

## UPDATE

### Diabetes and Cardiovascular Diseases (III)

# Prognosis of Diabetic Patients with Coronary Heart Disease

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The prevalence of diabetes in Spain is about 6% and increases with age and obesity. Diabetes is present in approximately 25% of patients with coronary heart disease (CHD). Pre-diabetic and diabetic patients have a higher incidence of CHD and poorer prognosis, with high short- and long-term mortality. The protective effect of pre-menopause status is suppressed by diabetes. Diabetes has a synergic effect with other cardiovascular risk factors. Primary prevention in diabetic patients should be approached as in non-diabetic post-infarction patients. In diabetes, a healthy life-style and strict control of blood sugar and the other cardiovascular risk factors, particularly hypertension, is mandatory.

**Key words:** *Diabetes. Ischemic heart disease. Epidemiology. Prognosis.*

Full English text available at: [www.revespcardiol.org](http://www.revespcardiol.org).

## INTRODUCTION

The Framingham study demonstrated that the presence of diabetes mellitus (DM) considerably increased cardiovascular risk, particularly in women.<sup>1</sup> Since then, progress has continued until reaching the present concept, which considers that patients with type 2 DM have a risk of cardiovascular disease similar to that of patients with ischemic heart disease, peripheral arteriopathy, or cerebrovascular accident. Therefore, these

## Pronóstico de los pacientes diabéticos con cardiopatía isquémica

La prevalencia de la diabetes mellitus (DM) en la población española es cercana al 6%, y aumenta con la edad y la obesidad. Alrededor del 25% de los pacientes afectados de enfermedad coronaria tienen DM. Tanto los estados prediabéticos como la DM se asocian a una enfermedad arteriosclerótica temprana, extensa y especialmente agresiva. La DM elimina el efecto protector del ciclo hormonal menstrual y presenta un efecto sinérgico con el resto de los factores de riesgo cardiovascular. Los objetivos de la prevención primaria en los pacientes diabéticos serán los mismos que en aquellos no diabéticos que ya han sufrido un infarto de miocardio. Es especialmente importante aconsejar sobre hábitos de vida saludable, realizar un control estricto de la glucemia y de los factores de riesgo asociados, en particular de la hipertensión.

**Palabras clave:** *Diabetes mellitus. Cardiopatía isquémica. Epidemiología. Pronóstico.*

patients must be handled according to the guidelines of secondary prevention, even in the absence of symptomatic ischemic heart disease. Likewise, prediabetic states, like glucose intolerance, which are characterized by resistance to the action of insulin, increase the risk of arteriosclerotic disease.<sup>2</sup>

On the other hand, DM is an important prognostic factor that is associated with more extensive coronary artery disease (CAD), a more aggressive course and greater morbidity and mortality than in coronary patients without DM.<sup>3</sup> DM accelerates the process of atherogenesis through several mechanisms, such as anomalies in the lipoprotein concentration and composition, its association with hypertension, insulin resistance, and hyperinsulinemia, protein glycosylation in plasma and the arterial wall, lipid oxidation, a procoagulation and proinflammatory state, and disturbed endothelial function (Table 1).<sup>4</sup>

DM, prediabetic states, and their cardiovascular complications are one of the main epidemics of indus-

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**ABBREVIATIONS**

ARA II: angiotensin II receptor antagonists.  
 CAD: coronary artery disease.  
 DM: diabetes mellitus.  
 AHT: arterial hypertension.  
 AMI: acute myocardial infarction.  
 ACEI: angiotensin-converting enzyme inhibitors.

trialized countries, with an enormous impact on healthcare. It is calculated that the direct and indirect healthcare expenses of DM are responsible for more than 15% of the national healthcare budget of the U.S.<sup>5</sup>

**EPIDEMIOLOGY OF CORONARY ARTERY DISEASE IN DIABETES MELLITUS**

The prevalence of DM in the Spanish general population is approximately 6%, a figure that increases with the aging of the population and the presence of other cardiovascular risk factors, particularly obesity and a sedentary lifestyle.<sup>6</sup> In the 35 to 74 year old population, the prevalence of DM is about 12% in Spain.<sup>7</sup> In selective surveys of the population of advanced age, obese with a family history of blood sugar abnormality, prevalences in the general population of up to 23% are observed.<sup>8</sup> It is calculated that in Spain there are about 1.5 million diagnosed diabetics and, in addition, around half a million persons with undiagnosed type 2 DM. The annual incidence of DM in the Spanish population is about 0.8% per year for all ages. Assuming a constant incidence and mortality, it is easy to deduce that if nothing changes, the number of diabetic patients in Spain will double before 2010.<sup>6</sup>

