The Prognostic Importance of Impaired Fasting Glycemia in Chronic Coronary Heart Disease Patients

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ABSTRACT

Objectives Impaired glucose metabolism represents one the most important cardiovascular risk factors, with steeply raising prevalence in overall population. We aimed to compare mortality risk of impaired fasting glycaemia (IFG) and overt diabetes mellitus (DM) in patients with coronary heart disease (CHD).

Study design prospective cohort study

Methods A total of 1685 patients, 6–24 months after myocardial infarction and/or coronary revascularization at baseline, were followed in a prospective cohort study. Overt DM was defined as fasting glucose ≥ 7 mmol/L and/or use of antidiabetic treatment, while IFG as fasting glucose 5.6–6.99 mmol/L, but no antidiabetic medication. The main outcomes were total and cardiovascular mortality during 5 years of follow-up.

Results During follow-up of 1826 days, 172 patients (10.2 %) deceased, and of them 122 (7.2 %) from a cardiovascular cause. Both exposures, overt DM (n = 623, 37.0 % of the whole sample) and IFG (n = 436, 25.9 %) were associated with an independent increase of 5-year total mortality, compared to normoglycemic subjects [fully adjusted hazard risk ratio (HRR) 1.63 (95 %CI: 1.01–2.61)]; p = 0.043 and 2.25 (95 %CI: 1.45–3.50); p < 0.0001, respectively]. In contrast, comparing both glucose disorders one with each other, no significant differences were found for total mortality [HRR 0.82 (0.53–1.28); p = 0.33]. Taking 5-years cardiovascular mortality as outcome, similar pattern was observed [HRR 1.96 (95 %CI: 1.06–3.63) and 3.84 (95 %CI: 2.19–6.73) for overt DM and IFG, respectively, with HRR 0.63 (95 %CI: 0.37–1.07) for comparison of both disorders].

Conclusions Impaired fasting glycaemia adversely increases mortality of CHD patients in the same extent as overt DM.

Introduction

Impaired glucose metabolism belongs to classical cardiovascular risk factors. Presence of overt diabetes mellitus in patients with manifest vascular disease (coronary heart disease or ischemic stroke) increases mortality risk of these patients more than twofold [1]. On the other hand, the exact definition of impaired glucose metabolism remains disputable. It is generally accepted, that several "pre-diabetic" conditions with identical etiology exists as intermediate state between normoglycemia and overt diabetes mellitus (metabolic syndrome, impaired glucose tolerance as well as impaired fasting glycaemia). Several studies, almost exclusively set in general population, have shown that even pre-diabetic subjects are already at excessive risk of future major cardiovascular event [2–5]. Similarly, in patients with manifest coronary heart disease (CHD), there's a plethora of reports related to overt diabetes mellitus, but the pre-diabetic population is largely unexplored and available data are more or less anecdotical [6–10]. As a consequence, in guidelines related to secondary prevention of CHD,

those chapters dealing with glucose metabolism, predominantly address diabetic patients [11].

Thus, in a present paper we aim to assess the mortality impact of pre-diabetic state, comparing an attributable risk of impaired fasting glycaemia and overt diabetes mellitus in well-defined sample of stable patients with chronic CHD.

Methods

Design and study population

The study represents a secondary analysis of EUROASPIRE survey data in the Czech Republic, a prospective follow-up of four pooled independent cohorts (EUROASPIRE I, II, III, and IV examined in 1995–96, 1999–2000, 2006–7 and 2012–13) of patients with stable manifest CHD (i. e. baseline examination was done at least 6 months after its first manifestation). A detailed sample selection was described elsewhere [12–15]. Briefly, patients aged less than 71 years hospitalized for any of the following discharge diagnosis were retrospectively identified from hospital records. The diagnoses included: first coronary artery bypass grafting (CABG), first percutaneous transluminal coronary angioplasty (PTCA) and acute myocardial infarction or ischemia. Recruitment of patients started with the most recent hospital record and proceeded backward until the required sample of 525 subjects in each campaign (EUROASPIRE I, II, III, and IV) was achieved. These patients were invited for an interview/clinical examination and responders (81.8 % of the initially identified pool of patients) included in the survey. All 4 campaigns of the EUROASPIRE survey were conducted in the same two centers in the Czech Republic: University Hospital in Pilsen and Department of Cardiology, Institute for Clinical and Experimental Medicine in Prague under an almost identical protocol. Each interview/clinical examination took place 6–24 months after the qualifying index event (i. e., acute coronary syndrome or first elective revascularization) and for the purpose of the present analysis used as baseline visit for prospective follow-up.

