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

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OBJECTIVE

Three tests are recommended for identifying dysglycemia: fasting glucose (FPG), 2-h postload glucose (2h-PG) from an oral glucose tolerance test (OGTT), and glycated hemoglobin A_{1c} (HbA_{1c}). This study explored the prognostic value of these screening tests in patients with coronary artery disease (CAD).

RESEARCH DESIGN AND METHODS

FPG, 2h-PG, and HbA_{1c} were used to screen 4,004 CAD patients without a history of diabetes (age 18–80 years) for dysglycemia. The prognostic value of these tests was studied after 2 years of follow-up. The primary end point included cardiovascular mortality, nonfatal myocardial infarction, stroke, or hospitalization for heart failure and a secondary end point of incident diabetes.

RESULTS

Complete information including all three glycemic parameters was available in 3,775 patients (94.3%), of whom 246 (6.5%) experienced the primary end point. Neither FPG nor HbA_{1c} predicted the primary outcome, whereas the 2h-PG, dichotomized as <7.8 vs. ≥7.8 mmol/L, was a significant predictor (hazard ratio 1.38, 95% CI 1.07–1.78; P = 0.01). During follow-up, diabetes developed in 78 of the 2,609 patients (3.0%) without diabetes at baseline. An FPG between 6.1 and 6.9 mmol/L did not predict incident diabetes, whereas HbA_{1c} 5.7–6.5% and 2h-PG 7.8–11.0 mmol/L were both significant independent predictors.

CONCLUSIONS

The 2h-PG, in contrast to FPG and HbA_{1c}, provides significant prognostic information regarding cardiovascular events in patients with CAD. Furthermore, elevated 2h-PG and HbA_{1c} are significant prognostic indicators of an increased risk of incident diabetes.

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Undetected dysglycemia, defined as diabetes and its prestates impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), is common in patients with coronary artery disease (CAD) (1,2), and its presence influences the prognosis of CAD unfavorably (3–5). Early identification of dysglycemia is a prerequisite for the institution of preventive measures according to contemporary guidelines (6–8).

For the diagnosis of diabetes, IGT and IFG, fasting plasma glucose (FPG), 2-h postload glucose (2h-PG) from an oral glucose tolerance test (OGTT), and glycated hemoglobin A_{1c} (HbA_{1c}) can all be used (6,9,10). The definition of diabetes with a break point at an FPG >7 mmol/L relates to the increasing risk for retinopathy in patients with diabetes (11). From a macrovascular point of view this cut point may not be similarly useful. HbA_{1c}, historically used for monitoring of glycemic control and to identify patients with a high risk of microvascular complications (i.e., retinopathy and microalbuminuria) (9), was added as a diagnostic tool of diabetes in 2010 by the American Diabetes Association (ADA) and shortly thereafter adopted by the World Health Organization (10,12).

There is an ongoing debate regarding the most preferable test to identify dysglycemia in the presence of CAD. The debate is mainly focused around the lower sensitivity of FPG and HbA_{1c} than OGTT, but the latter test is more time consuming, and the reproducibility of 2h-PG has been questioned (13,14). Guidelines from the ADA endorse all three methods to detect diabetes as equally appropriate (10), whereas the European Society of Cardiology guidelines recommend that screening should be initiated with FPG and/or HbA_{1c}, followed by an OGTT if these tests are negative (6). Besides feasibility, sensitivity, and reproducibility, the prognostic information regarding cardiovascular events and the development of incident diabetes is crucially important when defining the most appropriate screening method for dysglycemia in CAD patients, but the availability of such information is limited.

The EUROpean Action on Secondary and Primary prevention through Intervention to Reduce Events (EUROASPIRE IV) survey compared the diagnostic features of HbA_{1c}, FPG, and 2h-PG in 4,004 well-characterized patients with CAD without previously known diabetes (15). The objective of the present follow-up of this cohort was to study the prognostic information of FPG, 2 h-PG, and HbA_{1c} as regards subsequent cardiovascular events and the predictive value for incident diabetes.

