Long-Term Cardiovascular Risk in Type 2 Diabetic Compared With Nondiabetic First Acute Myocardial Infarction Patients

A population-based cohort study in southern Europe

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OBJECTIVE — The aim of this study was to determine whether long-term cardiovascular risk differs in type 2 diabetic patients compared with first acute myocardial infarction patients in a Mediterranean region, considering therapy, diabetes duration, and glycemic control.

RESEARCH DESIGN AND METHODS — A prospective population-based cohort study with 10-year follow-up was performed in 4,410 patients aged 30–74 years: 2,260 with type 2 diabetes without coronary heart disease recruited in 53 primary health care centers and 2,150 with first acute myocardial infarction without diabetes recruited in 10 hospitals. We compared coronary heart disease incidence and cardiovascular mortality rates in myocardial infarction patients and diabetic patients, including subgroups by diabetes treatment, duration, and A1C.

RESULTS — The adjusted hazard ratios (HRs) for 10-year coronary heart disease incidence and for cardiovascular mortality were significantly lower in men and women with diabetes than in myocardial infarction patients: HR 0.54 (95% CI 0.45–0.66) and 0.28 (0.21–0.37) and 0.26 (0.19–0.36) and 0.16 (0.10–0.26), respectively. All diabetic patient subgroups had significantly fewer events than myocardial infarction patients: the HR of cardiovascular mortality ranged from 0.15 (0.09–0.26) to 0.36 (0.24–0.54) and that of coronary heart disease incidence ranged from 0.34 (0.26–0.46) to 0.56 (0.43–0.72).

CONCLUSIONS — Lower long-term cardiovascular risk was found in type 2 diabetic and all subgroups analyzed compared with myocardial infarction patients. These results do not support equivalence in coronary disease risk for diabetic and myocardial infarction patients.

Diabetes Care **33:2004–2009, 2010**

The prevalence of diabetes is reaching epidemic proportions in developed countries (1). For example, the U.S. has 18 million diabetic patients, Spain has >2 million diabetic patients, and management of the disease costs >$132 and >$3.3 billion per year, respectively (2).

Some studies (3–5), several of them with great influence on important guidelines for cardiovascular prevention (3), suggest that the cardiovascular risk of diabetic patients is similar to that of coronary heart disease secondary prevention patients. Other reports, however, do not confirm these observations (6–10).

Part of the discrepancy may stem from differences in the duration of diabetes, type of treatment, and baseline glucose control of diabetic patients included in the studies (3–5). These limit comparability, given the fact that time of evolution and treatment required to attain appropriate glycemic control are key determinants of prognosis (10–16).

Among population-based cohort studies that compared the prognosis of diabetic patients with that of myocardial infarction patients without diabetes (3–10), only two analyzed the role of diabetes duration (11,12). Even these studies did not include unstable angina among the end points and risk was not stratified by type of treatment. To our knowledge, the effect of type 2 diabetes on coronary heart disease incidence has barely been studied in southern Europe, a region known for low cardiovascular mortality (17). The aim of this study was to determine whether long-term cardiovascular risk differed between type 2 diabetic patients and first acute myocardial infarction patients and to assess the influence of diabetes duration, type of treatment, and glycemic control at baseline.

RESEARCH DESIGN AND METHODS

— We designed a cohort study in Catalonia (northeast Spain) that included two groups of patients aged 30–74 years: consecutive first acute myocardial infarction patients without diabetes who survived at least 28 days after index myocardial infarction symptom onset and a random sample of type 2 diabetic patients without coronary heart disease. The study was approved by a local ethics committee (Institut Municipal d'Investigació Mèdica) and complied with

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Received 24 March 2010 and accepted 31 May 2010. Published ahead of print at http://care.diabetesjournals.org on 8 June 2010. DOI: 10.2337/dc10-0560.
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all the laws and international ethics guidelines (Declaration of Helsinki).

