

# Type 2 Diabetes Mellitus and Cardiovascular Disease in Spain: A Narrative Review

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**Introduction.** In spite of having a high prevalence of diabetes mellitus the prevalence of ischemic heart disease is low in Spain.

**Methods.** A narrative review of the bibliography was performed to search for potential particularities in the epidemiology, pathogenecity, and care of diabetes mellitus in Spain.

**Results.** The age-adjusted prevalence of diabetes in Spain is close to 10% (90% type 2) ranging from 6.1% to 13.3% (higher in Canary Islands), with an increased North-to-South gradient. Men have a 27%-42% higher prevalence than women. The incidence ranges from 5 to 8 cases per 1000 inhabitants-year. Spanish patients with diabetes have similar incidences and prevalences of cardiovascular complications and related mortality compared with those reported in other countries. Several studies have shown a consistent underuse of preventive therapies both in patients with and without cardiovascular diseases, and low rates of achievement of therapeutic goals. Despite their much worse prognosis, and contrary to current recommendations, diabetic patients with acute vascular events are not treated differently compared with non-diabetics.

**Conclusions.** The age-adjusted prevalence and incidence estimates of diabetes mellitus in Spain appear to be similar to those in high-incidence countries. Diabetic patients show a high cardiovascular risk profile but the control of risk factors is poor, particularly in women and in patients with established cardiovascular disease. Initial and later care of diabetic patients with acute vascular events in Spain is far away from optimal. There is a huge opportunity for improving cardiovascular prevention and care in diabetic patients with and without cardiovascular disease in Spain.

**Key words:** *Diabetes mellitus. Cardiovascular disease. Prevention. Epidemiology. Spain.*

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## Diabetes mellitus tipo 2 y enfermedad cardiovascular en España: una revisión descriptiva

**Introducción.** A pesar de la elevada prevalencia de diabetes mellitus, la prevalencia de la cardiopatía isquémica es baja en España.

**Métodos.** Se ha elaborado una revisión descriptiva de la bibliografía para intentar identificar posibles particularidades de la epidemiología, patogenia y asistencia de la diabetes mellitus en España.

**Resultados.** La prevalencia de la diabetes en España, ajustada para la edad, está próxima al 10% (el 90% de los casos son de tipo 2) y oscila entre el 6,1% y el 13,3% (la cifra más alta es la de las islas Canarias), con un gradiente de aumento Norte-Sur. La prevalencia es un 27%-42% más alta en los varones que en las mujeres. La incidencia oscila entre 5 y 8 casos por 1.000 habitantes-años. Los pacientes españoles con diabetes presentan incidencias y prevalencias de complicaciones cardiovasculares y de mortalidad relacionada con la enfermedad similares a las descritas en otros países. En diversos estudios se ha puesto de manifiesto que hay un uso insuficiente uniforme de los tratamientos preventivos en los pacientes con o sin enfermedades cardiovasculares, y un bajo porcentaje de consecución de los objetivos terapéuticos. A pesar de su pronóstico mucho peor, y contrariamente a lo indicado en las recomendaciones actuales, los pacientes diabéticos con episodios vasculares agudos no reciben un tratamiento diferente al de los no diabéticos.

**Conclusiones.** Las estimaciones ajustadas respecto a la edad de la prevalencia e incidencia de la diabetes mellitus en España parecen ser similares a las de los países de alta incidencia. Los pacientes diabéticos presentan un perfil de riesgo cardiovascular elevado pero el control de los factores de riesgo es malo, en especial en las mujeres y en los pacientes con una enfermedad cardiovascular establecida. La asistencia inicial y posterior de los pacientes diabéticos con episodios vasculares agudos en España está lejos de ser óptima. Existe una clara oportunidad para mejorar la prevención y la asistencia cardiovasculares en los pacientes diabéticos con o sin enfermedad cardiovascular en España.