Data collection

The standard protocol of EUROASPIRE (EA) survey was followed as described elsewhere [12–15]. Information on personal and demographic characteristics, personal and family history of CHD, lifestyle and pharmacotherapy were obtained. The following standardized examinations were performed: height and weight were measured in light indoor clothes without shoes using SECA 707 (EAI and II) and SECA 701 (EA III and IV) scales and measuring stick (SECA, Hamburg, Germany). Waist circumference was measured using a tape measure. Blood pressure (BP) was measured twice in the sitting position on the right arm using standard mercury sphygmomanometers. Breath carbon monoxide was measured by a SMOKERLYSER device (Bedfont Scientific, Upchurch, UK) to verify smoking status (with 10 ppm of breath carbon monoxide as the cut-off point). Venous blood samples were drawn after at least 12 hours of overnight fast. Laboratory examinations included estimation of total and HDL cholesterol, triglycerides (TG) and glucose, and were performed in the central study laboratory of the respective EUROASPIRE survey. Again, laboratory methods were described elsewhere [12–15]. LDL cholesterol was calculated using the Friedewald equation, i. e., LDL = total cholesterol – HDL – (TG/2.22). HbA1c (glycated hemoglobin) was estimated from frozen samples by ionex liquid chromatography using G7 analyser (TOSOH, Tokyo, Japan).

Vital status of patients was registered up to March 31, 2017 using the National Registry of the Institute of Health Information and Statistics of the Ministry of Health. Death certificates and available documentation in hospital information systems were used to specify the cause of death.

Outcomes and data management

Death from any cause was used primary outcome. Secondary outcome was defined as death from any cardiovascular cause as stated in hospital records (discharge letter, inspection list, etc.) or, if not available (for those dying at home) stated as the primary cause of death (ICD-10 codes were used) in the death certificate. In patients with active malignancy, the cause of death was considered non-cardiovascular, even if the immediate cause of death was cardiovascular (for example, pulmonary embolism). Because of very variable length of follow-up for the purpose of present analysis it was arbitrary unified to 1826 days (5 years)

Impaired glucose metabolism as primary exposure was defined in two levels: a) "overt diabetes mellitus", i. e. fasting serum glucose ≥ 7 mmol/L and/or use of antidiabetic treatment and/or self-reported diabetes plus diabetic diet; and "impaired fasting glycaemia", i. e. fasting serum glucose 5.6–6.99 mmol/L (and no use of antidiabetic treatment). Other conventional risk factors were dichotomized using cut-off points proposed by the Joint European Guidelines for Cardiovascular Prevention [16].

Statistical analyses were performed using STATISTICA 8 (StatSoft Inc, Tulsa, OK, USA) and STATA 8 (STATA Corp LP, College Station, TX, USA). Conventional descriptive methods were applied, i. e., mean and standard deviation for continuous variables or frequency for categorical ones. Using a Cox proportional hazard model, univariate analysis was performed to identify the crude relation between exposure (overt diabetes or impaired fasting glycaemia) and total/cardiovascular mortality. As a second step, we adjusted all models for conventional confounders (age and gender) and then also other (dichotomized) cardiovascular risk factors (smoking, body mass index, blood pressure, LDL cholesterol), treatments with a presumable effect on cardiovascular mortality (statin, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers), as well as a history of coronary revascularization (before inclusion into study) and sequence of the primary survey (i. e. EUROASPIRE I, II, III or IV). Censored data were used for final analysis. P values < 0.05 were considered significant.