Acute myocardial infarction patients were recruited consecutively between 1990 and 2003 in the context of the population-based REGICOR (Registre Gironí del Cor [Girona Heart Registry]) study (17). The reference population was ~600,000 individuals. All 10 public and private hospitals in the region participate in REGICOR, using the same standards to diagnose acute myocardial infarction: non–Q-wave and Q-wave myocardial infarction, determined by a discharge electrocardiogram in patients who presented with chest pain lasting >20 min on admission, followed by typical changes in serial electrocardiograms and an abnormal increase in the cardiac enzymes or troponin value curve.

We excluded patients outside the selected age range and those meeting the National Diabetes Data Group 1979 and American Diabetes Association 1997 criteria for diabetes (18,19), including patients with two consecutive fasting plasma glucose values ≥7.8 or ≥7 mmol/l during admission, before and after 1998, previous acute myocardial infarction, or other diseases that shortened life expectancy to <1 year.

Type 2 diabetic patients were randomly recruited between 1993 and 1998 in the 53 primary health care centers in Catalonia participating in the GEDAPS (Grupo de Estudio de la Diabetes en Atención Primaria de Salud [Primary Health Care Diabetes Study Group]) network. The total adult population attending the participating primary health care centers was 982,567. Diagnosis of type 2 diabetes was based on National Diabetes Data Group 1979 criteria, i.e., two fasting plasma glucose values ≥7.8 mmol/l or 2-h plasma glucose values ≥11.1 mmol/l during oral glucose tolerance test (18). We excluded patients not within the age range of the study, with BMI <22 kg/m^2, diseases that shortened life expectancy to <1 year or history of any coronary heart event or ketoacidosis.

Baseline study

For all participants, we recorded age, sex, follow-up (in days), and, from medical records, their history of dyslipidemia and hypertension and smoking habit. For diabetic patients we also collected A1C concentration (fructosamine levels were not considered), treatment (diet, oral drugs, or insulin), and duration of diabetes in years. In acute myocardial infarction patients, the presence of a Q-wave in the electrocardiogram was recorded.

Follow-up and end points

In 2008, we completed up to 10 years follow-up by telephone, medical examination, or clinical record review. Participating physicians verified all clinical record events. We also cross-linked our databases with the official Mortality Registry of Catalonia.

The individual end points considered were all-cause death, coronary death, stroke death, cardiovascular death, nonfatal acute myocardial infarction, and unstable angina. Two composite end points were used in the analyses: cardiovascular mortality (coronary, stroke, and other cardiovascular deaths) and coronary heart disease incidence (unstable angina or fatal or nonfatal acute myocardial infarction). The first cardiovascular event, regardless of its severity, was considered in the analysis.

Deaths were considered of coronary heart disease origin in cases of suggestive necropsy findings, clinical records of hospitalized patients, or the presence on death certificates of ICD-9 codes 410–412, 414, 429.9, 798.1, and 798.2 or ICD-10 codes I210–I214, I219–I229, I236, I240–I249, I250–I259, I46.1, R960, and R961).

Stroke was defined by suggestive necropsy findings, clinical records for hospitalized patients, or ICD-9 codes 430–434 and 436–438 (excluding 437.4–437.8) or ICD-10 codes I619–I639, I64, I670–I679, I688, and I690–I698.

Other cardiovascular deaths were similarly defined. The applicable ICD-9 codes were 401–405, 426–428, and 429.1–429.9 and ICD-10 codes were I10–I110, I50–I52, I440–I499, I500–I509, I250, and I511–I519.

Nonfatal acute myocardial infarction was diagnosed when patients presented with chest pain lasting >20 min on admission, followed by typical changes in serial electrocardiograms and an abnormal increase in the cardiac enzymes or troponin value curve.

Unstable angina during follow-up was diagnosed by the presence of angina symptoms without an abnormal increase in the cardiac enzymes or troponin and with electrocardiographic changes in serial electrocardiograms or when, with or without electrocardiographic changes, suggestive symptoms were recorded during the event and confirmed by a positive stress test, with or without isotopic stress gammagraphy, or a positive coronary angiogram (stenosis >70%).

