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Prediabetes and Risk for Cardiac Death among Coronary Artery Disease Patients: the ARTEMIS study

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STRUCTURED ABSTRACT

Objective

To compare cardiac mortality in CAD patients with prediabetes to those with normal glycemic status and type 2 diabetes.

Research Design and Methods

The ARTEMIS study included CAD patients after revascularization (79%) and/or optimal medical therapy with type 2 diabetes (n=834), impaired glucose tolerance (IGT, n=314) or fasting glucose (IFG, n=103) or normal glycemic status (n=697), defined by oral glucose tolerance test. The primary end-point was cardiac death. Major adverse cardiac event (MACE=cardiac death or heart failure or acute coronary syndrome) and all-cause mortality were secondary end-points.

Results

During a mean follow-up of 6.3±1.6 years (101 cardiac deaths, 385 MACEs, and 208 deaths), patients with IGT tended to have 49% (p=0.069) and 32% (p=0.076) lower adjusted risk for cardiac death and all-cause mortality, respectively, and had 36% (p=0.011) lower adjusted risk for MACE compared to patients with type 2 diabetes. The patients with IFG had 82% (p=0.015) lower adjusted risk for all-cause mortality compared to the patients with type 2 diabetes, whereas risk for cardiac death and MACE did not differ significantly. The adjusted risk of patients with IGT and IFG for cardiac death, MACE and all-cause mortality did not significantly differ from those with normal glycemic status.

Conclusions

Cardiac mortality or incidence of MACE of CAD patients with prediabetes, i.e. IGT or IFG, after revascularization and/or optimal medical therapy does not differ from those with normal glycemic status.

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Type 2 diabetes is an epidemic health issue in western societies which is expanding as well worldwide (1). Cardiovascular diseases, coronary artery disease (CAD) in particular, are the most common comorbid states in type 2 diabetes (1). Importantly, type 2 diabetes has a significant adverse effect on the prognosis of patients with CAD (2) and recent myocardial infarction (3; 4).

Prediabetes is a state of natural progression from normoglycemia to type 2 diabetes. It is defined by the presence of either impaired glucose tolerance (IGT) in an oral glucose tolerance test (OGTT) or an impaired fasting glucose (IFG) level (5). The 2-h postload glucose in OGTT associates particularly well with an increased mortality risk in population-based samples, outperforming fasting glucose and glycated hemoglobin (HbA1c) in risk analyses, suggesting greater mortality risk in IGT compared to IFG (6-8). However, there are less data about the prognostic significance of prediabetes in patients with a previously diagnosed stable CAD. Increased plasma glucose and HbA1c identified at admission for acute myocardial infarction have been associated with a worse prognosis in patients with type 2 diabetes (9), as have HbA1c and 2-h postload glucose in patients without known type 2 diabetes who are hospitalized for CAD (10-13). In the EUROASPIRE IV registry-based survey, short-term (2 years) prognostic significance of glucose markers were assessed in a more stable phase of CAD, i.e. 6-36 months after hospitalization due to CAD (14). The 2-h postload glucose provided significant prognostic value for cardiovascular events independently of fasting glucose and HbA1c, while 2-h postload glucose and HbA1c were important risk factors for new onset of type 2 diabetes independently of each other. However, in a limited sample of CAD patients, prediabetes was not associated with increased risk for cardiovascular events after revascularization compared to normoglycemic patients (15). Therefore, confirmatory studies are warranted to establish longer-term prognostic significance of CAD patients with prediabetes who have undergone revascularization, if indicated, or who are on contemporary medical therapy, if not revascularized.

The present study was designed to assess the relationship between prediabetes, particularly IGT, and cardiac mortality in patients with CAD after coronary angiography and revascularization, if considered necessary. It was hypothesized that patients with prediabetes would have an increased risk for cardiac death compared to normoglycemic CAD patients, albeit lower than those with type 2 diabetes. Secondary aims were to assess prognostic significance of prediabetes regarding major adverse cardiac events (MACE) and all-cause mortality.