RESEARCH DESIGN AND METHODS

Study Population

The EUROASPIRE IV survey was conducted at 79 centers in 24 European countries during May 2012 to April 2013. Men and women aged ≥18–80 years had been hospitalized for a first or recurrent CAD event at a time 6–36 months before enrollment in the survey: *1*) coronary artery bypass grafting (CABG), *2*) percutaneous coronary intervention (PCI), *3*) acute myocardial infarction (AMI) (ICD-10 code 121), and *4*) acute myocardial ischemia (ICD-10 code 120). A detailed description of the survey has been given elsewhere (15). The present population comprised 4,004 patients without any history of diabetes at the baseline investigation. Screening for dysglycemia with an OGTT and HbA_{1c} revealed that 1,161 individuals (29%) had previously unrecognized diabetes (15).

Methods

Trained research staff collected data at a baseline outpatient visit according to standardized methods, including an interview and examination supported by information from relevant hospital records. A detailed description of this procedure and applied definitions has been presented elsewhere (15). Methods of particular relevance for the present investigation are described here. Height (cm) and weight (kg) were recorded in light indoor clothes without shoes (Scales 701 and Measuring stick model 220; SECA Medical Measuring Systems and Scales, Birmingham, U.K.). Waist circumference was measured using a metal tape applied horizontally at the point midway in the midaxillary line between the lowest rim of the rib cage and the tip of the hip bone (superior iliac crest) with the patient standing (16). Blood pressure was recorded with the patient sitting with an automatic sphygmomanometer (Omron M6; OMRON Corporation, Kyoto, Japan). Physical activity was assessed by means of the International Physical Activity Questionnaire (IPAQ; IPAQ core group, Karolinska Institutet, Stockholm, Sweden). Anxiety and depression scores were estimated by means of the Hospital Anxiety and Depression Scale (HADS) questionnaires.

Laboratory Investigations

Venous blood was drawn in the fasting state (≥10 h). Total and HDL cholesterol and triglycerides were analyzed on a clinical chemistry analyzer (Abbot Architect Analyzer; Abbott Laboratories, Abbott Park, IL) using an enzymatic method for measuring total cholesterol. LDL cholesterol was calculated according to the Friedewald formula. HbA_{1c} (mmol/mol and %), aligned with the Diabetes Control and Complications Trial (DCCT), was measured with an immunoturbidimetric International Federation of Clinical Chemistry and Laboratory Medicine–aligned method (Abbot Architect Analyzer) in fasting venous whole blood sampled in an EDTA tube. All of these analyses were performed at a central laboratory (Disease Risk Unit, National Institute for Health and Welfare, Helsinki, Finland) accredited by the Finnish Accreditation Service fulfilling the requirements of the standard SFS-EN International Organization for Standardization/International Electrotechnical Commission 17025:2005.

An OGTT (75 g glucose in 200 mL water) was performed in the morning after a fast of ≥10 h. Blood for FPG was drawn from the EDTA tube, which was collected for HbA_{1c} before intake of glucose. Samples for the 2h-PG were drawn from whole venous blood. Plasma glucose was analyzed locally with a photometric point-of-care technique (Glucose 201+; HemoCue, Ängelholm, Sweden). The values were converted from whole venous blood to plasma by applying the formula by Carstensen et al. (17): plasma glucose = 0.558 + 1.119 × whole blood glucose. The standardized use of the HemoCue equipment was ascertained via central training of all data collectors. Further details on the point-of-care glucose measurements can be derived from Gyberg et al. (15).

Definitions

Dysglycemia was defined according to the ADA and World Health Organization (7,11) as outlined in Table 1.

Overweight was defined as a BMI 25.0–29.9 kg/m^2 and obesity as a BMI ≥30 kg/m^2. Central obesity was defined as a waist circumference of ≥88 cm for women and ≥102 cm for men (16).

Blood pressure was defined as elevated if systolic blood pressure (SBP) was ≥140 mmHg and/or diastolic blood pressure (DBP) was ≥90 mmHg.