Statistical analyses

Our study was sufficiently powered (>90%) to identify a statistically significant hazard ratio (HR) ≤0.80 for type 2 diabetic patients compared with first acute myocardial infarction patients, assuming >25% 10-year coronary heart disease incidence among the latter and a correlation <0.3 of the type 2 diabetes variable with potential confounders. The two groups were approximately equally represented in the study: 51% diabetic and 49% myocardial infarction patients. Differences between myocardial infarction and diabetic patients at 10 years were assessed by a χ^2 test for categorical variables and by Student's *t* test for continuous variables or the nonparametric equivalents, as appropriate.

Cox proportional hazards models were fitted to estimate the adjusted HR of cardiovascular mortality and coronary heart disease incidence at 10 years. Demographic, comorbidity, clinical, and severity variables that showed at least marginally significant differences ($P \leq 0.10$) between type 2 diabetes and acute myocardial infarction patients, as well as variables considered important based on clinical judgment, were included as potential confounders in the multivariate analyses. Because the two cohorts were conducted at different time points, the results were adjusted for recruitment year, and a sensitivity analyses was performed in 2,260 diabetic patients and 828 acute myocardial infarction patients recruited in the same time periods (1993–1998). We considered tertiles of diabetes duration, comparing the third tertile versus the first and second together and two groups of glycemic control (A1C <7% and ≥7%) and therapy (diet alone, only oral drugs, and insulin).

Survival curves were estimated with the Kaplan-Meier method and compared by Mantel-Cox statistics. Calculations were made with R (2.6.2 package; The R Foundation for Statistical Computing, Free Software Foundation, Boston, MA).

RESULTS — The study included 2,260 type 2 diabetic patients and 2,154 first acute myocardial infarction patients who survived 28 days after symptom onset. Baseline characteristics of patients are shown in Table 1. Acute myocardial infarction patients were younger and less fre-

Table 1—*Baseline characteristics in non–coronary heart disease type 2 diabetic patients compared with nondiabetic first acute myocardial infarction survivors*

	Type 2 diabetes	AMI	*P* value
n	2,260	2,154	
Sex (women)	1,219 (53.9)	309 (14.3)	<0.001
Age (years)	61.8 ± 8.4	59.3 ± 10.5	<0.001
Risk factors			
Dyslipidemia*	1,156 (53.9)	806 (40.9)	<0.001
Hypertension*	1,334 (59.9)	909 (43.5)	<0.001
Smoking	282 (14.4)	57 (11.4)†	0.105
A1C‡	7.5 ± 1.7	—	—
A1C <7%‡	821 (46.6)	—	—
Type 2 diabetes duration in years (median, quartiles)	5.0 (3.0–10.0)	—	—
Therapy type 2 diabetes*			
Diet alone	586 (27.8)	—	—
Only oral drugs	1,030 (48.9)	—	—
Insulin	416 (19.7)	—	—
Oral drugs and insulin	75 (3.6)	—	—
Non-Q wave myocardial infarction	—	436 (20.3)	—
Follow-up in days (median, range)	3,452 (142–3,653)	2,597 (32–3,653)	—

Data are *n* (%) or means ± SD unless specified otherwise. AMI, acute myocardial infarction. *Some missing values in these variables (<5%). †Evaluated in a sample of 499 patients at 6 months. ‡Included only patients with A1C: fructosamine alone was used in 497 (22%) patients.

quently than the diabetic participants were women, hypertensive, and dyslipidemic.

The incidence rate for all event types was significantly worse among acute myocardial infarction patients, except for stroke death and unstable angina (Table 2). These differences held after adjustment for sex, age, and baseline dyslipidemia, hypertension, and recruitment year. These findings were similar in both sexes, except for unstable angina: diabetic women had a significantly lower risk.

Figure 1 shows the Kaplan-Meier curves of cardiovascular mortality and coronary heart disease incidence, respectively, comparing myocardial infarction patients with diabetic patients stratified by duration of type 2 diabetes, A1C, and therapy. All type 2 diabetes strata had significantly lower risk of both end points than acute myocardial infarction patients.