METHODS

Study protocol and study population

The ARTEMIS (Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection; NCT1426685, ClinicalTrials.gov), a prospective observational study, recruited CAD patients with or without type 2 diabetes 3-6 months after coronary angiography and revascularization, if indicated, or with contemporary medical treatment, if revascularization was not needed (2). Patients without type 2 diabetes or prediabetes were matched with type 2 diabetes patients at a group level for age, gender, prior myocardial infarction (non-ST-elevation or ST-elevation myocardial infarction) and revascularization from a consecutive series of patients who had undergone coronary angiography at Division of Cardiology, Oulu University Hospital. The initial examinations and determination of inclusion/exclusion criteria were conducted at least 3 months after coronary angiography and/or the last revascularization. Significant coronary artery disease (CAD) was defined by coronary angiography as stenosis >50% in at least 1 major epicardial artery.

At the initial enrollment visit, OGTT was performed in all patients without a prior diagnosis of type 2 diabetes to identify those subjects with undiagnosed type 2 diabetes, IFG or IGT. Type 2 diabetes was

defined as fasting capillary plasma glucose levels ≥7.0 mmol/l or a 2-h postload value in the OGTT ≥12.2 mmol/l or both, according to the WHO definition and diagnostic criteria for type 2 diabetes and prediabetes. Impaired glucose tolerance (IGT) was defined as fasting capillary plasma glucose <7.0 mmol/l and 2-h postload glucose ≥8.9 mmol/l but <12.2 mmol/l. Impaired fasting glucose (IFG) was defined as fasting capillary plasma glucose ≥6.1 mmol/l but <7.0 mmol/l and 2-h postload glucose <8.9 mmol/l. IGT, IFG or both were considered as prediabetes conditions (5).

Subjects who fulfilled the guidelines criteria for prophylactic implantation of cardioverter defibrillator (LV ejection fraction <35%) were excluded from the study. Additionally, subjects with life expectancy less than 1 year were excluded from the study which included patients in whom revascularization procedures could not be performed. Medical therapy for all patients was optimized during the qualifying visit by a specialist in endocrinology and diabetes care, and a cardiologist. The study population included 834 subjects with type 2 diabetes (102 new diagnoses), 314 with IGT, 103 with IFG and 695 with normal glucose metabolism (NG). Laboratory samples were obtained after 12-hour overnight fast using standardized methods. The HbA1c is reported as mmol/mol and %, the former being primarily used in the statistical analyses. Echocardiography was performed to quantify left ventricular ejection fraction and mass and was normalized to body surface area. SYNTAX Score was calculated by 3 experienced interventional cardiologists using the Web-based calculator version 2.11 on SYNTAX Score Web site (www.syntaxscore.com) after index angiography and revascularization. All patients included in the study gave their informed consent and the study was approved by the local ethics committee. The study complies with declaration of Helsinki.

Outcomes

The mode of death was evaluated by death certificates, autopsy data, hospital records and interviews with next of kin. Hospital records and paramedic data of resuscitation were used to determine aborted cardiac arrest. The cause and mode of death was reviewed by two independent investigators, and if needed decided by consensus of 2 investigators (MJJ, HVH). The primary end-point in this study was cardiac death or resuscitation from cardiac arrest, which ever occurred first. Major adverse cardiac event (including cardiac death, hospitalization due to acute coronary syndrome [ACS] or congestive heart failure [CHF]) and all-cause mortality were secondary end-points. Study subjects were contacted with a mailed questionnaire and by telephone to inquire the possible interim hospitalization and new diagnosis of type 2 diabetes at 2 years and 5 years of follow up. Hospitalization due to ACS and CHF and new type 2 diabetes were ascertained from medical records.