Results

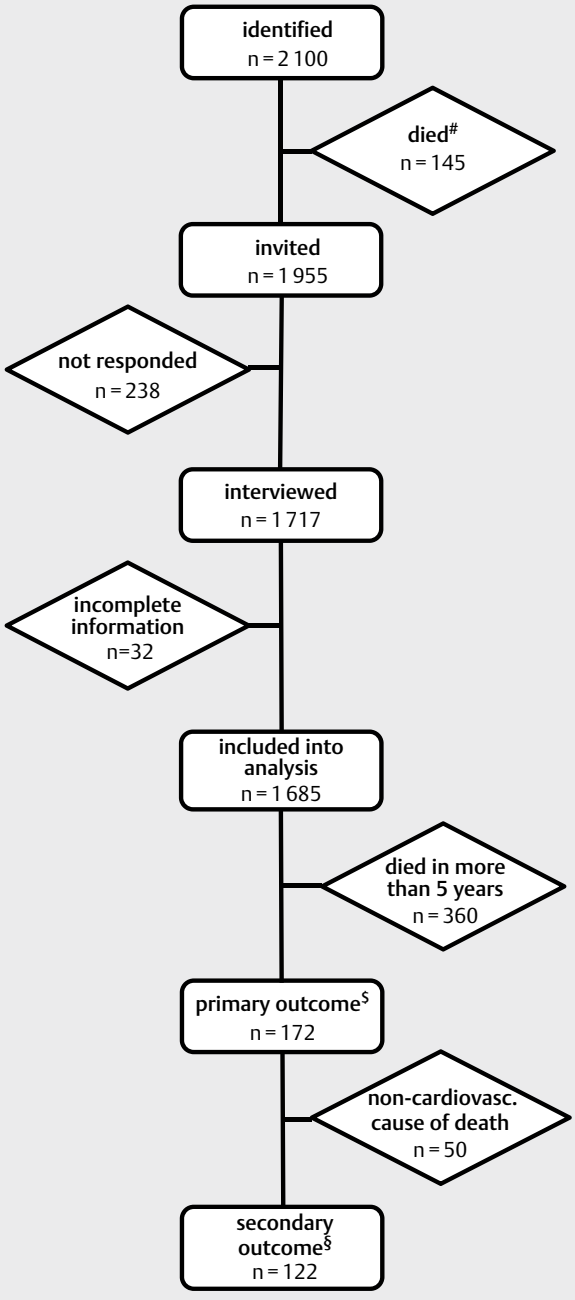
Baseline cross-sectional data and outcomes

Initially, a total of 1717 patients (1312 men and 405 women; mean age 62.7 ± 9.0 years) after myocardial infarction and/or coronary revascularization were interviewed; median time (interquartile range) between the qualifying cardiovascular event and interview was 1.02 (0.96–1.78) years. However, exact information about vital status, cause of death or any other crucial variable was missing in 32 patients – these subjects were excluded from the final analysis.

▶ **Table 1** Basic characteristics of study sample [mean (standard deviation) or factor proportion]

n	1685
age [years]	62.1 (9.0)
gender [% of males]	*7634*
history of coronary revascularization[%]	*81.5*
current smoking [%]	*20.1*
body mass index [kg/m^2]	29.3 (4.4)
body mass index ≥ 30 kg/m^2[%]	*38.6*
waist circumference [cm]	101.4 (11.8)
increased waist circumference$^{\#}$[%]	*58.2*
systolic blood pressure [mmHg]	140.2 (20.5)
diastolic blood pressure [mmHg]	83.5 (11.3)
raised blood pressure$^{\#}$[%]	*51.4*
total cholesterol [mmol/L]	4.94 (1.28)
LDL-cholesterol [mmol/L]	2.91 (1.08)
LDL-cholesterol ≥ 2.5 mmol/L [%]	*61.0*
HDL- cholesterol [mmol/L]	1.21 (0.33)
low HDL cholesterol§[%]	*31.7*
triglycerides [mmol/L]	1.84 (1.42)
triglycerides ≥ 1.8 mmol/L [%]	*42.4*
fasting glycemia [mmol/L]	6.99 (2.37)
concomitant treatments [%]:	
betablockers	*78.3*
ACEi or ARBs	*60.9*
statins	*61.3*
antidiabetics	*19.1*
glucose metabolism categories:	
overt diabetes$^{\#\#}$[n (%)]	623 *(37.0)*
impaired fasting glycemia$^{\$\$}$[n (%)]	436 *(25.9)*
normoglycemia [n (%)]	626 *(37.1)*

LDL, low density lipoprotein; HDL, high density lipoprotein; ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; #waist circumference ≥ 102 cm in males or ≥ 88 cm in females;; $^{\$}$ systolic blood pressure ≥ 130 and/or diastolic blood pressure ≥ 85 mmHg; § < 1.0 mmol/L in males or < 1.3 mmol/L in females; $^{\#\#}$ fasting glycaemia ≥ 7 mmol/L and/or treatment with antidiabetics or self-reporting diabetes mellitus *plus* diabetic diet; $^{\$\$}$ fasting glycemia *5.6–6.9* mmol/L and no treatment with antidiabetics



▶ **Fig 1** Flow chart of sample recruitment process and follow-up. # Deceased between discharge from hospitalization for coronary heart disease manifestation (qualifying event) and the interview (baseline visit); $ total death; § cardiovascular death;

Thus, the final cohort consisted of 1285 men and 407 women whose baseline characteristics are listed in ▶ **Table 1**.