All subgroups of diabetic patients had significantly lower risk of both composite end points than their acute myocardial infarction counterparts (Table 3). Patients with type 2 diabetes receiving insulin therapy, with >8 years of disease duration and A1C ≥7% were at significantly higher risk of coronary heart disease incidence or cardiovascular mortality than were those receiving dietary therapy alone or only oral drugs, with ≤8 years of evolution and A1C <7%, respectively. Other cutoff points of A1C (<6.5 vs. ≥6.5% and <6.5, 6.5–7.5, and >7.5%) showed similar HRs for cardiovascular mortality and coronary heart disease incidence. At the cutoff point <6.5 vs. ≥6.5%, the HR for cardiovascular mortality was 0.16 (95% CI 0.10–0.27) and 0.23 (0.17–0.32) and for coronary heart disease incidence was 0.34 (0.25–0.45) and 0.44 (0.36–0.53), respectively. For the cutoff points <6.5, 6.5–7.5, and >7.5%, the HR for cardiovascular mortality was 0.16 (0.10–0.27), 0.22 (0.14–0.36), and 0.24 (0.16–0.35) and for coronary heart disease incidence was 0.34 (0.25–0.45), 0.37 (0.28–0.50), and 0.48 (0.38–0.60), respectively.

Sensitivity analyses produced similar results. For example, the adjusted HR for 10-year coronary heart disease incidence and cardiovascular mortality was 0.53 (95% CI 0.42–0.67) and 0.30 (0.20–0.44) and 0.24 (0.17–0.34) and 0.23 (0.12–0.44) in men and women, respectively.

CONCLUSIONS — The results of our study indicate that type 2 diabetic patients without previous coronary heart disease not only have lower 10-year cardiovascular mortality but also have lower coronary heart disease incidence than first acute myocardial infarction patients without diabetes. These differences held after adjustment for potential confounders and in subgroups of diabetic patients.

Results of previous studies may have found similar cardiovascular event rates due to differences in prognosis. In some cases, the population-based diabetes samples included only patients receiving drug treatment, which would exclude up to

Table 2—*Incidence rate and adjusted HR of different cardiovascular end points at 10 years for initially non–coronary heart disease diabetic patients compared with nondiabetic first acute myocardial infarction survivors in all participants and by sex*

			HR (95% CI)		
	Type 2 diabetes	AMI	All participants	Men	Women
n	2,260	2,154			
All-cause death	289 (12.8)	482 (22.4)*	0.39 (0.32–0.46)	0.44 (0.36–0.54)	0.28 (0.20–0.39)
Coronary death	41 (1.8)	206 (9.6)*	0.12 (0.08–0.18)	0.16 (0.10–0.25)	0.09 (0.05–0.17)
Stroke death	24 (1.1)	27 (1.3)	0.66 (0.34–1.27)	0.64 (0.32–1.31)	0.82 (0.09–7.33)
Cardiovascular mortality	99 (4.4)	280 (13.0)*	0.22 (0.17–0.28)	0.26 (0.19–0.36)	0.16 (0.10–0.26)
Unstable angina	184 (8.1)	145 (6.7)	0.95 (0.74–1.23)	1.24 (0.93–1.66)	0.46 (0.29–0.72)
Nonfatal myocardial infarction	126 (5.6)	175 (8.1)*	0.59 (0.45–0.77)	0.72 (0.53–0.98)	0.38 (0.24–0.61)
Fatal or nonfatal myocardial infarction	161 (7.1)	349 (16.2)*	0.33 (0.27–0.41)	0.41 (0.32–0.53)	0.22 (0.16–0.32)
Coronary heart disease incidence†	296 (13.1)	475 (22.1)*	0.43 (0.36–0.51)	0.54 (0.45–0.66)	0.28 (0.21–0.37)

Data are *n* (%) or HR (95% CI). All models are adjusted for sex, age, recruitment year, and baseline dyslipidemia and hypertension. AMI, acute myocardial infarction. *$P \leq 0.001$. †Unstable angina or fatal or nonfatal AMI.

