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

A population-based cohort study in southern Europe

J. Francisco Cano, MD, Jose M. Baena-Diez, MD, Josep Franch, MD, PhD, Joan Vila, MSC, Susana Tello, MSC, Joan Sala, MD, PhD, Roberto Elosua, MD, PhD, Jaume Marrugat, MD, PhD, on behalf of the REGICOR and GEDAPS Investigators *

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 billion per year, respectively (2).

From the 1Endocrinology and Nutrition Department, Hospital Universitari del Mar, Barcelona, Spain; the 2Cardiovascular Epidemiology and Genetics Research Group, Program of Research on Inflammatory and Cardiovascular Disorders, IMIM, Barcelona, Spain; the 3Primary Health Care Center La Marina, Fundació Jordi Gol i Gurina, Institut Català de la Salut, Barcelona, Spain; the 4Primary Health Care Center Raval Sud, Institut Català de la Salut, Barcelona, Spain; the 5Centro de Investigación Biomédica en Red Epidemi ology and Public Health, Barcelona, Spain; and the 6Cardiology Department, Hospital Universitari Josep Trueta, Institut Català de la Salut, Girona, Spain. Corresponding author: Jaume Marrugat, jmarrugat@imim.es.

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.

* A complete list of the researchers participating in REGICOR (Registre Gironí del Cor [Girona Heart Registry]) and GEDAPS (Grup de Estudi de la Diabetes en Atenció Primària de Salut [Primary Health Care Diabetes Study Group]) can be found at http://www.regicor.org/regicor_inv and http://www.regicor.org/gedaps_inv, respectively.

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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 local ethics committee (Institut Municipal d’Investigació Medica) and complied with...
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/m², 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 to be all-cause death, coronary death, stroke death, cardiovascular death, non-fatal 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 110–1110, 150–152, 1440–1499, 1500–1509, 1250, and 1511–1519.

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 gammagrapy, 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 χ² 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 ≤ 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-
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### 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      | 386 (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.

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 diet 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.

### 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

|                          | Type 2 diabetes | AMI            | All participants | Men | Women |
|--------------------------|-----------------|----------------|-----------------|-----|-------|
| n                        | 2,260           | 2,154          | 2,480           |     |       |
| 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) | 173 (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 ≤ 0.001. †Unstable angina or fatal or nonfatal AMI.

**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...
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
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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 treatment** |                          |                                   |
| 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 duration**  |                          |                                   |
| AMI patients           | 1 (reference)            | 1 (reference)                     |
| Diet alone             | 0.20 (0.14–0.29)†       | 0.42 (0.34–0.52)†                 |
| Only oral drugs        | 0.15 (0.09–0.26)†       | 0.34 (0.26–0.46)†                 |
| 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, 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 Regional 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 94/0359, FIS96/0026-01, FIS 97/1117, FIS99/0655, FIS99/0013-01, and FIS 99/9342), and the Catalan Agency for Management of Universities 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/editied the manuscript. J.F. and R.E. researched data, contributed to discussion, and reviewed/editied the manuscript. J.V. and S.T. contributed to discussion and reviewed/editied manuscript.

We are grateful to Marta Cabañeros, Lenny Franco, and Isabel Ramíó, Cardiovacular Epidemiology and Genetics Research Group, Program of Research on Inflammatory and Cardiovacular Disorders, for project and data management, Elaine Lilly, PhD, Writer’s First Aid, for the revision of the English text, and Anna Puigdefabregas and Rosa Gispert, Catalan Government’s Mortality Registry, for cross-linkage of our databases with the death certificate registry.

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