L.R. are responsible for conceptualization, statistical planning, quality assessment, data analysis, interpretation, literature search, manuscript drafting, critical revision, and administrative handling. D.D.B. is responsible for conceptualization, data analysis, interpretation, manuscript drafting, and critical revision. V.G., K.K., L.M., A.N., O.S., J.T., and D.W. contributed to planning, interpretation, and critical revision of the manuscript. I.E. and T.V. were responsible for sample analysis, quality assessment, data handling, and critical revision of the manuscript. All authors agreed to be accountable for all aspects of work, ensuring integrity and accuracy, and gave final approval of publication. G.F. and L.R. are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Rawshani A, Rawshani A, Franzén S, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2018;379:633–644
2. Shahim B, De Bacquer D, De Backer G, et al. The prognostic value of fasting plasma glucose, two-hour postload glucose, and HbA_{1c} in patients

- with coronary artery disease: a report from EUROASPIRE IV: a survey from the European Society of Cardiology. *Diabetes Care* 2017;40:1233–1240
3. International Diabetes Federation. *IDF Diabetes Atlas*, 9th edition, 2019. Accessed 29 April 2022. Available from <https://www.diabetesatlas.org/en/>
 4. Norhammar A, Tenerz A, Nilsson G, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet* 2002;359:2140–2144
 5. Hu DY, Pan CY; China Heart Survey Group. The relationship between coronary artery disease and abnormal glucose regulation in China: the China Heart Survey. *Eur Heart J* 2006;27:2573–2579
 6. Johansen OE, Birkeland KI, Brustad E, et al. Undiagnosed dysglycaemia and inflammation in cardiovascular disease. *Eur J Clin Invest* 2006;36:544–551
 7. De Bacquer D, Ueda P, Reiner Ž, et al.; EUROASPIRE IV and V National Coordinators. Prediction of recurrent event in patients with coronary heart disease: the EUROASPIRE risk model. *Eur J Prev Cardiol* 2022;29:328–339
 8. Standl E, Schnell O, McGuire DK, Ceriello A, Rydén L. Integration of recent evidence into management of patients with atherosclerotic cardiovascular disease and type 2 diabetes. *Lancet Diabetes Endocrinol* 2017;5:391–402
 9. Sattar N, Preiss D. Screening for diabetes in patients with cardiovascular disease: HbA1c trumps oral glucose tolerance testing. *Lancet Diabetes Endocrinol* 2016;4:560–562
 10. Rydén L, Gyberg V, Schnell O; EUROASPIRE IV investigators. Oral glucose tolerance testing and cardiovascular disease. *Lancet Diabetes Endocrinol* 2016;4:732–733
 11. American Diabetes Association Professional Practice Committee. 2. Classification and diagnosis of diabetes: *Standards of Medical Care in Diabetes—2022*. *Diabetes Care* 2022;45:S17–S38
 12. Meijnikman AS, De Block CEM, Dirinck E, et al. Not performing an OGTT results in significant underdiagnosis of (pre)diabetes in a high risk adult Caucasian population. *Int J Obes* 2017;41:1615–1620
 13. Gyberg V, De Bacquer D, Kotseva K, et al.; EUROASPIRE IV Investigators. Screening for dysglycaemia in patients with coronary artery disease as reflected by fasting glucose, oral glucose tolerance test, and HbA1c: a report from EUROASPIRE IV—a survey from the European Society of Cardiology. *Eur Heart J* 2015;36:1171–1177
 14. Tamita K, Katayama M, Takagi T, et al. Newly diagnosed glucose intolerance and prognosis after acute myocardial infarction: comparison of post-challenge versus fasting glucose concentrations. *Heart* 2012;98:848–854
 15. Schnell O, Doerr R, Ludwig V, Weissmann J, Lohmann T. A 3-year follow-up of the Silent Diabetes Study. *Diabetologia* 2014;57:2596–2598
 16. Cosentino F, Grant PJ, Aboyans V, et al.; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020;41:255–323
 17. Viscoli CM, Brass LM, Carolei A, et al.; IRIS Trial investigators. Pioglitazone for secondary prevention after ischemic stroke and transient ischemic attack: rationale and design of the Insulin Resistance Intervention after Stroke Trial. *Am Heart J* 2014;168:823–9.e6
 18. Kernan WN, Viscoli CM, Furie KL, et al.; IRIS Trial Investigators. Pioglitazone after ischemic stroke or transient ischemic attack. *N Engl J Med* 2016;374:1321–1331
 19. Reaven GM. Banting lecture 1988: role of insulin resistance in human disease. *Nutrition* 1997;13:64; discussion 65, 66
 20. 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;28:412–419
 21. Odegaard JI, Chawla A. Pleiotropic actions of insulin resistance and inflammation in metabolic homeostasis. *Science* 2013;339:172–177