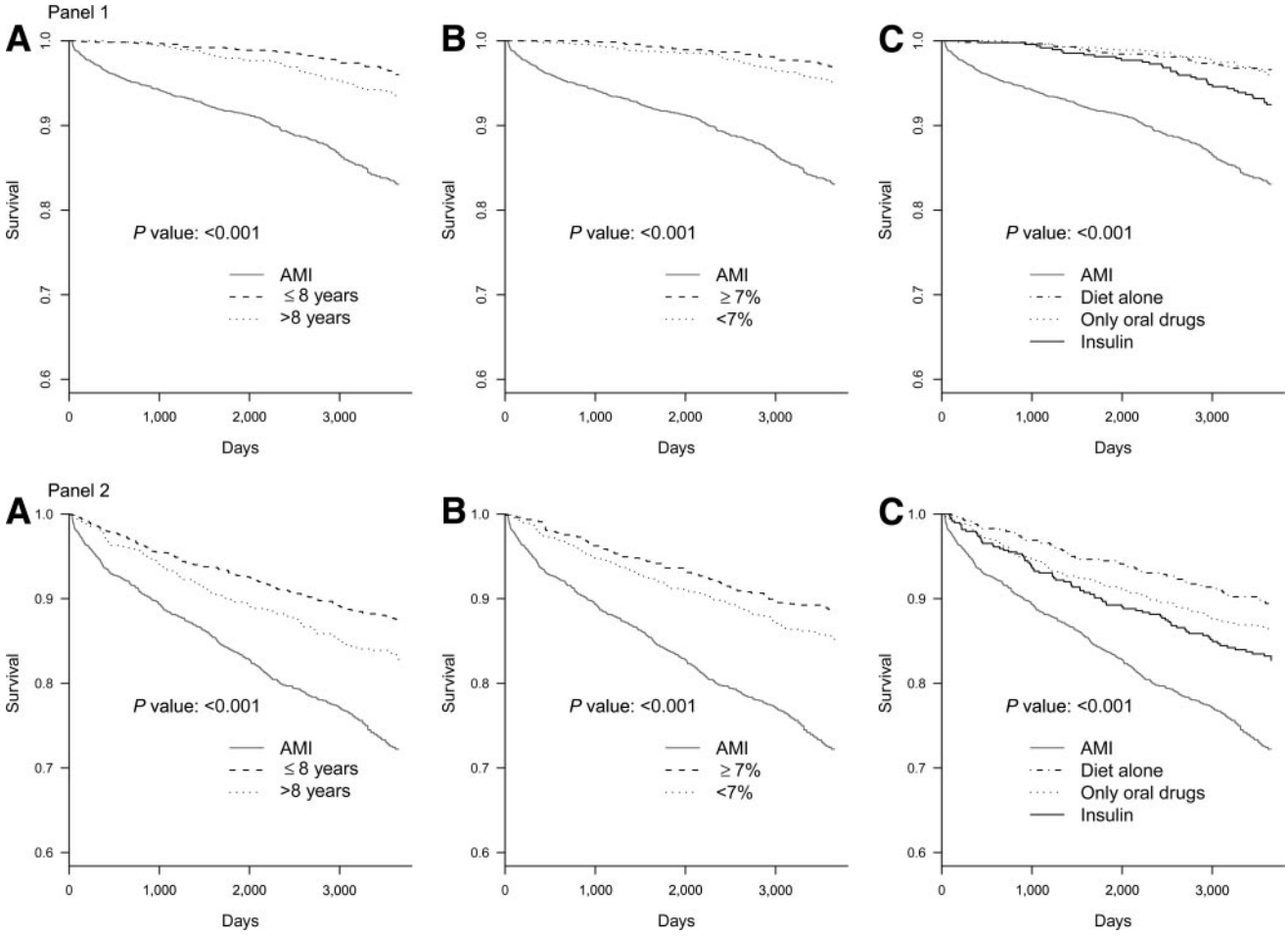

Figure 1—*Free of cardiovascular mortality (panel 1) and free of coronary heart disease (panel 2) survival curves among initially non–coronary heart disease diabetic patients compared with nondiabetic first acute myocardial infarction (AMI) survivors.* A*: According to time of evolution of type 2 diabetes (cut point 8 years).* B*: According to A1C levels (cut point 7%).* C*: According to diabetes treatment (diet alone, only oral drugs, or insulin).*

25% of the total diabetic population (3–5). In several cohorts of diabetic patients from Finland, Scotland, and U.S. selected irrespective of treatment status, patients with myocardial infarction had more events than those with diabetes (6–10). In our study the results suggest that diabetic patients receiving insulin or oral drug treatment may have a worse prognosis at 10 years than those treated with diet alone. However, diabetic patients treated with any of these modalities had significantly lower risk than myocardial infarction patients.