In the Spanish population the prevalence of glucose intolerance, a metabolic disorder intermediate between normality and DM, is almost 27%, and up to 30% of these persons will develop DM.<sup>7</sup>

Although DM is a powerful and independent predic-

**TABLE 1. Etiopathogenic factors of arteriosclerotic disease in diabetes**

- Diabetic dyslipidemia
- Procoagulation state
- Insulin resistance and hyperinsulinemia
- Advanced protein glycation in plasma and the arterial wall
- GlucO-oxidation and oxidation
- Proinflammatory state
- Proliferation of smooth muscular cells
- Hyperhomocysteinemia

Adapted from Sánchez-Recalde and Kaski.<sup>4</sup>

**TABLE 2. Prevalence of cardiovascular risk factors in patients with myocardial infarction and unstable angina in different studies including populations of Spanish origin**

	Diabetes	Dyslipidemia	Arterial hypertension	Smoking
General population				
PANES, 45-74 years <sup>11</sup>	14.3%	24.2%	31.1%	34.6%
MANRESA, men of working age <sup>12</sup>	0.3%	33.7%	46.8%	58.8%
Myocardial infarction				
EUROASPIRE <sup>13</sup>	23.2%	65.0%	50.0%	50.3%
IBERICA <sup>14</sup>	17.6%	38.6%	46.1%	43.4%
PREVESE <sup>15</sup>	25.2%	36.3%	44.2%	46.1%
PRIAMHO <sup>16</sup>	24.2%	28.6%	37.6%	42.4%
REGICOR <sup>17</sup>	27.1%	40.0%	45.0%	48.9%
PRINVAC <sup>12</sup>	24.9%	36.3%	46.8%	58.8%
3C <sup>19</sup>	31.0%	74.3%	56.0%	40.6%
Unstable angina				
RESCUE <sup>20</sup>	25%	ND	55%	28%
PEPA <sup>21</sup>	30%	33%	60%	11%

tor of CAD, the high prevalence of unrecognized DM (23%) or undetected glucose intolerance (27%) in the Spanish population is noteworthy.<sup>9,10</sup>

DM is present in 20% to 30% of subjects with an acute coronary event (Table 2).<sup>11-21</sup> It has been estimated that the prevalence of DM in patients with CAD is between 40% and 50% in the U.S. using the oral glucose tolerance test to diagnose DM and echocardiography to diagnose CAD.<sup>22</sup>

Arteriosclerotic diseases cause 80% of all deaths and 75% of all hospital admissions in patients with DM (Figure 1). DM is the commonest cause of CAD in young people. Likewise, more than 50% of patients recently diagnosed as type 2 DM have CAD at the time that DM is diagnosed.<sup>23</sup> The relative risk of acute myocardial infarction (AMI) is 50% and 150% greater in men and women with DM, respectively. Patients with type 2 DM who have still not developed CAD have the same risk of developing it and a similar mortality as non-diabetic individuals who already suffer CAD. In addition, sudden death due to CAD is 150% and 300% more frequent in men and women with DM, respectively, than in the non-diabetic population. On the other hand, diabetics present AMI and silent ischemia more frequently, a greater morbidity and mortality after AMI, slower reperfusion speeds after thrombolytic treatment, a larger number of vessels involved, more diffuse distribution and more severe narrowing of the left coronary artery, and a higher rate of restenosis after coronary angioplasty. In spite of this evidence, it is noteworthy that less than one-third of diabetic patients are aware of their greater cardiovascular risk.<sup>24</sup>