**Palabras clave:** *Diabetes mellitus. Enfermedad cardiovascular. Prevención. Epidemiología. España.*

**ABBREVIATIONS**

ACS: acute coronary syndromes  
 ADA: American Diabetes Association  
 CHD: coronary heart disease  
 CVD: cardiovascular disease  
 DM: diabetes mellitus  
 IDF: International Diabetes Federation  
 LDL-C: LDL-cholesterol  
 WHO: World Health Organization

**INTRODUCTION**

Type 2 diabetes mellitus (DM) is a strong cardiovascular risk factor. Spain is a country with a high prevalence of DM<sup>1</sup> but one of the lowest of ischemic heart disease in the Western world.<sup>2</sup> Due to this apparent paradox, we tried to address whether there is any specific feature in the epidemiology, pathogenicity or care of type 2 DM in Spain, the most common phenotype of diabetes. Type 1 diabetes is beyond the scope of this paper and can be reviewed elsewhere.<sup>3-5</sup>

**EPIDEMIOLOGY**

**Prevalence and incidence of type 2 diabetes mellitus in Spain**

DM is among the diseases with the greatest impact on the Spanish population and healthcare system due to its high prevalence, the frequency of chronic complications and its high mortality. According to the World Health Organization (WHO), diabetes

prevalence is expected to increase in Spain 40% by 2025 compared to year 2000.<sup>6</sup>

A number of epidemiological studies have shown that Spain is a country with an intermediate to high prevalence of DM compared with other nations.<sup>7-10</sup> However, prevalence comparisons within and between populations must be made with caution due to the potential use of different diagnostic criteria (eg, American Diabetes Association, WHO), screening tests (eg, self reported, physician based, prescription records), populations (eg, general population, population at risk for type 2 diabetes, different population structure), designs and sampling techniques. As a result, eight studies using similar methodology were identified in the literature to assess the prevalence of diabetes in Spain (Table 1).<sup>11-18</sup> The age-adjusted prevalence ranged from 6.1% to 13.3% showing an increased North-to-South gradient, with higher prevalence in men compared to women (27%-42% higher). Overall, these data are consistent with the 2003 IDF estimations, in which Spain was ranked as the tenth country with the highest prevalence of diabetes in the 20-79 age group in the world.<sup>1</sup> According to the same report, the overall prevalence of diabetes is 9.9% (90% of whom were type 2 diabetes mellitus). This implied that Spain had to spend in 2003 the 6% of total healthcare budget (2.4-2.6 million euros) to treat nearly 3 million patients with DM.<sup>1</sup> Although not strictly comparable due to the use of different standard populations and ethnic differences, the total prevalence of diabetes in the US was 9.3% between 1999 and 2002 (7.9% for non-Hispanic whites), suggesting that Spain and the U.S. probably have similar prevalences of DM.<sup>19</sup> As far as incidence of type 2 DM is concerned, of the published papers providing an estimate,<sup>9,20-23</sup> only a few accounted for

**TABLE 1. Cross sectional studies in Spain for diabetes mellitus prevalence estimation\***

Author (reference)	Dates of survey	Location	Age range	Final sample (% response)	Diagnostic criteria, year and method	Overall age-adjusted prevalence
Soriguer <sup>16</sup>	1994	Pizarra town (Andalusia)	18-65	982 (78.5%)	ADA, 1997, 1-FPG	13.3
de Pablos <sup>14</sup>	1991	Guia county (Canary Islands)	≥30	691 (76.3%)	WHO, 1985, F-PG	12.4
Masiá <sup>15</sup>	1995-96	Province of Gerona (Catalonia)	25-74	1748 (72%)	ADA, 1997, 1-FPG	10.0
Boronat <sup>11</sup>	1998	Telde city (Canary Islands)	≥30	1030 (86.3%)	ADA, 1997, 1-FPG and WHO, 1985, 1-FPG	9.9 (ADA) 9.0 (WHO)
Valverde <sup>18</sup>	2001-03	Murcia	≥20	1556 (60.7%)	ADA, 1997	7.6
Botas <sup>12</sup>	1998-99	Asturias	30-75	1034 (63.6%)	WHO, 1985, 1-FPG	6.5
Tamayo <sup>17</sup>	1993-94	Aragon	10-74	935 (92%)	WHO, 1985, 1-FPG	6.4
Castell <sup>13</sup>	1994-95	Catalonia	30-89	3839 (66.7)	WHO, 1985, 2-FCG	6.1

\*All studies used Segi (30-64 years) as reference population.