Duration of diabetes was a determinant of cardiovascular outcomes in our study, which concurs with other reports (7,11,16). Our cut point (third tertile) was 8 years; other authors found that twice this evolution time (16 years) was required to worsen prognosis at 25 years (11).

Patients with A1C ≥7% had worse prognosis. Diabetic patients in our series had lower levels of mean A1C at baseline than those included in the intensive branch of the UKPDS, 7.5 vs. 8.1%, respectively (14). Despite differences in study design, our results support the relationship reported by the UKPDS between high levels of A1C and worse prognosis. The UKPDS approach is probably more realistic and correct than the stricter targets (A1C <6.5%) proposed in some intervention studies (20) that did not find significant differences or an increased number of cardiovascular events in the more intensive intervention arm. Some studies with stricter targets have shown the important role of hypoglycemia episodes in the poor prognosis of patients randomly assigned to intensive treatment (21).

We found that incidence of unstable angina was similar in men with myocardial infarction and in men with diabetes, but lower in diabetic women than in their myocardial infarction counterparts. Mortality due to stroke was similar in both groups of patients and in both sexes. This observation adds to the existing controversy, with some authors finding positive (3,11) and some negative (5,7) differences. The low number of events, due to the age range selection in our study and to the fact that only fatal events were considered, hampers a more conclusive result.

Our findings, taken together with the opposite observation in some high cardiovascular mortality countries (3–5) and intermediate observations in central-western Europe (6) and the U.S. (7), suggest that geographic variation exists. In Europe, the south-to-north gradient is persistently observed in myocardial infarction incidence and mortality rates. The paradox of high cardiovascular risk factor prevalence that contrasts with relatively low acute myocardial infarction incidence rates has been described in Spain (17). Our findings also support such a gradient: the risk of fatal and nonfatal

Table 3—*Adjusted HR of 10-year end points for type 2 diabetes patients by baseline tertiles of duration, glycemic control, and therapy compared with nondiabetic first acute myocardial infarction survivors*

	Cardiovascular mortality	Coronary heart disease incidence*
Diabetes duration		
AMI patients	1 (reference)	1 (reference)
First and second tertiles (≤8 years)	0.20 (0.14–0.28)†	0.40 (0.33–0.49)†
Third tertile (>8 years)	0.29 (0.20–0.41)†‡	0.54 (0.43–0.68)†‡
Glycemic control		
AMI patients	1 (reference)	1 (reference)
A1C <7%	0.16 (0.10–0.25)†	0.34 (0.27–0.44)†
A1C ≥7%	0.25 (0.18- 0.35)†‡	0.46 (0.37–0.57)†‡
Diabetes treatment		
AMI patients	1 (reference)	1 (reference)
Diet alone	0.15 (0.09–0.26)†	0.34 (0.26–0.46)†
Only oral drugs	0.20 (0.14–0.29)†	0.42 (0.34–0.52)†
Insulin	0.36 (0.24–0.54)†‡	0.56 (0.43–0.72)†‡

Data are HR (95% CI). AMI, acute myocardial infarction. *Unstable angina or fatal or nonfatal AMI. †$P <$ 0.05 compared with reference category (myocardial infarction patients). ‡$P < 0.05$ compared with immediately previous category. All models are adjusted for sex, age, recruitment year, and baseline dyslipidemia and hypertension.

myocardial infarction in diabetic patients was 0.33 (95% CI 0.27–0.41); in similar cohorts, it was 0.42 (0.33–0.54) in the U.K. (6) and 0.69 (0.54–0.88) in Finland (8). Therefore, primary prevention measures may need to be adapted to the particularities of cardiovascular and diabetes diseases by country or region.