Table 1—Definitions of dysglycemia

Test/diagnostic tool	Cutoff level	
HbA_{1c}	% DCCT	mmol/mol
High-risk HbA_{1c}	5.7–6.4	39–47
Diabetes	≥6.5	≥48
Plasma glucose	mmol/L	mg/dL
IFG		
Fasting	6.1–6.9	110–125
2h-PG	<7.8	<140
IGT		
Fasting	<7.0	<126
2h-PG	≥7.8–11.0	≥140–199
Diabetes		
Fasting	>7.0	>126
2h-PG	≥11.1	≥200

Smoking was defined as self-reported smoking or an exhaled carbon monoxide >10 ppm (18).

The physical activity target was defined as vigorous physical activity outside work for ≥20 min at least once per week.

The educational level was defined as low if only primary school or less had been completed.

Follow-up

All centers were asked to complete a single-page follow-up questionnaire for all interviewed and examined participants. To be eligible for the follow-up part of the EUROASPIRE IV survey, information had to cover ≥12 months on ≥90% of the patients from the respective center. Cardiovascular death was recorded as death from CAD, stroke, and other vascular diseases. Noncardiovascular death was recorded as death from cancer or other causes. Deaths without any reported cause were classified as "without known cause." Nonfatal events were recorded as hospitalization for PCI, CABG, AMI, stroke/transient ischemic attack, and heart failure. Follow-up information was obtained from patient interviews, medical records, or external registries or databases (mortality registries, municipal records, and archives) or, if needed, by contacting relatives or a family doctor. Information was requested on vital status and, in case of death, date and cause of death. Information was also obtained on diabetes diagnosed since the baseline investigation. The information on follow-up was based on self-reported information from the patients in 63%, from hospital records in 27%, from external databases in 27%, and from a patient's family member or the family doctor in 3%.

End Points

The primary, composite end point was defined as the first occurrence of one of the following cardiovascular events: cardiovascular death or hospitalization for AMI, stroke/transient ischemic attack, or heart failure. New onset of diabetes constituted the secondary end point.

Data Management

The EURObservational Research Program at the European Heart House, Nice, France, was in charge of data management. All data were collected electronically through a Web-based case record form using a unique identification number for country, center, and individual. The data were submitted online to the data management center, where checks for completeness, internal consistency, and accuracy were performed. All data were stored under the provisions of the National Data Protection Regulations.

Statistical Analyses

Distributions of the baseline characteristics were summarized using means, SDs, and proportions. Included and excluded patients (Table 1) were compared according to Mann-Whitney and χ^2 tests. Hazard ratios (HRs) for the primary and secondary outcomes, their 95% CIs, and statistical significances were estimated using the Cox proportional hazards model. To allow regional variation in the form of the underlying hazard function, Cox regression models were stratified for country. First, HRs and their statistical significance were adjusted for age and sex. Relevant variables (education level, current smoking, BMI, systolic blood pressure, LDL-cholesterol, statin use, level of physical activity, and HADS anxiety and depression score) were then added in a multivariate model to study the independent prognostic role of markers of dysglycemia. The goodness of fit of the models was assessed through the log-likelihood statistic. All statistical analyses were undertaken using SAS 9.3 statistical software at the Department of Public Health, Ghent University, Belgium.

Ethics

The study complies with the Declaration of Helsinki, and national coordinators were responsible for obtaining approvals from Local Research Ethics Committees. Written, informed consent was obtained from each participant.

RESULTS

Information on FPG, OGTT, and HbA_{1c} was available in 4,004 EUROASPIRE IV participants. Follow-up data were obtained from 72 centers in 22 of the participating countries. Seven centers representing 229 patients did not meet the eligibility criteria and were excluded, leaving 3,775 (94.3%) with complete follow-up information (Fig. 1). During the original screening, 1,079 of these patients had diabetes and 2,696 were free from diabetes. Information on incident diabetes was available in 2,609 (97%) of those without diabetes.