ADA: American Diabetes Association; FPG: venous fasting plasma glucose; FCG: capillary fasting whole blood glucose

age structure in Spain.<sup>20-23</sup> Vázquez et al.<sup>22</sup> showed an annual age-adjusted cumulative incidence of 8 cases per 1000 inhabitants-year, using WHO-1985 criteria after 10 years of follow-up.<sup>22</sup> Another study, using similar diagnostic criteria and methodology in the Basque Country, found an age-standardized cumulative incidence of 5 per 1000 inhabitants-year.<sup>22</sup> Finally, Valdes et al.<sup>23</sup> showed that incidence of type 2 diabetes adjusted for the age and sex structure of Asturias was 10.8 cases/1,000 persons years (95% CI 7.8-14.6) after 6.3 years of mean follow-up, using WHO 1999 criteria. These results are also comparable with the United States for similar populations, where an estimated age-adjusted annual cumulative incidence of 6.0 per 1000.<sup>24</sup>

### **Type 2 diabetes mellitus and cardiovascular disease**

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among individuals with diabetes. Adults with DM have a two- to fourfold higher risk of CVD compared with those without diabetes.<sup>25</sup> In Spain, published longitudinal studies reporting the incidence of cardiovascular events in individuals with diabetes are scarce. Tomas et al.<sup>26</sup> (n=1059 men) showed in the Manresa Study that the estimated age-adjusted 28-years cumulative incidence for coronary heart disease (CHD) was 17.6% for individuals with basal glycemia greater than 110 mg/dL or previously diagnosed diabetes. Rius et al.<sup>27</sup> reported an outpatient-based clinic longitudinal study (6.3 years of mean follow-up) with 176 patients free of CVD. They observed a cumulative incidence of macroangiopathy, defined as CHD, stroke and intermittent claudication of 15.9% and, specifically, 6.3% of CHD, 8% of cerebrovascular disease and 4% of peripheral arterial disease. Cañón-Barroso et al.<sup>28</sup> retrospectively identified in a general practice clinic a cohort of patients with type 2 DM free of CVD at baseline. They observed a 14.7%, 10-year cumulative incidence of CHD (angina, fatal, and non-fatal myocardial infarction), 13.3% for men and 16.0% for women. Using a similar design, Jimeno et al.<sup>29</sup> found a 17% cumulative incidence of CHD (18.5% in men and 15.2% in women) after 10 years of follow-up. Overall, these data are consistent with Morrish et al.,<sup>30</sup> who showed in a cohort (n=497) over a period of 8.33 years of follow-up for patients with type 2 DM a 18.8 incidence of myocardial infarction, 5.9 of cerebrovascular disease, and 5.2 of peripheral arterial disease.

On the other hand, several cross-sectional studies reported crude prevalence estimates of macrovascular complications in Spain.<sup>31-38</sup> These studies reported a wide prevalence range for peripheral arterial disease (5.6%-24.5%). Estimates for CHD ranged between 10.5% and 19.8%, and between 3.3% and 11.8% for

stroke. Obviously, prevalence rates vary according to different methodologies and clinical characteristics of the population such as the duration of the disease. Arteagoitia et al.<sup>20</sup> studied 2920 diabetic patients in the Basque Country using a sentinel practice network during year 2000. They found a 21.6% prevalence of macroangiopathy in new onset cases (12.4% of CHD, 9.8% of stroke, and 14.1% of peripheral vascular disease), and 33% among cases of known diabetes (7% CHD, 4% stroke, and 14% peripheral artery disease). They showed that macrovascular disease was more likely to be reported in men compared to women (odds ratio [OR] for incident DM, 2.3; 95% confidence interval, 1.2-4.6; OR for prevalent DM, 1.5; 95% CI, 1.5-2.1).