Characteristics and limitations of the study

We have shown that lipid profile and blood pressure diagnosis and control improved between 1995 and 2005 in the region we studied (22). Our sample of myocardial infarction and diabetic patients is population-based in a region of northeast Spain, where risk factor prevalence and myocardial infarction incidence and mortality are well studied by the REGICOR group (23). Over the follow-up period, many improvements occurred simultaneously in the management of both acute myocardial infarction and type 2 diabetes, which may have influenced the outcomes. In Spain, a decrease in 28-day and 1-year mortality between 1995 and 2000 has been associated with increased use of reperfusion strategies and medical therapies (23). These changes were paralleled by intensified management of patients' cardiovascular risk factors and glycemic targets, following the UKPDS results (14) and international recommendations (American Diabetes Association and European Association for the Study of Diabetes) in primary care centers within the GEDAPS network. The proportion of diabetic patients who smoked was very similar to the proportion of smokers at 6 months after the index event that was reported in a sample of the acute myocardial infarction patients. Finally, asymptomatic myocardial infarction is known to occur to a greater degree in patients with diabetes than in the general population. In our study we did not undertake a systematic screening procedure to rule out silent events.

Clinical implications of our study

Type 2 diabetes is on the increase in developed countries, a trend related to the epidemics of obesity observed in the past two decades. For example, in the U.S. between 1994–1995 and 2003–2004, the annual incidence of diabetes increased by 23% and prevalence by 62% in individuals >65 years (24). The economic and clinical practice consequences of considering diabetic patients, who represent >10% of the adult population in developed countries, for secondary prevention therapies are very important: benefits and effectiveness must be assessed and balanced, particularly in regions with low coronary heart disease incidence and mortality.

Type 2 diabetes is not a coronary heart disease equivalent for cardiovascular risk in the region studied. In fact, this equivalence also has not been found in countries with high cardiovascular risk (6–10). Although patients with diabetes are at higher risk than the general nondiabetic population (7), individual cardiovascular risk scores are required before implementation of the level of treatment (statins, antiplatelet therapy, and intensification of hyperglycemia treatment) that has been shown to be useful in high-risk patients (25).

Our study confirms that type 2 diabetic patients initially free of coronary heart disease are at lower adjusted 10-year cardiovascular mortality and coronary heart disease incidence risk than patients with a first acute myocardial infarction without diabetes. Our findings also contribute to showing that length of diabetes, type of treatment, and glycemic control should be taken into account in future studies on prognosis of patients with type 2 diabetes initially free of coronary heart disease.

Acknowledgments— This work was supported by the Spanish Ministry of Science and Innovation, Carlos III Health Institute/European Reginal Development Fund (ERDF) (Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III/FEDER) (Red HERACLES RD06/0009), the Health Research Fund (Fondo de Investigación Sanitaria) (FIS 94/0539, FIS96/0026-01, FIS 97/1117, FIS99/0655, FIS99/0013-01, and FIS 99/9342), and the Catalan Agency for Management of University and Research Grants (Agència de Gestió d'Ajuts Universitaris i de Recerca) (2005SGR00577).

No potential conflicts of interest relevant to this article were reported.

J.F.C., J.M.B.-D., J.S., and J.M. researched data, contributed to discussion, wrote the manuscript, and reviewed/edited the manuscript. J.F. and R.E. researched data, contributed to discussion, and reviewed/edited the manuscript. J.V. and S.T. contributed to discussion and reviewed/edited manuscript.

We are grateful to Marta Cabañero, Leny Franco, and Isabel Ramió, Cardiovascular Epidemiology and Genetics Research Group, Program of Research on Inflammatory and Cardiovascular Disorders, for project and data management; Elaine Lilly, PhD, Writer's First Aid, for the revision of the English text; and Anna Puigdefàbregas and Rosa Gispert, Catalan Government's Mortality Registry, for cross-linkage of our databases with the death certificate registry.

References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–1053
2. Oliva J, Lobo F, Molina B, Monereo S.