Statistical analysis

One-way ANOVA or Kruskal-Wallis followed by post-hoc tests (Bonferroni or Mann-Whitney U-test), corrected for multiple comparisons, were conducted for continuous variables between the study groups, depending on the distribution of the data (Gaussian if |skewness| < 1). Chi-square was used for categorical variables. Univariate Cox regression was performed and followed by adjustment for predefined covariates (age, sex, body mass index, resting systolic and diastolic blood pressure, Canadian Cardiovascular Society [CCS] grading for angina pectoris, syntax score and LV ejection fraction) (2). Additional Cox regression was performed to assess risk for new type 2 diabetes among patients without type 2 diabetes at the baseline, adjusted for age, sex, body mass index and waist-hip ratio. Interactions between sex and glycemic status in the risks were also studied by Cox regression. Kaplan-Meier analysis was used to illustrate survival curves of type 2 diabetes, IGT, IFG and NG groups. The data were analyzed using SPSS software (IBM SPSS Statistics 21, IBM Corp., New York, USA). A p-value <0.05 was considered as statistically significant.

Results

Baseline characteristics of the study groups are presented in Table 1. During the mean follow-up of 6.3 years (SD: 1.6 years), cardiac mortality was 8.2%, 3.8%, 2.9% and 2.6% for type 2 diabetes, IGT, IFG and NG groups, respectively. The IGT group had higher all-cause mortality than the NG group and lower incidence of MACE than the patients with type 2 diabetes. The IFG group had lower cardiac and all-cause mortality and lower incidence of MACE than the patients with type 2 diabetes (Table 1).

In the Cox regression analyses, the risk for cardiac death, hospitalization due to ACS or CHF and MACE did not differ between the IGT, IFG and NG groups (Table 2, Figure 1). The IGT group had higher univariate risk for all-cause mortality compared to the NG group, which did not remain significant after adjustments. The IGT group had significantly reduced univariate risk for cardiac death, hospitalization due to CHF and MACE compared to the type 2 diabetes group; the risk for MACE remaining significant after adjustments for potential confounders and risk for cardiac death (p=0.069) and death (p=0.076) trending so (Table 2). The IFG group had lower risk for death and MACE compared the patients with type 2 diabetes. The mortality risk remained significant after adjustments and tendency was observed in the adjusted risk for MACE (p=0.070). When the IFG and IGT were pooled, the adjusted risk for cardiac death, MACE or all-cause mortality did not differ between the IFG/IGT and NG groups. The IFG/IGT group had significantly lower adjusted risk for cardiac death (0.44, 95%CI: 0.22-0.89, p=0.021), MACE (0.63, 95%CI: 0.46-0.86, p=0.003) and all-cause mortality (0.57, 95%CI: 0.37-0.86, p=0.008) compared to patients with type 2 diabetes. No significant sex*glycemic status interactions were observed. Fasting or 2-h postload glucose or HbA1c were not associated with these outcomes in the multivariate Cox regression, when they were assessed as continuous variables in the patients without type 2 diabetes at the baseline; except the association

between 2-h postload glucose and all-cause mortality (hazard ratio: 1.18 per unit increase, 95%CI: 1.03-1.35, p=0.014).

Among the patients with newly diagnosed type 2 diabetes at the baseline (n=102), six cardiac deaths (5.9%), 12 ACSs (14.5%), 6 CHFs (7.1%), 21 MACEs (20.6%) and 13 deaths (12.7%) were observed. Newly diagnosed type 2 diabetes involved 3.0-fold risk for CHF (95%CI: 1.2-7.7, p=0.024) and 2.2-fold (95%CI: 1.8-3.6, p=0.014) for all-cause mortality compared to patients with normal glucose metabolism in univariate analysis but not independently of covariates. The risks related to newly diagnosed type 2 diabetes did not differ from the patients with IFG, IGT or previously diagnosed type 2 diabetes.