The mean follow-up time was 2.03 (SD 0.43) years, and the total number of observed person-years was 7,675. The median age was 64.5 years. Only 9.2% of the patients were younger than 50 years old, and 1.2% were younger than 40 years old. The youngest patient was 26 years old. Seventy-seven percent of the patients were males. Clinical characteristics of patients at the baseline interview and those who were excluded (n = 229) are presented in Table 2. Excluded patients were slightly younger, smoked more often, were less physically active, and had a higher LDL cholesterol and FPG and a higher level of anxiety. There were no major differences in the proportion of the patients with newly detected diabetes (HbA_{1c} ≥6.5% [≥48 mmol/mol], FPG ≥7 mmol/L [>126 mg/dL], and 2h-PG ≥11.1 mmol/L [≥200 mg/dL; data not shown]).

During the follow-up period, 83 deaths (2.2%) were registered. After redistribution of the 15 patients with unknown cause of death according to the same ratio as observed in the deaths with known causes, 42 deaths (51%) were from cardiovascular causes. The all-cause mortality rate was 10.8 per 1,000 person-years in men and in women, and the cardiovascular mortality rate was 4.6 per 1,000 person-years. The primary composite cardiovascular end point occurred in 246 patients (6.5%) (Fig. 1).

The prognostic value of FPG, 2h-PG, and HbA_{1c} in the 3,775 patients with CAD in relation to the primary composite end point, adjusted for age and sex, is presented in Table 3. FPG was not related to the end point when dichotomized below or above 6.1 mmol/L (≥110 mg/dL) or when modeled as a continuous, explanatory variable in a Cox regression

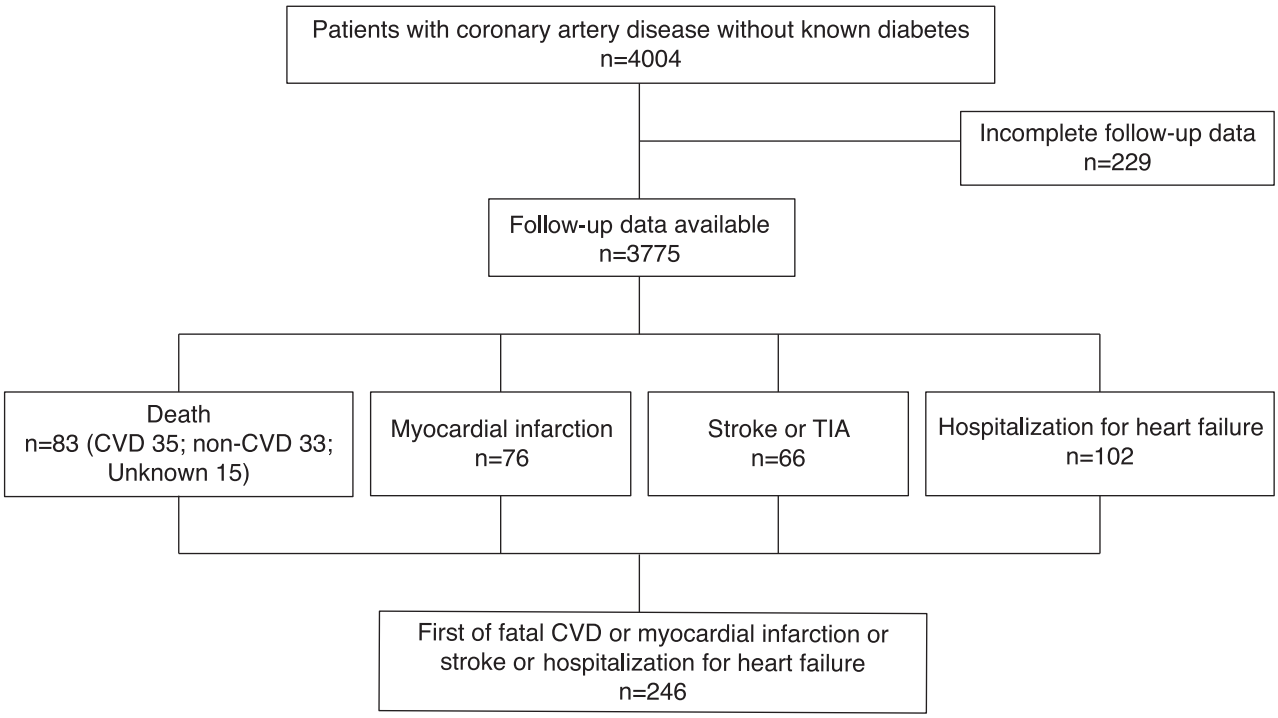

Figure 1—Patient flowchart including information on the components of the composite end point. CVD, cardiovascular disease; TIA, transient ischemic attack.