 22. Lu MC, Fang WC, Li WC, Yeh WC, Shieh YH, Chen JY. The association between insulin resistance and cardiovascular disease risk: a community-based cross-sectional study among Taiwanese people aged over 50 years. *Int J Environ Res Public Health* 2020;17:7195
 23. Kotseva K, De Backer G, De Bacquer D, et al.; EUROASPIRE V Investigators. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. *Eur J Prev Cardiol* 2019;26:824–835
 24. Ferrannini G, De Bacquer D, De Backer G, et al.; EUROASPIRE V collaborators. Screening for glucose perturbations and risk factor management in dysglycemic patients with coronary artery disease—a persistent challenge in need of substantial improvement: a report From ESC EORP EUROASPIRE V. *Diabetes Care* 2020;43:726–733
 25. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation [article online], 2020. Accessed 13 June 2022. Available from <https://apps.who.int/iris/handle/10665/43588>
 26. Lean ME, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. *BMJ* 1995;311:158–161
 27. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. *Diabetes Care* 1998;21:2191–2192
 28. Segerhag E, Gyberg V, Ioannides K, et al. Accuracy of a simplified glucose measurement device—the HemoCue Glucose 201RT. *Diabetes Technol Ther* 2015;17:755–758
 29. D’Orazio P, Burnett RW, Fogh-Andersen N, et al.; IFCC-SD-WG-SEPOCT. Approved IFCC recommendation on reporting results for blood glucose: International Federation of Clinical Chemistry and Laboratory Medicine Scientific Division, Working Group on Selective Electrodes and Point-of-Care Testing (IFCC-SD-WG-SEPOCT). *Clin Chem Lab Med* 2006;44:1486–1490
 30. American Diabetes Association. 2. Classification and diagnosis of diabetes: *Standards of Medical Care in Diabetes—2021*. *Diabetes Care* 2021;44(Suppl. 1):S15–S33
 31. World Health Organization. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus: Abbreviated Report of a WHO Consultation, 2019. Accessed 6 October 2021. Available from <https://www.ncbi.nlm.nih.gov/books/NBK304267/>
 32. Ritsinger V, Tanogldi E, Malmberg K, et al. Sustained prognostic implications of newly detected glucose abnormalities in patients with acute myocardial infarction: long-term follow-up of the Glucose Tolerance in Patients with Acute Myocardial Infarction cohort. *Diab Vasc Dis Res* 2015;12:23–32
 33. Chattopadhyay S, George A, John J, Sathyapalan T. Adjustment of the GRACE score by 2-hour post-load glucose improves prediction of long-term major adverse cardiac events in acute coronary syndrome in patients without known diabetes. *Eur Heart J* 2018;39:2740–2745
 34. Færch K, Johansen NB, Witte DR, Lauritzen T, Jørgensen ME, Vistisen D. Relationship between insulin resistance and β -cell dysfunction in subphenotypes of prediabetes and type 2 diabetes. *J Clin Endocrinol Metab* 2015;100:707–716
 35. NCD Risk Factor Collaboration (NCD-RisC). Effects of diabetes definition on global surveillance of diabetes prevalence and diagnosis: a pooled analysis of 96 population-based studies with 331,288 participants. *Lancet Diabetes Endocrinol* 2015;3:624–637
 36. Diabetes Prevention Program Research Group. HbA1c as a predictor of diabetes and as an outcome in the diabetes prevention program: a randomized clinical trial. *Diabetes Care* 2015;38:51–58
 37. Hanefeld M, Fischer S, Julius U, et al. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia* 1996;39:1577–1583
 38. Herman C. What makes a screening exam “good”? *Virtual Mentor* 2006;8:34–37
 39. Ascaso JF, Pardo S, Real JT, Lorente RI, Priego A, Carmena R. Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. *Diabetes Care* 2003;26:3320–3325
 40. Fox CS, Massaro JM, Hoffmann U, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. *Circulation* 2007;116:39–48
 41. Sung HH, Park CE, Gi MY, et al. The association of the visceral adiposity index with insulin resistance and beta-cell function in Korean adults with and without type 2 diabetes mellitus. *Endocr J* 2020;67:613–621
 42. D’Agostino RB Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA* 2001;286:180–187
 43. Golden SH, Folsom AR, Coresh J, Sharrett AR, Szklo M, Brancati F. Risk factor groupings related to insulin resistance and their synergistic effects on subclinical atherosclerosis: the Atherosclerosis Risk in Communities study. *Diabetes* 2002;51:3069–3076
 44. Di Pino A, DeFronzo RA. Insulin resistance and atherosclerosis: implications for insulin-sensitizing agents. *Endocr Rev* 2019;40:1447–1467
 45. 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;31:36–38