### **Type 2 diabetes mellitus, cardiovascular risk factors and risk of coronary heart disease**

The prevalence of CHD disease in Spain is among the lowest in the Western countries<sup>2</sup> despite the high prevalence of risk factors.<sup>39,40</sup> However, individuals with type 2 DM usually have higher prevalence of traditional risk factors posing them into the highest risk category for CVD and, particularly for ischemic heart disease, in the "coronary risk equivalence."<sup>41,42</sup> In terms of cardiovascular risk estimation, several Spanish authors<sup>28,29,35,43</sup> examined the risk of coronary events using available risk engines in order to predict the most common complication in this population.<sup>44</sup> For the Framingham-REGICOR risk engine<sup>45</sup>, the 10-year likelihood of coronary events were between 5.6% and 15% in men, and between 6% and 10% in women. Using the diabetes-specific risk engine UKPDS,<sup>46</sup> they found that men had a 10-year risk of CHD between 19% and 38%, while the risk ranged from 11% and 28% for women. Finally, when the SCORE calculator to estimate 10-year risk of fatal coronary disease<sup>47</sup> was applied, Lahoz<sup>35</sup> found that women had a 2% compared to 4% in men.

### **Mortality and impact of type 2 diabetes mellitus in Spain**

In Spain, CVD are the cause of death in at least half of type 2 DM,<sup>30,48</sup> although other reports find it up to 75%-80%.<sup>9</sup> In 2005, CVD was the leading cause of death, accounting in Spain for 32.8% of the deaths.<sup>49</sup> Diabetes constituted the seventh cause of death, raking the 8th-9th for men and 5th-6th for women depending on the year.<sup>49,50</sup> These estimates are also very similar to the United States, where diabetes was the sixth leading cause of death.<sup>51</sup> However, it must be acknowledged that direct comparison of these mortality rates is incorrect due to the lack of standardization to the same population.

According to the Spanish National Institute of Statistics, ischemic heart disease accounted for 90.98

**TABLE 2. Use of pharmacological preventive therapies in a sample of Spanish diabetic patients without cardiovascular disease enrolled in TranSTAR study**

Pharmacological therapy	Diabetes n (%)	No diabetes n (%)	P value
Lipid lowering therapy	n= 179	n= 173	
Statins	88 (49)	55 (32)	<0.001
Fibrates	11 (6)	10 (6)	0.9
Anti-hypertensive therapy	n= 316	n= 345	
ACEI	75 (24)	42 (12)	<0.001
ARB	42 (14)	36 (10)	0.2
Diuretics	31 (10)	38 (11)	0.6
Beta-blockers	7 (2)	7 (2)	0.9
CCB	24 (8)	10 (3)	<0.01

ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin II receptor blockers; CCB: Calcium channel blockers

deaths and cerebrovascular disease 80.23 per 100 000 inhabitants-year compared to the diabetes-specific death rate of 23.3 deaths per 100 000 inhabitants-year. Concordantly with the prevalence estimates for DM, diabetes-related mortality showed an increasing North-South gradient.<sup>49,50,52</sup> Locally, Ruiz et al<sup>53</sup> analyzed the trends of mortality due to diabetes in Andalusia during 1975-1994. Using age standardization (direct method) from European population, they found that mortality due to DM decreased from 24.45 to 19.15 deaths per 100 000 persons-year in men, and from 33.55 to 22.43 in women, in that time period. Compared to the United States, the diabetes-specific age standardized mortality rate for whites, using U.S. population as standard, was 27.0 for males and 19.9 for females per 100 000 inhabitants/year.<sup>51</sup> In the U.K. a recent study showed that for the period of 1993-1999, the specific age-standardized mortality rate (using European population as the reference), was 32.0 for women and 38.7 per 100 000 inhabitants-years for men.<sup>54</sup> Considering the important limitations of the population attributable fraction,<sup>55</sup> Banegas et al<sup>56</sup> suggested that the attributable population fraction for diabetes is approximately 8.3% for CHD and 3.7% for cerebrovascular disease. They estimated that 2% of coronary mortality and 1.6% of cerebrovascular mortality was attributable to diabetes in men, but as much as 10.4% and 3.9%, respectively, in women.