model. The HR associated with a 1 SD increase in FPG was 1.04 (95% CI 0.92–1.18; $P = 0.52$) after additional adjustment for age and sex. There was no U- or J-shaped relationship between FPG and the primary end point. Adding FPG as a quadratic (or even cubic) effect in the Cox model did not reveal a curvilinear association ($P = 0.27$ for the quadratic term). Likewise, HbA_{1c} was not predictive of the primary end point when indicating diabetes (≥6.5% [≥48 mmol/mol]) or when labeled as expressing high risk for diabetes (5.7–6.4% [39–47 mmol/mol]). In contrast, the 2h-PG indicating IGT or diabetes (i.e., dichotomized as <7.8 [<140 mg/dL] vs. ≥7.8 mmol/L [≥140 mg/dL]) was a statistically significant predictor of the primary end point, with an adjusted HR of 1.38 (95% CI 1.07–1.78; $P = 0.01$). Excluding patients aged 50 years or younger from the analyses did not alter the main results.

In a multivariate Cox regression model adjusted for age, sex, education level, current smoking, BMI, systolic blood pressure, LDL cholesterol, statin use, level of physical activity, and HADS anxiety and depression score, an increment of a 1 mmol/L increase in 2h-PG increased the primary event risk by 6% (HR 1.06; 95% CI 1.01–1.13; $P = 0.03$) independently of the level of HbA_{1c} and FPG. The corresponding increase in the HR for a 1 SD (2.7 mmol/L) increase in 2h-PG was 1.18 (95% CI 1.01–1.38; $P = 0.03$).

Incident diabetes developed during follow-up in 78 of the 2,609 patients free from diabetes at baseline (3%). The associations between FPG, 2h-PG, and HbA_{1c} and incident diabetes are presented in Fig. 2. An FPG between 6.1 and 6.9 mmol/L (110 and 125 mg/dL) was not predictive, whereas HbA_{1c} between 5.7 and 6.4% (39 and 47 mmol/mol) and 2h-PG between 7.8 and 11.0 mmol/L (≥140 and 199 mg/dL) were both significant predictors. Furthermore, HbA_{1c} and 2h-PG provided prognostic information independently of each other.

CONCLUSIONS

The main finding in this comparison of the predictive value of three currently recommended tests for the detection of dysglycemia in patients with CAD and previously undetected dysglycemia was that 2h-PG, but not FPG or HbA_{1c}, added important prognostic information regarding future cardiovascular events. Both elevated 2h-PG and HbA_{1c} but not FPG served as independent indicators of an increased risk of incident diabetes.

Population-based studies have investigated the predictive value of an OGTT. For example the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) and Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia (DECODA) studies comprising people of different ethnicities, with or without known cardiovascular disease, observed that the 2h-PG was a better predictor of all-cause mortality and future cardiovascular events than FPG (19,20). The 2h-PG was compared with HbA_{1c} in two studies that were part of DECODE. Both tests predicted all-cause mortality, but neither FPG nor HbA_{1c} added significant information if 2h-PG was entered into the statistical model (21). In the observational Framingham Offspring Study in people free from cardiovascular disease and treated diabetes, postload glucose was a stronger predictor of future cardiovascular events during a 4-year period than fasting hyperglycemia and HbA_{1c} (22). The Australian Diabetes, Obesity and Lifestyle (AusDiab) Study of 10,026 people without diagnosed diabetes and any history of cardiovascular disease reported that fasting and postload glucose but not HbA_{1c} predicted all-cause