The incidence of new type 2 diabetes was higher in the IGT and IFG groups than the NG group (Table 1, p<0.001 for both), the adjusted hazard ratios being 2.78 (95%CI: 1.50-5.16, p=0.001) and 2.68 (95%CI: 1.19-6.03, p=0.017) compared to the NG group, respectively. The IFG and IGT groups did not differ in this respect. In univariate Cox regression, new onset of type 2 diabetes involved 2.4-fold risk for ACS (95%CI: 1.4-4.1, p=0.003, 109 events), 4.6-fold risk for CHF (95%CI: 1.5-13.9, p=0.007, 18 events) and 2.2-fold risk for MACE (95%CI: 1.3-3.8, p=0.003, 123 events) compared to those who remained free of type 2 diabetes. New onset of type 2 diabetes tended to associate with 2.9-fold univariate risk (95%CI: 1.0-8.6, p=0.054, n=22) for all-cause mortality but not with cardiac death mortality (HR: 1.9, 95%CI: 0.2-15.5, p=0.548). Limited by the number of cardiac deaths was observed among patients in whom follow-up data for the incidence of new type 2 diabetes was available (1 event [1.9%] in patients with the new onset of type 2 diabetes [n=52] and 7 events [0.9%] in patients without [n=746]).

Discussion

The main finding in this study is that among revascularized CAD patients with prediabetes, or those with optimal medical therapy, the risk of cardiac events does not differ significantly from those with a normal glycemic status and is significantly lower than among CAD patients with type 2 diabetes. This finding suggests that that prediabetes does not significantly increase the risk for cardiac death and major cardiac morbidities when compared to CAD patients with normal glycemic status in the current treatment era. However, new onset of type 2 diabetes during the 5-year follow-up period of observation was more likely in patients who had prediabetes at baseline. That development worsened the prognosis of CAD patients without prior type 2 diabetes. Thus, the progression from prediabetes to type 2 diabetes warrants effective countermeasures to improve prognosis in CAD.

While the detrimental effects of type 2 diabetes on prognosis are well-established in stable CAD (2) and among patients with recent myocardial infarction (3; 4), less is known about the prognostic significance of prediabetes in CAD patients who have been treated according to current guidelines, such as revascularization if deemed necessary. Plasma glucose and HbA1c at admission and, to less extent, 2-h postload glucose have been used as predictive markers and shown a significant association with cardiac events (9-13; 15). Notably, the 2-h postload glucose seems to provide additional prognostic value to the established risk model of Global Registry of Acute Coronary Events (GRACE) score for cardiac events, unlike fasting glucose (13). The present findings did not support our primary hypothesis based on previous studies in population-based samples and the EUROASPIRE IV survey (6-8; 14) that prediabetes, particularly IGT, is associated with an increased cardiac mortality and MACE. It appears that a glucose metabolism disorder suggesting prediabetes may not accelerate cardiac disease-associated event expression, when criteria for overt type 2 diabetes are not fulfilled. This conclusion is limited by the fact that our study population consisted of subjects with known CAD

at baseline, and does not permit extrapolation of the findings to possible role of prediabetes as a risk marker for CAD development. Contradictory results between the present study and the EUROASPIRE IV multicenter survey may not be fully explained. However, the strength of present study is that it was prospective observational study with considerably longer follow-up. While revascularization characteristics of these populations seem to be comparable, patients with advanced cardiac disease (LV ejection fraction <35% or life expectancy < 1 year) were excluded in the present study which may explain the differences. Also, modest differences in medical treatment may play a role.

Moreover, an increase in cardiac morbidities was observed among patients who had newly diagnosed to have type 2 diabetes during the follow-up. As prediabetes is a phase in the progression from normoglycemia to type 2 diabetes, it was plausible to expect that the incidence of type 2 diabetes would be higher in patients with IFG or IGT compared to those with NG. However, this did not occur to an extent that would worsen the prognosis of the IFG and IGT groups compared to the NG group. Even higher age, body mass index and prevalence of CAD symptoms (CCS class) in the patients with IGT did not imply greater risk for cardiac mortality compared to normoglycemic patients. However, many CAD patients with initially normal glycemic status of prediabetes, may have developed type 2 diabetes during the follow-up as OGTT or HbA1c were not formally assessed during the follow-up. Prevalence of undiagnosed type 2 diabetes may be up to 30% (16). These aspects likely explain lower 5-year incidence of new type 2 diabetes in patients with prediabetes (11.4%) compared e.g. to the NAVIGATOR trial (33.9%) (17).