Whereas CHD mortality is decreasing among diabetic men over the last three decades, it seems to be increasing among women.<sup>57</sup> In Spain, available data suggest a similar pattern. However, while the prevalence of diabetes is slightly superior in men, Spanish women tend to have a worse control of their risk factors compared to men.<sup>58</sup> Moreover, women have a worse prognosis once they are affected by cardiovascular diseases.<sup>59</sup> According to an Andalusian study, unadjusted mortality rate is higher in women compared to men, especially when cohorts become older.<sup>53</sup> These results are comparable with those reported in other countries.<sup>30</sup>

## CARDIOVASCULAR PREVENTION IN DIABETIC PATIENTS IN SPAIN

Glycemic control, detection, and treatment of associated co-morbidities are essential to prevent future macrovascular complications. A number of Spanish studies have addressed the health status of diabetic patients at a national<sup>31,32,60</sup> and local level.<sup>35,61,62</sup> They consistently showed a suboptimal control of cardiovascular risk factors in this patient population. In average, one quarter of patients had glycosylated hemoglobin (A1C) levels >8%; at least half of the individuals were diagnosed of hypertension and between 50%-70% were above optimal levels (>130/85 mm Hg); LDL-C levels were elevated (>115 mg/dL)<sup>63</sup> in up to 90% of patients; current smokers accounted for 9%-17%; obesity, defined as a body mass index >30 kg/m<sup>2</sup>, was present in 30%-60% of subjects; and when physical activity was reported,<sup>31,60</sup> between 60%-80% of patients had a sedentary lifestyle. These data are consistent with other European<sup>64</sup> and American studies.<sup>65,66</sup>

In primary prevention, a subanalysis of the 316 diabetic and 345 non-diabetic patients without prior CVD enrolled in the Trans-STAR study—a Spanish national prospective case-control study performed in 326 primary care centers during a week in October 2001 that recruited 776 patients (388 diabetics and 388 non-diabetics)<sup>32</sup>—has shown a low rate of use of pharmacological preventive therapies (Table 2) in spite of the high prevalence of known dyslipidemia (50%) and hypertension (51%) among diabetics. In addition, a low proportion of these patients had their risk factors measured during the year previous to the interview (Table 3). When the control of risk factors was ascertained in the diabetic group according to the JNC VI and NCEP III recommendations, extremely low rates of LDL-C and systolic blood pressure control were found (Table 3). Interestingly, fewer patients (7%) with known high LDL levels reached established goals in comparison to those without high LDL levels

**TABLE 3. Degree of risk factor control according to JNC VI and NCEP III in a sample of 316 Spanish diabetic cases, and 345 non diabetic controls without cardiovascular disease enrolled in TranSTAR study**

	Values measured n (%)		Values (mean ±SD)		Patients (%) with tight control		Percentage of diabetics with or without known risk factor*	
	Diabetes n (%)	No diabetes n (%)	Diabetes	No diabetes	Diabetes n (%)	No diabetes n (%)	With	Without
<b>Lipid control (mg/dL)</b>								
LDL	159 (50)	146 (42)	143 ± 36	141 ± 41	13 (8)	99 (68)	7	10
Total cholesterol	211 (67)	185 (54)	225 ± 39	219 ± 42	64 (30)	130 (70)	12	58
Triglycerides	197 (62)	182 (53)	155 ± 68	137 ± 70	100 (51)	160 (88)	32	78
<b>Blood pressure control (mmHg)</b>								
SBP	237 (75)	237 (69)	146 ± 18	139 ± 20	32 (14)	121 (51)	6	28
DBP	237 (75)	237 (69)	84 ± 9	82 ± 12	55 (23)	120 (51)	33	45
<b>Glucose control (%)</b>								
A1C	239 (76)	—	7.3 ± 1.4	—	58 (24)	—	—	—

LDL: Low-density lipoproteins; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; A1C: glycosilated hemoglobin  
 \*Known risk factor refers to the presence of hyperlipidemia or hypertension at the beginning of the study.