Table 2—Baseline characteristics of the patients with complete and incomplete follow-up data

Variable	Follow-up data available (*n* = 3,775)	Follow-up data incomplete (*n* = 229)	*P*
Recruiting event			0.15
CABG	11.1 (419/3,775)	12.2 (28/229)	
PCI	55.2 (2,083/3,775)	48.9 (112/229)	
AMI	23.2 (877/3,775)	29.3 (67/229)	
Ischemia	10.5 (396/3,775)	9.6 (22/229)	
Age at interview (years)	63.8 (9.69)	60.8 (11.0)	<0.0001
Female sex	23.6 (891/3,775)	22.3 (51/229)	0.69
Time since hospital discharge (years)	1.5 (0.69)	1.5 (0.73)	0.52
Low educational level	16.8 (632/3,750)	20.7 (47/227)	0.15
Current smoking	15.3 (578/3,775)	22.3 (51/229)	0.007
Regular physical activity	45.0 (1,563/3,471)	29.5 (62/210)	<0.0001
BMI (kg/m^2)	28.6 (4.3)	28.2 (4.6)	0.10
Obesity	33.1 (1,249/3,771)	29.0 (66/228)	0.22
Central obesity	54.6 (2,041/3,737)	56.7 (122/215)	0.57
Blood pressure (mmHg)			
Systolic	132.5 (18.8)	128.4 (17.5)	0.002
Diastolic	78.3 (10.8)	78.9 (10.8)	0.38
Cholesterol (mmol/L)			
Total	4.5 (1.09)	4.8 (1.01)	0.15
LDL	2.6 (0.91)	2.7 (0.89)	0.04
Plasma glucose			
Fasting (mmol/L)	5.7 (0.42)	5.8 (0.46)	0.003
2h-PG (mmol/L)	6.4 (0.90)	6.3 (0.97)	0.58
HbA_{1c} DCCT (%)	7.9 (2.71)	8.1 (2.59)	0.22
HADS Anxiety score	5.2 (3.81)	6.3 (4.31)	0.0008
HADS Depression score	4.4 (3.53)	5.0 (3.82)	0.04
Pharmacological treatment			
Antiplatelet	93.2 (3,504/3,761)	94.7 (215/227)	0.42
Lipid lowering	85.9 (3,231/3,761)	83.2 (189/227)	0.28
β-Blockers	81.9 (3,080/3,761)	80.2 (182/227)	0.54
ACE inhibitors	58.8 (2,212/3,761)	54.2 (123/227)	0.19
ARB	15.9 (599/3,761)	16.3 (37/227)	0.85
ACE inhibitors or ARB	74.2 (2,790/3,761)	69.2 (157/227)	0.10
Diuretics	24.5 (920/3,761)	26.4 (60/227)	0.52

The data are presented as proportions (% = *n*/*N* of observations × 100) or as mean (SD). ARB, angiotensin receptor blocker.

mortality, whereas all measures were significant predictors of cardiovascular mortality (23).

In coronary patient populations, the present findings are consistent with those from the Silent Diabetes Study comparing the prognostic capacity of HbA_{1c} with that of an OGTT in 1,015 patients without previously known diabetes undergoing coronary angiography. Postload glucose was closely related to the severity of CAD and future mortality during a 3-year period and, in this respect, superior to FPG, whereas there was no association with HbA_{1c} (24). In a prospective, observational, single-center study of 301 patients with AMI and newly detected diabetes, IGT, or IFG, an OGTT combined with HbA_{1c} provided prognostic information on all-cause mortality, but none of these tests predicted the long-term prognosis when used separately (25). In a recent report from the Glucose Tolerance in Patients with Acute Myocardial Infarction (GAMI) cohort, dysglycemia, based on 2h-PG performed at the time of hospital discharge after an AMI in patients without previously known dysglycemia, was significantly associated with an increased risk for a major cardiovascular event during the following decade. As in the current study, neither FPG nor HbA_{1c} was a significant predictor in GAMI (26).