When glucose metabolism markers were analyzed as continuous variables in patients without type 2 diabetes, prognostic value of 2-h postload glucose, reported from the EUROASPIRE trial (14), was partly confirmed in the present study, as 2-h postload glucose showed independent association with all-

cause mortality. Also, we found univariate associations of fasting and 2-h postload glucose to cardiac death and fasting glucose and HbA1c to hospitalization due to CHF were observed. However, these observations did not remain significant after adjustment for potential confounders. Notably, none of glucose metabolism markers were associated to MACE or ACS – the latter being the major component MACE. Therefore, it seems that variation in glucose metabolism markers, within subclinical range for type 2 diabetes, may not be an important risk factor for ACS in stable CAD. This observation is contradictory to the meta-analysis by Liu et al., who reported prognostic significance of HbA1c, particularly among CAD patients without type 2 diabetes but not among CAD patients with type 2 diabetes (10). However, the univariate association of glucose metabolism markers with hospitalization due to CHF and cardiac death may suggest that they may contribute to progression of CHF, which is a potent association for increased mortality observed in CAD patients with type 2 diabetes (2; 18). Nonetheless, the lack of independent association of glucose metabolism markers to the cardiac outcomes underscores the significance of clinical variables used in multivariate analyses.

These results suggest that prediabetes in established CAD is not associated with increased risk for cardiac events compared to normoglycemia and does not have similar predictive value as type 2 diabetes in patients with CAD. This can particularly be seen especially in development of interim heart failure. The results are reassuring since increasing numbers of CAD patients also have prediabetes. Preventive efforts should be made to impede progression of prediabetes to type 2 diabetes. Exercise and diet interventions after diagnosis of CAD are potentially relevant issue for such focus (1; 20).

The present study is partly limited by the small number of end-points, particularly regarding cardiac death among patients without type 2 diabetes. We have recently reported that in CAD patients without type 2 diabetes cardiac mortality, specifically sudden cardiac mortality, is almost equal to that observed

at the population level (2). Therefore, substantial analyses of secondary fatal and non-fatal end-points were conducted to verify the present observations regarding cardiac mortality. Although, follow-up data for non-fatal end-points were not available for all patients at this point, their number was considerable to complement the main findings. At the time of the present study, SGLT2 or DDP4 inhibitors and GLP-1 analogues were not commonly used and, thus, the effect of the newer medications on the present findings is presumably low. However, the present results may not fully represent the current differences in prognosis between patients with IFG or IGT and those with type 2 diabetes, while the results may well correspond to the current clinical practice regarding comparison of the IFG/IGT and NG groups. Finally, the present study is limited by the lack of formal and consistent OGTT during the follow-up for new onset of type 2 diabetes, IFG or IGT and the lack of information about the history of IFG and IGT.

In conclusion, the risk of cardiac events among CAD patients with prediabetes is comparable to CAD patients with normal glycemic status and lower than those with type 2 diabetes when CAD is treated by revascularization and/or optimal medical therapy.

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guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Characteristics of the coronary artery disease patients with type 2 diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG) and normal glucose metabolism (NG).