During follow-up (i. e., between baseline visit and March 31, 2017), death occurred in 532 patients, of which number the cause of death was identified as cardiovascular in 395 (74.3 %) individuals; median follow-up time (interquartile range) was 3782 days (1636–6264). During follow-up of 5 years (1826 days) at most, 172 patients (10.2 %) died of which number 122 (7.2 %) from a cardiovascular cause (details of the selection and follow-up processes are shown in ▶ **Fig. 1**)

Glycemic status and mortality

Survival curves according to glucose metabolism categories are shown in ▶ **Fig. 2**. Presence of both overt diabetes and impaired fasting glycaemia was associated with worse survival than normal glycemic status (fasting glycaemia < 5.6 mmol/L). The univariate (crude) 5-years total hazard risk ratios (HRRs) and 95 % confidence intervals (95 % CIs) for overt diabetes or impaired fasting glycaemia were 2.05 (1.40–2.98) or 1.79 (1.19–2.70), respectively. Mortality risk associated with overt diabetes was similar to impaired fasting glycaemia 1.15 (0.81–1.65).

Multivariate regression analyses revealed confirming results (▶ **Table 2**). After adjustment for age, gender, other conventional risk

factors and treatments, impaired fasting glycaemia was associated with more than two-fold higher risk of 5-year total mortality). Moreover, mortality risk associated with impaired fasting glycaemia did not statistically differ from risk associated with overt diabetes (▶**Table 2**).

In a next step, we repeated all above described analyses using 5-years cardiovascular (instead of total) mortality as outcome with analogous results to former one (▶**Fig. 2** – unadjusted analysis; ▶**Table 2** – adjusted analysis) .The observed association between glucose metabolism categories and cardiovascular mortality was even stronger. Indeed, impaired fasting glycaemia was associated with more than 3.8 times higher risk of 5-years cardiovascular mortality (after full adjustment for potential covariates).

Furthermore, in exploratory analysis we investigate potential role of HbA1c. Concentrations of HbA1c were available in 972 patients (≈ 58 % subsample, EUROASPIRE III and IV subjects only), mean age 64.3(± SD 9.0) years, 79.4 % of males; mean concentration of HbA1c was 44.2 mmol/mol (± SD 12.7) and frequency of primary outcome (5-year total death) was 11.5 %. Taking HbA1c ≥ 48 mmol/mol as an alternate criterion for pre-diabetic status did not change real prevalence of impaired fasting glucose category (23.7 % with HbA1c ≥ 48 mmol/mol as alternate criterion). Its predictive power in terms of primary outcome risk was as follows: HRR 2.22 (95 %CI: 1.44–3.50). Further, we tested lower cut-off point for HbA1c ≥ 42 mmol/mol for pre-diabetic status definition. The prevalence of pre-diabetic status, defined as fasting glucose 5.6–6.99 or HbA1c ≥ 42 mmol/mol raised to 27.6 % , but was no longer associated with primary outcome [HRR 1.65 (95 %CI: 0.93–2.91), p = 0.085].

▶**Table 2** 5-years mortality risk associated with categories of impaired glucose metabolism [Hazard risk ratios (95 % confidence intervals] by Cox proportional hazard model]