In contrast to these reports, the current study adds new information by incorporating hospitalization for heart failure in the primary end point, which usually only includes cardiovascular death, nonfatal MI, and stroke. There are important reasons to include heart failure as part of major adverse cardiovascular events in diabetes. Heart failure emerges as a common (27) and very serious complication of diabetes in the setting of CAD (28). In the GAMI cohort, severe heart failure was almost as common as AMI in patients with newly identified IGT or diabetes (26). Moreover, a systematic review of cardiovascular outcome trials of glucose-lowering drugs reported that heart failure, although often poorly validated and underreported in some trials, was as frequent as nonfatal AMI and stroke in some trials and, when present, was associated with a poorer prognosis (29). The latter finding was underlined by a recent report from the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) of patients with type 2 diabetes randomized to alogliptin or placebo within 15 to 90 days of an acute coronary syndrome (30). The subsequent mortality

Table 3—Prognostic value of FPG, 2h-PG, and HbA_{1c} for the primary composite end point in 3,775 coronary heart disease patients free of diabetes at baseline

	N	Composite end point, HR (95% CI)	*P**
FPG (mmol/L)			
<6.1	1,502	1	
6.1–6.9	1,461	1.07 (0.80–1.42)	0.66
≥7	812	1.18 (0.85–1.64)	0.33
2h-PG (mmol/L)			
<7.8	2,098	1	
7.8–11.0	1,242	1.36 (1.04–1.80)	0.03
≥11.1	435	1.44 (0.99–2.10)	0.06
HbA_{1c} (%)			
<5.7	1,797	1	
5.7–6.4	1,804	1.14 (0.88–1.47)	0.33
≥6.5	174	1.00 (0.54–1.86)	0.99
FPG (mmol/L)			
<6.1	1,502	1	
≥6.1	2,273	1.10 (0.85–1.43)	0.45
2h-PG (mmol/L)			
<7.8	2,098	1	
≥7.8	1,677	1.38 (1.07–1.78)	0.01
HbA_{1c} (%)			
<5.7	1,797	1	
≥5.7	1,978	1.12 (0.87–1.45)	0.36

HR (95% CI) and *P* value adjusted for age and sex. *$P < 0.05$ is statistically significant.

effect of a first nonfatal cardiovascular event was higher in patients who had been hospitalized for heart failure than in those with stroke and AMI. The importance of heart failure is further emphasized by the results of the Empagliflozin Cardiovascular Outcome Event Trial (EMPA-REG OUTCOME) in patients with type 2 diabetes at high cardiovascular risk. The sodium–glucose cotransporter 2 inhibitor was associated with an impressive 36% reduction in cardiovascular mortality, which was driven by a decrease in hospitalizations for heart failure (31). These results suggests that the use of empagliflozin in patients with type 2 diabetes and CAD at high risk for heart failure should be encouraged as recommended in the most recent European guidelines for management of heart failure (32). Then early detection of CAD patients at increased risk of heart failure is essential, and the best-suited screening tool is the OGTT, which should be a prerequisite in risk profiling of CAD patients.

In the current study, the 2h-PG indicating IGT (*n* = 1,242) was significantly associated with the primary end point, whereas the 2h-PG indicating diabetes (*n* = 435) showed a similar trend with a borderline statistical significance. In the report from the GAMI cohort, newly detected abnormal glucose tolerance, defined as IGT or diabetes, was an important predictor of cardiovascular events in patients with a recent AMI. Further support for this position is derived from a study by George et al. (4), who found that IGT and newly detected diabetes were both independent predictors of the incidence of first occurrence of cardiovascular death, nonfatal MI, severe heart failure, or stroke. There was a significant 38% increased risk for the primary end point in patients with dysglycemia in the current study. Thus, the evidence is accumulating that it is more important to find out whether CAD patients have dysglycemia, defined as IGT or diabetes, which only can be done using an OGTT, than to classify them as having IGT or diabetes. The latter is an arbitrary division that was introduced to distinguish people with dysglycemia who had diabetes from those who were at high risk of developing diabetes (33).