Variable		Type 2 diabetes, n=834	IGT, n=314	IFG, n=103	NG, n=695
Age (years)		67 (8)‡	69 (8)*†	66 (8)	66 (9)
Men		577 (69%)	193 (62%)*	71 (69%)	486 (70%)
Body mass index (kg/m²)		30.0 (4.9)*†‡	27.5 (4.2)*	28.4 (3.9)*	26.6 (3.6)
Waist-hip ratio		0.99 (0.08)*†‡	0.95 (0.09)	0.96 (0.07)	0.94 (0.09)
Resting heart rate (bpm)		64 (11)*†‡	62 (10)*	61 (11)	58 (9)
Resting systolic blood pressure (mmHg)		147 (23)	148 (25)	142 (23)	144 (23)
Resting diastolic blood pressure (mmHg)		78 (11)*	76 (11)	76 (10)	77 (10)
Smoking status	Current	74 (9%)	20 (6%)	11 (11%)	62 (9%)
	Ex-smoker	387 (47%)	122 (39%)	38 (37%)	286 (41%)
History of prior myocardial infarction		383 (46%)	159 (51%)	57 (55%)	330 (48%)
NSTEMI		262 (32%)	97 (31%)	43 (42%)	212 (31%)
STEMI		139 (17%)	65 (21%)	19 (19%)	131 (19%)
History of revascularization	No	172 (20%)	69 (22%)	18 (18%)	141 (20%)

PCI	453 (54%)	173 (55%)	58 (56%)	416 (60%)
CABG	209 (25%)	71 (23%)	27 (26%)	138 (20%)
CCS class ≥ 2	414 (50%)*	154 (49%)*	40 (39%)	231 (33%)
Syntax Score	2 (0-6)*‡	0 (0-4)	0 (0-5)	0 (0-5)
Duration of type 2 diabetes (years)	5 (2-12)	-	-	-
Echocardiography				
Left ventricular ejection fraction (%)	63 (10)‡	65 (9)	64 (9)	64 (8)
Left ventricular mass index (g/m^2)	110 (28)*	107 (31)	103 (24)	106 (25)
Medication				
β-blockers	757 (91%)*	280 (89%)	89 (86%)	579 (84%)
Angiotensin converting enzyme inhibitors or receptor blockers	645 (77%)*†‡	214 (68%)*	59 (57%)	413 (59%)
Calcium channel blockers	273 (33%)*†‡	72 (23%)	16 (16%)	114 (16%)
Diuretics	406 (49%)*†‡	87 (28%)	25 (24%)	149 (21%)
Statins	758 (91%)	291 (93%)	94 (91%)	635 (91%)
Oral diabetes medication	617 (74%))	-	-	-
Insulin	215 (26%)	-	-	-
Oral diabetes medication + Insulin	153 (18%)	-	-	-

Laboratory analyses				
Glycated hemoglobin (mmol/mol)	53 (13)*†‡	42 (5)*	41 (4)	40 (4)
Glycated hemoglobin (%)	7.0 (1.2)*†‡	6.0 (0.5)*	5.9 (0.4)	5.8 (0.4)
Fasting glucose (mmol/L)	7.6 (2.2)*†‡	5.9 (0.6)*†	6.5 (0.3)*	5.4 (0.4)
2-h postload glucose (mmol/L)	13.0 (2.0)*†‡§	10.3 (0.9)*†	7.4 (1.1)	7.1 (1.1)
Total cholesterol (mmol/L)	3.89 (0.86)*†	4.03 (0.94)	4.24 (0.92)	4.05 (0.85)
High-density lipoprotein cholesterol (mmol/L)	1.18 (0.29)*†‡	1.30 (0.32)	1.29 (0.27)	1.35 (0.33)
Low-density lipoprotein cholesterol (mmol/L)	2.22 (0.74)*†	2.33 (0.80)	2.48 (0.88)	2.32 (0.77)
Triglycerides (mmol/L)	1.40 (1.04-1.92)*†‡	1.19 (0.89-1.59)*	1.29 (0.90-1.59)*	1.06 (0.82-1.40)
Creatinine clearance (mL/min)	101 (40)*‡	84 (29)†	97 (30)	89 (28)
U-Albumin/Creatinine-ratio	1.0 (0.7-2.0)*†‡	0.8 (0.5-1.2)	0.7 (0.5-1.0)	0.8 (0.5-1.1)
End-points				
Death‖	127 (15.2%)*†	34 (10.8%)*	5 (4.9%)	42 (6.0%)
Cardiac death‖	68 (8.2%)*†	12 (3.8%)	3 (2.9%)	18 (2.6%)
ACS (5-year follow-up, n=1698)	132 (18.1%)	35 (13.3%)	13 (14.6%)	89 (14.5%)
CHF (5-year follow-up, n=1676)	53 (7.4%)*	8 (3.1%)	2 (2.3%)	15 (2.5%)
MACE‖	212 (25.4%)*†‡	48 (15.3%)	14 (13.6%)	111 (16.0%)
New type 2 diabetes (5-year follow-up, n=798,	-	25 (11.2%)*	9 (12.2%)*	18 (3.6%)