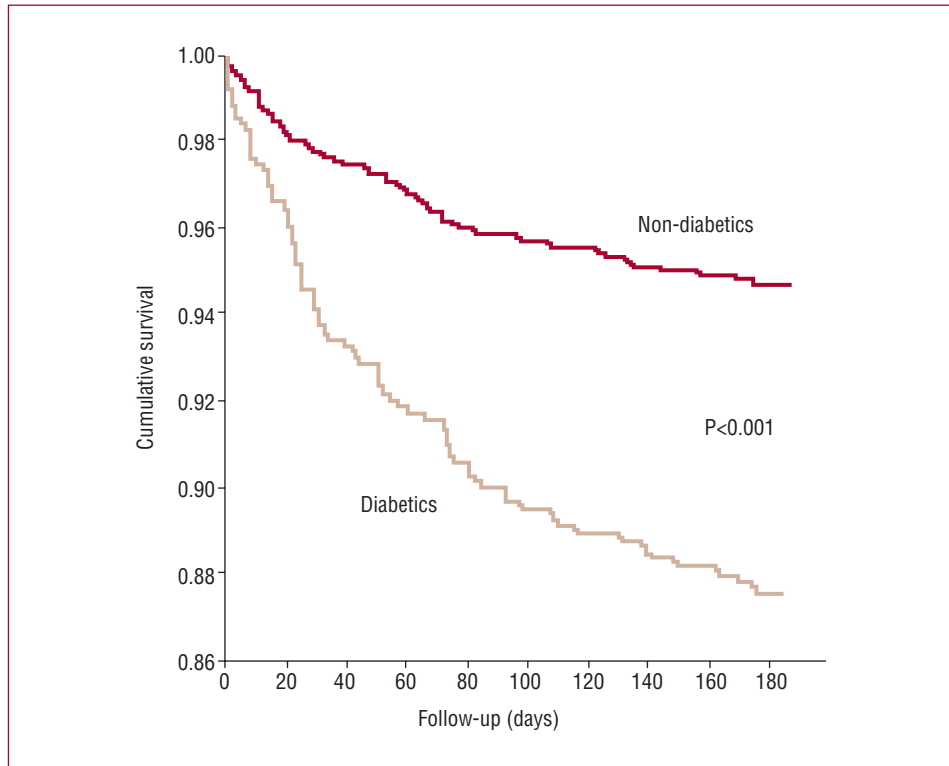
(10%). Similarly, fewer patients with known systolic or diastolic hypertension (6% vs 33%) reached goals in comparison to those without known hypertension (28% and 45%,  $P < .001$ ). Underuse of lipid-lowering and antihypertensive therapies in diabetic patients as well as low proportions of patients reaching therapeutic goals have been described throughout the world.<sup>67-70</sup>

The degree of control of cardiovascular risk factors in patients with established cardiovascular disease is particularly disturbing. González-Juanatey et al<sup>71</sup> in a nationwide sample of clinics involving 1275 patients showed that blood pressure was controlled (<130/80 mm Hg) in less than 30%, LDL-C levels were above 100 mg/dL in more than 90% of patients, and use of current established therapies for secondary prevention were underused in 60%-74% depending on the drug. The DIETRIC study<sup>72</sup> showed similar results among 628 patients. Although more than 60% of patients presented 3 or more related risk factors, only 15% had adequate control of blood pressure (<139/80 mm Hg), 7.5% had adequate control of plasma lipids (LDL-C <100 mg/dL, and triglycerides <150 mg/dL), and 57.2% had A<sub>1c</sub> > 6.5%. The same direction showed a major study in the field. Mostaza et al<sup>73</sup> included 8,817 patients from primary care clinics who were hospitalized for a coronary event. They found that only 7% had optimum control of all their risk factors. Specifically, “the percentage of diabetic subjects attaining objectives for smoking habit, low-density lipoprotein cholesterol, blood pressure, and glycated hemoglobin were 90.7%, 29%, 38.2%, and 49.7%, respectively.” Even more, recent data suggests that