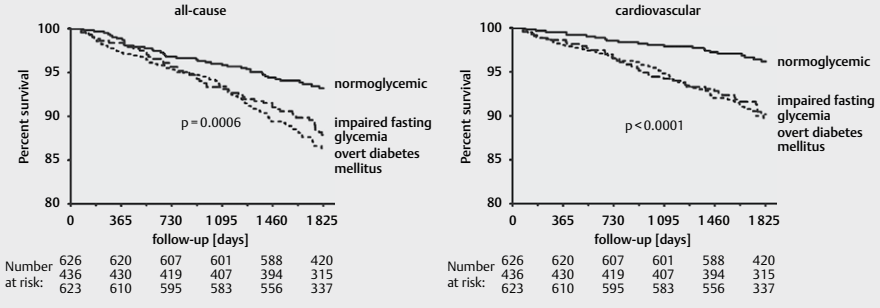
	total		cardiovascular	
	HRR (95 % CI)	**p**	**HRR (95 % CI)**	**p**
adjusted for age, gender and survey:				
normoglycaemia	1	-	1	-
impaired fasting glycemia	1.85 (1.22–2.79)	0.004	2.80 (1.67–4.71)	<0.0001
overt diabetes	1.77 (1.21–2.61)	0.004	2.47 (1.49–4.08)	<0.0001
overt diabetes	1	-	1	-
impaired fasting glycemia	0.98 (0.68–1.41)	0.915	0.88 (0.58–1.32)	0.531
fully adjusted#:				
normoglycaemia	1	-	1	-
impaired fasting glycemia	2.25 (1.45–3.50)	<0.0001	3.84 (2.19–6.73)	<0.0001
overt diabetes	1.63 (1.01–2.61) $	0.043	1.96 (1.06–3.63) $	0.033
overt diabetes	1	-	1	-
impaired fasting glycemia	0.82 (0.53–1.28) $	0.328	0.63 (0.37–1.07) $	0.086

adjusted for age, male gender, survey (EUROASPIRE I, II, III or IV), history of coronary revascularization, current smoking, BMI ≥ 30 kg/m^2, increased waist circumference, raised blood pressure, LDL ≥ 2.5 mmol/L and treatment with statins, betablockers, ACEi or ARBs; $*plus* treatment with antidiabetics

Discussion

The key finding of our study is that impaired fasting glycemia represents major indicator of increased residual mortality risk in patients with stable manifest CHD. Pre-diabetic subjects had more than 3.8 times higher relative risk of fatal cardiovascular event during 5- years of follow-up comparing to those with fasting glucose in physiological range. Moreover, patients with impaired fasting glycemia had comparable mortality risk as patients with overt diabetes mellitus. It is also necessary to stress that impaired fasting glycemia is highly prevalent condition in CHD patients (one quarter of patients in our sample) with evident increase over time in last 20 years [17].

In contrast, using different cut-off values for HbA1c did not improve either diagnostics of the pre-diabetic state or assessment of risk associated with pre-diabetes better than fasting glucose concentration to rule-out. Cut-off point of HbA1c ≥ 48 mmol/mol (proposed by Guidelines[16] as “maximal safe treatment target” in diabetic patients) was not in our study associated with substantially better sensitivity. In fact, only three patients with HbA1c ≥ 48 mmol/mol (0.3 % among those with available HbA1c value)



▶**Fig 2** Kaplan-Meier survival curves according to glucose metabolism categories. (p value by Mantel-Cox log rank test)

were "misclassified" as normoglycemic (based on fasting glycemia criterion only), while 9 patients (0.9 %) re-classified into pre-diabetes category. We also repeated the mortality analysis after "re-classification" according to HbA1c concentration (i. e. subjects with ≥ 48 mmol/mol were considered as overt diabetes), with very similar results. Moreover, when we used HbA1c 42–47 mmol/mol as alternate criterion to fasting glucose (5.6–6.9 mmol/l) of pre-diabetes classification, its predictive power is no more significant. This negative result contrasts to those from general population. A prospective cohort analysis by Warren and colleagues reported that pre-diabetes definition based on HbA1c provided at least modest improvements in the risk discrimination for cardiovascular outcomes and other diabetes complications [18]. Another way how to increase sensitivity of glucose metabolism disorder screening is measurement of 2-hour post-load glucose concentrations - this approach was applied in EUROASPIRE IV cohort; we have data available in ≈ 29 % of sample). In this subsample, none of nominally normoglycemic patients (with fasting glucose < 5.6 mmol/L) had the 2-hour post-load glucose level over 11 mmol/L (WHO criteria for overt diabetes). However, another 51 normoglycemic patients had 2-hour post-load glucose concentrations ≥ 7.8 mmol/L. Use of this alternate criterion increased prevalence of pre-diabetes to 27 %. Shahim and colleague [10] recently reported that CHD patients with 2-hour post-load glucose concentrations ≥ 7.8 mmol/L showed significant 38 % higher risk of fatal or non-fatal cardiovascular events. Furthermore, the CHD patients with 2-hour post-load glucose concentrations ≥ 7.8 mmol/L had higher risk of incident diabetes during 2-years of follow-up [10]. Thus, 2-hour post-load glucose concentrations may further improve the screening for individual high-risk CHD patients, moderated by impaired glucose metabolism.

