Type 2 diabetes and coronary artery disease: Preserved ejection fraction and sudden cardiac death

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BACKGROUND Previous studies have shown that type 2 diabetes (DM2) is associated with sudden cardiac death (SCD) risk in post–myocardial infarction patients. The treatment of coronary artery disease (CAD) as well as DM2 has changed over time.

OBJECTIVE The purpose of this study was to compare the incidence of SCD in DM2 and nondiabetic patients with CAD and preserved ejection fraction (EF) in a prospective observational study (ARTEMIS study).

METHODS In 834 DM2 patients and 1112 nondiabetic patients with CAD enrolled, the EF measured ≥3 months after qualifying was 63% ± 10% in DM2 patients and 65% ± 8% in nondiabetic patients ($P < .01$). The primary end point was SCD or resuscitation from sudden cardiac arrest (SCA). All-cause mortality, cardiac mortality, non-SCD, hospitalization for heart failure, and acute coronary syndrome were secondary end points.

RESULTS During a mean follow-up of 6.3 ± 1.6 years, SCDs/SCAs occurred in 50 patients. The prevalence of SCD/SCA was higher in DM2 patients (4.1%) than in nondiabetic patients (1.4%) (adjusted hazard ratio 2.6; 95% confidence interval 1.3–5.3; $P < .01$). However, the non-SCD component of cardiac mortality was not significantly different between DM2 and nondiabetic patients. In addition, heart failure hospitalizations were more common in DM2 patients (8.4%) than in nondiabetic patients (2.9%) ($P < .001$). The annual cardiac mortality in nondiabetic patients with CAD was 0.50%, which was lower than the 0.59% reported in the general Finnish population.

CONCLUSION DM2 is an independent risk factor for SCD/SCA in CAD patients with preserved EF. Cardiac mortality in nondiabetic CAD patients is slightly lower than that in the general population in the present treatment era.

KEYWORDS Cardiac death; Coronary artery disease; Outcome; Sudden cardiac death; Type 2 diabetes

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Introduction

Type 2 diabetes (DM2) is a major health issue in Western society, and it is also rapidly evolving as a global health hazard.[1] An association between DM2 and cardiovascular disease is well recognized, and macrovascular disease such as coronary artery disease (CAD) is often the first manifestation of DM2.[2] Cardiac mortality in DM2 patients with prior myocardial infarction (MI) is significantly higher than that in nondiabetic subjects, although the mode of death and events preceding death are largely unknown.[3,4] In contrast, the incidence of cardiac mortality in a lower risk population of CAD patients with DM2 is unclear. Major advances have been made in the treatment of acute coronary events, stable CAD, as well as treatment of DM2 patients, but the extent of this improvement is unclear, especially in the incidence of sudden cardiac death (SCD).[5]

The primary aim of this prospective study was to compare the incidence of SCD among CAD patients with or without DM2. In addition, we sought to compare the incidence of cardiac death, non-SCD, all-cause mortality, and hospitalization for congestive heart failure (CHF) or acute coronary syndrome (ACS) between DM2 and nondiabetic patients. Finally, we compared the annual incidence of cardiac mortality of CAD patients with and without DM2 in the present

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treatment era with that observed in the same age group in the general Finnish population.

Methods

Study protocol and study population

ARTEMIS is a prospective observational study (Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection; ClinicalTrials.gov identifier NCT01426685) that recruited patients with angiographically documented CAD, with or without DM2.[6] The study population was recruited from a series of patients enrolled in the coronary angiography registry at the Division of Cardiology, Oulu University Hospital, between August 1, 2007 and December 31, 2012. The initial examinations and determination of inclusion/exclusion status were conducted at least 3 months after coronary angiography and/or the last revascularization.