Direct health care costs of diabetic patients in Spain. Diabetes Care 2004;27:2616–2621
3. Haffner SM, Leh S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in non diabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–234
4. Juutilainen A, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Type 2 diabetes as a "coronary heart disease equivalent": an 18-year prospective population-based study in Finnish subjects. Diabetes Care 2005;28:2901–2907
5. Schramm TK, Gislason GH, Køber L, Rasmussen S, Rasmussen JN, Abildstrøm SZ, Hansen ML, Folke F, Buch P, Madsen M, Vaag A, Torp-Pedersen C. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. Circulation 2008;117:1945–1954
6. Evans JM, Wang J, Morris AD. Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort studies. BMJ 2002;324:939–942
7. Lee CD, Folsom AR, Pankow JS, Brancati FL, Atherosclerosis Risk in Communities (ARIC) Study Investigators. Cardiovascular events in diabetic and nondiabetic adults with or without history of myocardial infarction. Circulation 2004;109:855–860
8. Pajunen P, Koukkunen H, Ketonen M, Jerkkola T, Immonen-Räihä P, Kärjä-Koskenkari P, Kuulasmaa K, Palomäki P, Mustonen J, Lehtonen A, Arstila M, Vuorenmaa T, Lehto S, Miettinen H, Torppa J, Tuomilehto J, Kesäniemi YA, Pyörälä K, Salomaa V. Myocardial infarction in diabetic and non-diabetic persons with and without prior myocardial infraction: the FINAMI Study. Diabetologia 2005;48:2519–2524
9. Natarajan S, Liao Y, Sinha D, Cao G, McGee DL, Lipsitz SR. Sex differences in the effect of diabetes duration on coronary heart disease mortality. Arch Intern Med 2005;165:430–435
10. Natarajan S, Liao Y, Cao G, Lipsitz SR, McGee DL. Sex differences in risk for coronary heart disease mortality associated with diabetes and established coronary heart disease. Arch Intern Med 2003;163:1735–1740
11. Vaccaro O, Eberly LE, Neaton JD, Yang L, Riccardi G, Stamler J, Multiple Risk Factor Intervention Trial Research Group. Impact of diabetes and previous myocardial infarction on long-term survival 25-year mortality follow-up of primary screenees of the Multiple Risk Factor Intervention Trial. Arch Intern Med 2004;164:1438–1443
12. Fox CS, Sullivan L, D'Agostino RB Sr, Wilson PW, Framingham Heart Study. The significant effect of diabetes duration on coronary heart disease mortality. The Framingham Heart Study. Diabetes Care 2004;27:704–708
13. Donnan PT, Donnelly L, New JP, Morris AD. Derivation and validation of a prediction score for major coronary heart disease events in a U.K. type 2 diabetic population. Diabetes Care 2006;29:1231–1236
14. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UKPDS Group. Lancet 1998;352:837–853
15. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
16. Cho E, Rimm EB, Stampfer MJ, Willett WC, Hu FB. The impact of diabetes mellitus and prior myocardial infarction on mortality from all causes and from coronary heart disease in men. J Am Coll Cardiol 2002;40:954–960
17. Masiá R, Pena A, Marrugat J, Sala J, Vila J, Pavesi M, Covas M, Aubó C, Elosua R. High prevalence of cardiovascular risk factors in Gerona, Spain, a province with low myocardial infarction incidence. REGICOR Investigators. J Epidemiol Community Health 1998;52:707–715
18. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group. Diabetes 1979;28:1039–1057
19. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1187–1197
20. Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, Erqou S, Sattar N. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet 2009;373:1765–1772
21. Bloomgarden ZT. Glycemic control in diabetes: a tale of three studies. Diabetes Care 2008;31:1913–1919
22. Grau M, Subirana I, Elosua R, Solanas P, Ramos R, Masiá R, Cordón F, Sala J, Juvinyà D, Cerezo C, Fitó M, Vila J, Covas MI, Marrugat J. Trends in cardiovascular risk factor prevalence (1995-2000-2005) in northeastern Spain. Eur J Cardiovasc Prev Rehabil 2007;14:653–659
23. Heras M, Marrugat J, Arós F, Bosch X, Enero J, Suárez MA, Pabón P, Ancillo P, Loma-Osorio A, Rodríguez JJ, Subirana I, Vila J. Reduction in acute myocardial infarction mortality over a five-year period. Rev Esp Cardiol 2006;59:200–208
24. Sloan FA, Bethel MA, Ruiz D Jr, Shea AM, Shea AH, Feinglos MN. The growing burden of diabetes mellitus in the US elderly population. Arch Intern Med 2008;168:192–199
25. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580–591