Several studies, in particular DECODE/DECODA, have shown that IGT is a category of dysglycemia associated with an increased risk of all-cause and cardiovascular mortality (19,20), in keeping with our present results. Oxidative stress triggered by excessive postprandial hyperglycemia has been suggested as a pathogenetic link, for example, by stimulating low-grade inflammation, thereby reducing NO release and causing endothelial dysfunction and reduced fibrinolysis (34,35).

The strengths of the current study include the large sample size of a well-characterized population with CAD without previously known dysglycemia investigated with the three recommended indicators of hyperglycemia. The 2-year follow-up time may be considered relatively short, but the incidence of a first major cardiovascular event is higher during the first years of follow-up (25,26). The follow-up completeness rate was high, which is an important strength. The study population consisted predominantly of men, which could affect the generalizability of the results to women. However, our results reflect a

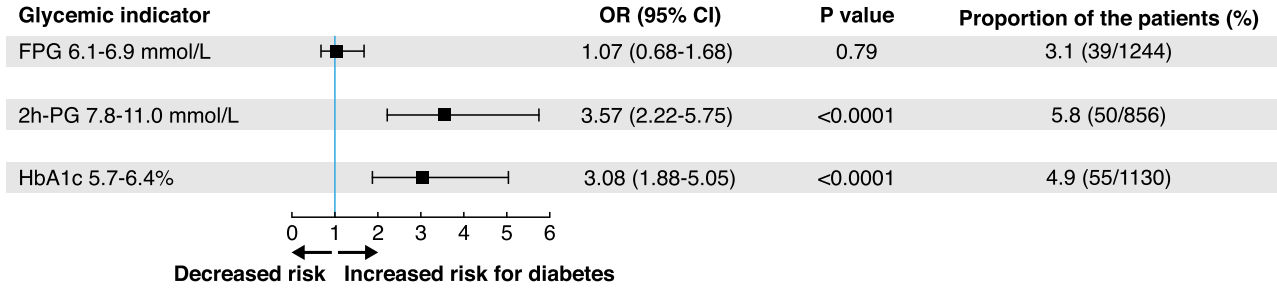

Figure 2—The capacity of FPG, OGTT 2h-PG, and HbA_{1c} to predict incident diabetes in 2,609 patients without this disease at the baseline investigation. Odds ratio (OR) 95% CI and *P* value adjusted for age and sex.

study population as reflected in daily clinical practice and are valid from that perspective.

Trained staff performed the OGTT, including blood sampling and glucose measurements, with a uniform method (HemoCue) and with the HbA_{1c} centrally analyzed. For logistical reasons, only one blood sample for FPG, 2h-PG, and HbA_{1c} each was collected at baseline. In a clinical perspective, the diagnosis of diabetes should be confirmed with repeated tests according to present guidelines. However, for the purpose of comparing prognostic capacity of a parameter measured at baseline, one test is sufficient because random variation can be controlled for with a proper sample size and statistical methods. The results of EUROASPIRE IV have been questioned (15) based on the assumption that postload glucose lacks reproducibility compared with FPG. In a study by Wallander et al. (36), patients were screened with an OGTT at 5 days, 3 months, and 12 months after an AMI. Of those who were identified to have diabetes at hospital discharge, 93% had dysglycemia (IGT or diabetes) after 12 months, indicating that the reproducibility of the 2h-PG is sufficient for the present purpose.

A major limitation of the current study is that the diagnosis of diabetes at follow-up was self-reported in more than 60% of the patients because a repeat OGTT could not be performed.

In summary, only a 2h-PG provides prognostic information on future cardiovascular events in patients with CAD and newly detected dysglycemia, but FPG and HbA_{1c} are not prognostic indicators. Both elevated 2h-PG and HbA_{1c} predicted incident diabetes. These results confirm guideline recommendations, stressing the importance of the use of OGTT as an important tool for the clinical evaluation of patients with CAD. In the era of evidence-based medicine, it seems inappropriate not to perform a simple OGTT in patients with CAD.

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