Nondiabetic patients were matched with DM2 patients for age, sex, prior MI (non–ST-segment elevation MI or ST-segment elevation MI), and revascularization. Significant CAD, (defined as $\geq$1 vessels with $\geq$50% stenosis) was confirmed by coronary angiography, and DM2 was diagnosed according to the World Health Organization criteria (ie, fasting glucose level $>$7.0 mmol/L or 2-hour glucose tolerance level $>$11.1 mmol/L).[7] At the initial enrollment visit, a 2-hour glucose tolerance test was performed on all subjects not previously diagnosed with DM2 to identify subjects who had undiagnosed DM2. Subjects who met the guidelines criteria for prophylactic implantation of implantable cardioverter-defibrillator (ICD), including all with a left ventricular (LV) ejection fraction (EF) of $<$35%, were excluded from the study regardless of whether an ICD was implanted, and subjects with a life expectancy of $\leq$1 year due to any comorbidity were excluded from the study.

Examinations during the enrollment visit included 12-lead electrocardiography, echocardiography, 24-hour Holter monitoring, exercise electrocardiography, and laboratory analyses. Medical therapy for both DM2 and coronary atherosclerosis was optimized during the visit by specialists in endocrinology and diabetes management and by cardiologists. After exclusions, the study population included 834 subjects with DM2 and 1112 nondiabetic subjects. The number of DM2 patients is lower than that of control patients because a proportion of DM2 patients did not consent to the study. Additional echocardiograms were recorded during follow-up visits in 121 DM2 subjects (15%) and 139 nondiabetic subjects (13%), a mean of 24 months after enrollment. All enrolled patients gave informed consent, and the study was approved by the institutional ethics committee. The study complies with the Declaration of Helsinki.

Outcomes

End points were determined from emergency rescue reports, hospital and physician records, autopsy data, death certificates, and interviews with the next of kin. The cause and mode of death were reviewed and adjudicated by 2 independent investigators; and if needed, disagreement or uncertainty was resolved in consultation with the investigators (M.J.J. and H.V.H.). The primary end point in this study was SCD or resuscitation from sudden cardiac arrest (SCA), whichever occurred first. The definition for *SCD* was a witnessed death within 1 hour of the onset of symptoms. For *unwitnessed deaths*, the definition was last being seen alive and stable 24 hours before discovery. A medicolegal autopsy is mandatory in Finland according to the law, and thus autopsy data were available in most cases. The secondary end points were all cardiac deaths, which included SCD, aborted SCA, and non-SCD, whichever occurred first. To compare the incidence of cardiac death with that in the general population in Finland, we obtained nationwide annual cardiac mortality (primary cause of death *International Classification of Diseases, Tenth Revision* codes I20–I25 and I30–I52) during 2015 in the age range of 60–80 years from Statistics Finland (http://stat.fi).

Additional secondary end points were all-cause mortality, non-SCD, and hospitalization for either heart failure or ACS, diagnosed according to the current guidelines. Study subjects were contacted through a mailed questionnaire and by telephone to inquire about the possible interim hospitalization at 2 and 5 years of follow-up. The final adjudication of the reason for hospitalization was ascertained from the primary discharge diagnosis from medical records.

Statistical analysis

A 2-tailed t test for independent samples or the Mann-Whitney U test was used to test the differences in continuous variables between DM2 and nondiabetic groups, depending on the distribution of the data (Gaussian if $|\text{skewness}| < 1$). The χ^2 test was used to test the differences in categorical variables. The risk related to DM2 was assessed by univariate Cox regression followed by adjustment for age, sex, body mass index, resting systolic and diastolic blood pressures, Canadian Cardiovascular Society grading for angina pectoris, SYNTAX score (www.syntaxscore.com), and LV EF. Kaplan-Meier plots was used to illustrate survival curves of DM2 and nondiabetic groups. Data were analyzed using SPSS version 21 (IBM Corp., Armonk, NY). A P value of $<$.05 was considered as statistically significant.

Results

There were several differences in baseline characteristics between DM2 and nondiabetic CAD groups despite matching for age, sex, prior MI, and revascularization. Subjects with DM2 had a higher body mass index (30.0 $\pm$ 4.9 kg/m^2 vs 27.0 $\pm$ 3.9 kg/m^2; $P < .001$) than did nondiabetic patients, as anticipated. Heart rate, systolic and diastolic blood pressures, and LV mass index were all increased statistically, and LV EF was significantly lower in DM2 patients than in nondiabetic patients, but in each case the absolute numerical differences and resulting clinical relevance were small (Table 1). Specifically, while the mean systolic blood pressure was higher than the desired goal in both groups, the mean