The crucial practical question is whether we should apply any specific therapeutic intervention in pre-diabetic CHD patients. Recent guidelines on cardiovascular prevention [11] mentioned pre-diabetic disorders in secondary prevention of CHD only anecdotically, while standards of care of diabetes are in the field of pre-diabetic disorders focused mainly to decreased the rate of "conversion" to overt diabetes (prevention or delay) [19]. Certainly we can recommend, as to all CHD patients, a tight control of other conventional risk factors and intensive non-pharmacologic treatment (specific diet recommendations, weight loss, intensive physical activity…). Randomized controlled trials revealed that intensive life-style modification was in general patients with pre-diabetic disorders very effective in terms of delayed conversion to overt diabetes [20, 21]. In spite, that we are lacking equivalent data, focused to recurrent cardiovascular events prevention in pre-diabetic patients with manifest CHD, life-style intervention remains first line measure. Theoretically we can start antidiabetic treatment earlier than in usual practice however there are several exclusions and whole concept remains in secondary prevention of CHD controversial, mainly because of lacking evidence. First of all, traditional antidiabetic drugs such as insulin and sulfonylureas showed U-shaped association between mortality and glycemic control. Stricter treatment targets were associated with increased risk of major cardiovascular events (MACE) [22–24]. Dipeptidyl-peptidase-4 inhibitors effectively decreased fasting glycaemia without substantial risk of hypoglycemia. Nonetheless their benefit in term of reduction of MACE was not observed [25] (several existing studies were pointed to cardiovascular safety only). Metformin is routinely used also in other indication than diabetes mellitus and in normoglycemic patients, but proof of cardiovascular benefit is lacking again [26]. In the recent studies, glucagon-like propeptide-1 and sodium-glucose transport protein-1 antagonists (liraglutid and empagliflozin) [27, 28] not only decreased glycaemia in patients with diabetes, but were also followed by reduction of MACE. However, no satisfactory evidence exists for these drugs in terms of safety and efficacy in CHD patients without overt diabetes. To our knowledge, only one study reported positive effect of antidiabetic treatment in pre-diabetic subjects regarding cardiovascular events incidence. STOP-NIDDM trial reported that treatment impaired glucose tolerance patients with acarbose was associated with a significant 49 % reduction of cardiovascular events [29]. Despite relative small sample size (less than 1400 subjects) and for clinical practice more-than-less useless drug class (acarbose is very poorly tolerated), this study represents single positive piece of knowledge in a whole concept of antidiabetic treatment in pre-diabetic patients.

Study limitations

First, we pooled four samples of patients interviewed at four different occasions. The initial management, control of risk factors, as well as related background mortality risk substantially changed (generally improved) over time [17]- we did our best to adjust data for all these factors to minimize their impact. From similar reasons we have available HbA1c concentrations only in part of the sample (EUROASPIRE III and IV) and this factor can be investigated only in the exploratory sub-analysis.

Second, our sample consisted from rather stable and probably initially less affected patients. Due to inclusion criteria (qualifying cardiovascular event at least 6 months before baseline visit), most severe patients died before inclusion into follow-up (≈ 7 % of identified pool of CHD patients) or were not physically fit to attend the interview. Therefore, any implications of our results should be limited to well-stabilized patients.

Moreover, no non-fatal cardiovascular events data were available to us.

Conclusions

In patients with stable CHD, mild increase of fasting glycaemia effectively identified subjects at high mortality risk. The risk associated with impaired fasting glycaemia was similar to overt diabetes. Interventional studies are needed to assess the therapeutic strategy in this prevalent subgroup of CHD patients.

Ethical Statement

All procedures performed in this study were in accordance with the Good Clinical Practice principles and ethical standards formulated in the 1964 Declaration of Helsinki and its later amendments. The study protocols were approved by the Ethics Committees of the University Hospital in Pilsen and Institute for Clinical and Experimental Medicine in Prague. The data were stored and evaluated under the provisions of the Czech Data Protection Act. Written in-

formed consent was obtained from all participants included in the study at baseline visit.

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Conflict of Interest

These are no conflicts of interest to disclose.

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