IGF/IGT and NG at entry)

Values are mean (SD), median (1st-3rd quartile) or n (% within group). *NSTEMI* non-ST elevation myocardial infarction, *STEMI* ST-elevation myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *CCS* Canadian Cardiovascular Society grading of angina pectoris, *ACS* hospitalization due to acute coronary syndrome, *CHF* hospitalization due to heart failure, * $p<0.05$ vs. NG, † $p<0.05$ compared to IFG, ‡ $p<0.05$ vs. IGT, § n=100, ‖ including aborted cardiac arrests.

Table 2. Mortality risk and risk for hospitalization in coronary artery disease patients with impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and type 2 diabetes compared to patients with normal glucose metabolism (NG).

	Cardiac death§, n=101	MACE§, n=385	Death§, n=208	ACS (5 years), n=269	CHF (5 years), n=78
Univariate	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
NG	1.00	1.00	1.00	1.00	1.00
IFG	1.10 (0.32-3.72)	0.83 (0.48-1.45)	0.78 (0.31-1.98)	0.98 (0.55-1.76)	0.92 (0.21-4.00)
IGT	1.48 (0.71-3.07)	0.94 (0.67-1.32)	1.80 (1.15-2.83)*	0.90 (0.61-1.34)	1.26 (0.54-2.98)
Type 2 diabetes	3.11 (1.85-5.23)*‡	1.65 (1.31-2.08)*†‡	2.47 (1.74-3.51)*†	1.29 (0.98-1.69)	3.13 (1.77-5.56)*‡
Multivariate‖					
NG	1.00	1.00	1.00	1.00	1.00
IFG	0.45 (0.06-3.42)	0.81 (0.44-1.47)	0.36 (0.09-1.49)	0.95 (0.50-1.79)	1.09 (0.24-4.83)
IGT	1.12 (0.49-2.53)	0.89 (0.62-1.28)	1.38 (0.85-2.24)	1.01 (0.67-1.52)	0.94 (0.36-2.47)
Type 2 diabetes	2.21 (1.24-3.92)*	1.39 (1.07-1.81)*‡	2.04 (1.39-2.98)*†	1.23 (0.90-1.68)	1.72 (0.91-3.28)

HR hazard ratio, *CI* confidence interval. *ACS* hospitalization due to acute coronary syndrome, *CHF* hospitalization due to heart failure, *MACE* major adverse cardiac event (cardiac death, ACS or CHF), * $p<0.05$ vs. NG, † $p<0.05$ vs. IFG, ‡ $p<0.05$ vs. IGT, § including aborted cardiac arrests, ‖ Adjusted for age, sex, body mass index, resting systolic and diastolic blood pressure, Canadian Cardiovascular Society grading for angina pectoris, syntax score and left ventricular ejection fraction.