Spanish women have worse control of cardiovascular risk factors compared to men.<sup>59</sup>

### MANAGEMENT OF ACUTE VASCULAR EVENTS IN DIABETIC PATIENTS

There is scarce information about the management of acute vascular events in Spanish diabetic patients. A small study performed in the Canary Islands showed that the subgroup of diabetic patients with for non ST-segment elevation acute coronary syndromes (ACS) were older, had a higher prevalence of risk factors and had higher incidences of heart failure, 28-day, and 6-month mortality. Despite these facts, they did not find different patterns of use of coronary angiography, angioplasty or surgical revascularization.<sup>74</sup> DESCARTES (*Descripción del Estado de los Síndromes Coronarios Agudos en un Registro Temporal Español*), a Spanish nation-wide registry of patients hospitalized for suspected ACS performed by the Working Group on Ischemic Heart Disease of the Spanish Society of Cardiology, recruited 1877 consecutive patients with ACS in 45 randomly selected hospitals in Spain stratified by 3 different levels of care between April and May, 2002.<sup>75</sup> The results of DESCARTES have shown a significant underutilisation of evidence-based therapies among patients with ACS in Spain, particularly those at higher risk.<sup>75,76</sup> Diabetes mellitus is considered as a high-risk feature in patients with ACS by the 2002 European Society of Cardiology task force, and an intermediate risk by the contemporary Spanish guidelines. According to these recommendations,



**Fig. 1.** Survival according to diabetes status in patients with non ST-segment elevation acute coronary syndromes in Spain (year 2002). Despite their worse prognosis, diabetic patients did not receive a more aggressive treatment than non-diabetics.

diabetic patients with ACS should undergo an aggressive pharmacological management including upstream use of glycoprotein IIb/IIIa inhibitors and an early (within 48 hours) invasive strategy. When the baseline clinical characteristics, hospital management and outcomes of the diabetic patients enrolled in DESCARTES with those without DM were compared (data not shown), diabetic patients were found at a significantly higher predicted risk regardless the way it was addressed (clinical characteristics, TIMI risk score, ESC criteria), and actually showed a higher short-term incidence of heart failure and death (figure 1). Despite this features, during hospitalization diabetic patients only received clopidogrel and angiotensin-converting enzyme inhibitors slightly more frequently than non diabetics, and the latter difference was attributed to the higher prevalence of hypertension among diabetics. On the contrary, none of the interventions recommended specifically for high-risk patients, i.e. glycoprotein IIb/IIIa inhibitors, early coronary angiography, and coronary revascularization were not used more frequently in diabetic patients. At 6 months, diabetic patients showed nearly a 3-fold increase in mortality compared with non-diabetics.<sup>77</sup> A small angiographic study on diabetic ACS confirmed the lack of use of early coronary angiography among these patients, despite the high prevalence of severe diffuse coronary artery disease.<sup>78</sup> Diabetic patients

hospitalised for stroke do not receive a different treatment compared with non-diabetics, although DM seems not to have an impact on prognosis in stroke patients.<sup>79</sup>

## CONCLUSIONS

In summary, the age-adjusted prevalence and incidence estimates of type 2 diabetes mellitus in Spain appear to be similar to those in the United States. Diabetes mellitus is one of the leading causes of death, but most patients die as a consequence of cardiovascular disease. Diabetic patients in Spain show a high cardiovascular risk profile, and furthermore, the control of risk factors is poor, particularly in women, and in patients with established cardiovascular disease. Acute care of diabetic patients with acute vascular events in Spain is far away from optimal, There is a huge opportunity for improving cardiovascular prevention and care in diabetic patients with and without cardiovascular disease in Spain.

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