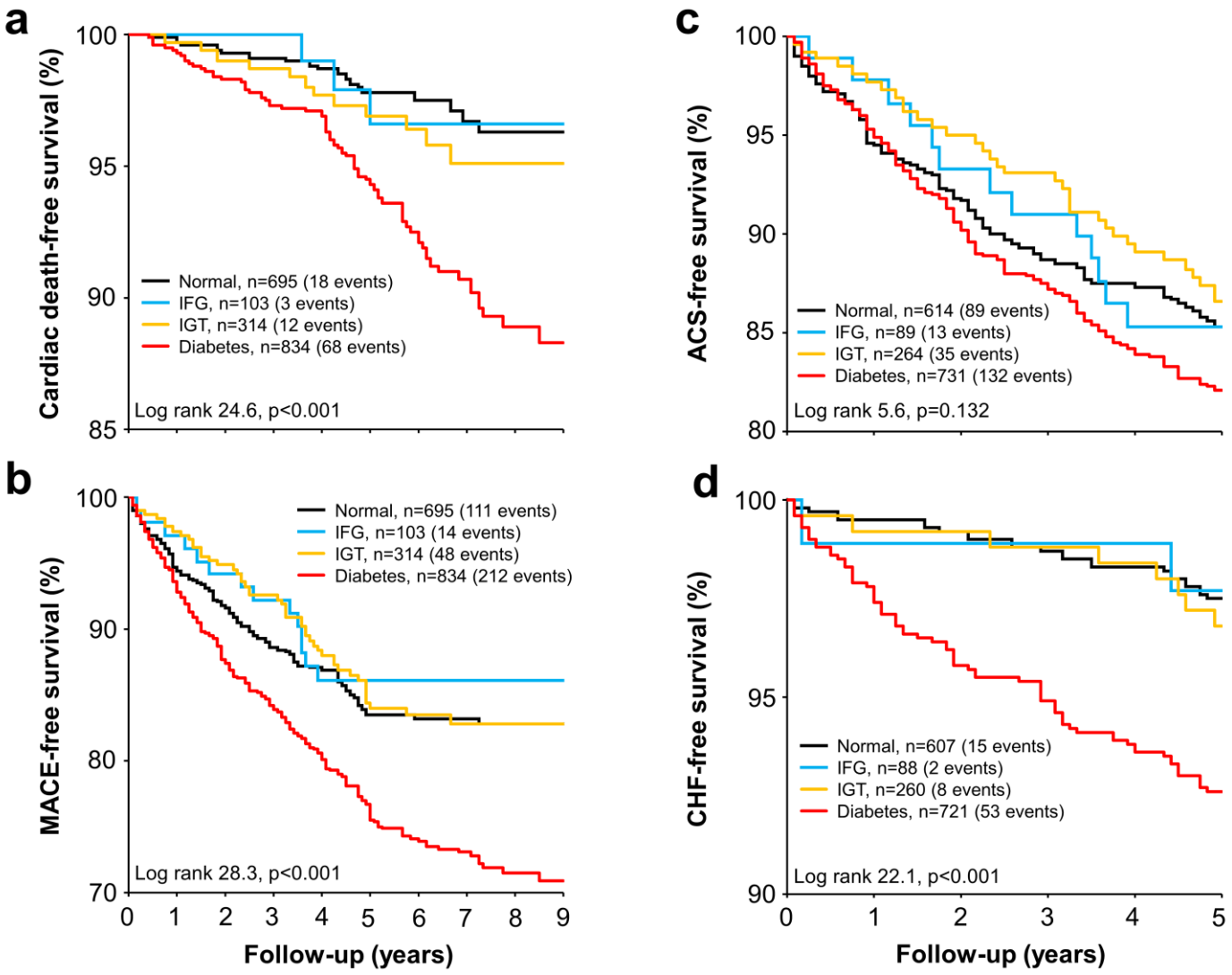

Figure 1. Kaplan-Meier survival curves for cardiac mortality (a), major adverse cardiac event (MACE, b) and hospitalizations due to acute coronary syndrome (ACS, c) and chronic heart failure (CHF, d).