These figures highlight the importance to knowing

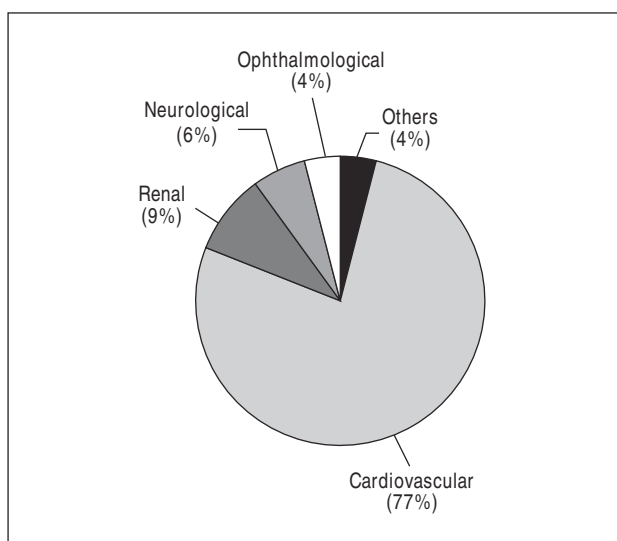


Fig. 1. Chronic complications of diabetes mellitus (adapted from Laakso<sup>23</sup>).

the behavior and natural history of DM and its relation with arteriosclerotic disease, as well as the need to inform diabetic patients of their greater cardiovascular risk so that energetic preventive measures can be adopted as soon as possible.

## NATURAL HISTORY OF CORONARY ARTERY DISEASE IN THE PROGNOSIS OF DIABETES MELLITUS AND ITS IMPLICATIONS

### Coronary artery disease and type 2 diabetes mellitus

Type 2 diabetics represent 90% of the diabetic population and CAD is the main cause of death in these patients. It has been demonstrated consistently that the relative risk of CAD in type 2 DM compared with the general population increases 2- to 4-fold. This increased risk is greater in women, since they lose their protection against CAD associated with the menstrual hormonal cycle.<sup>25</sup>

Although the degree and duration of hyperglycemia are the main risk factors for microvascular complications, in type 2 DM there is no clear association between the extension and severity of macrovascular complications and the duration or severity of DM. Some studies indicate that glycosylated hemoglobin can be an independent risk factor for CAD, particularly in women. In type 2 DM it has not been determined if a glycemia threshold exists for atherogenesis. However, expert committees recognize as endpoints preprandial blood glucose concentrations of less than 126 mg/dL and HbA<sub>1c</sub> of less than 7%.<sup>26</sup> In fact, greater risk of CAD is found both in persons who present only abnormal glucose tolerance, with normal or minimally raised blood glucose, and in patients with type 2 DM.<sup>27</sup> This

fact suggests that CAD can originate in a prediabetic stage. Insulin resistance and its association with other atherogenic factors may be the most important nexus between glucose intolerance, type 2 DM, and CAD. In persons who are genetically predisposed, insulin resistance is the earliest detectable defect and can take place 15-25 years before the clinical onset of DM. The family members of patients with type 2 DM present insulin resistance more frequently and a higher prevalence of metabolic syndrome than the rest of the population. Some authors recommend the determination of sensitivity to insulin using a simple method like the HOMA (*homeostasis model assessment*), a mathematical model that uses glucose and insulin levels in blood as variables in the detection of family members of diabetic patients at high risk of developing metabolic syndrome and, therefore, at a greater risk of CAD.<sup>28</sup> In this sense, it is especially important to know the genetic markers associated with insulin resistance in order to be able to promptly detect persons at high risk for the development of CAD.<sup>29</sup>

Diabetic nephropathy affects approximately 40% of patients with type 2 DM and has become the main cause of terminal nephropathy. Recent prospective studies demonstrate that microalbuminuria is an independent predictive factor of cardiovascular mortality in patients with type 2 DM. Proteinuria increases by 2- to 4-fold the risk of mortal CAD in these patients.<sup>30</sup> The mechanisms that link microalbuminuria with cardiovascular mortality seem to be related with the potentiation of atherogenic mechanisms present in DM. Therefore, in the diabetic population it is important to avoid or delay kidney damage and the appearance of microalbuminuria, which must be considered a marker of subclinical atherosclerosis. Control of blood glucose decreases albuminuria and delays the development of diabetic nephropathy.<sup>31</sup>

### Coronary artery disease and type 1 diabetes mellitus

The long-term follow-up of patients with Type 1 DM at the Joslin Center Diabetes demonstrated an excess of cardiovascular mortality in comparison with the general population. Until 30 years later, no excess coronary risk was detected in patients with type 1 DM. The first cases of CAD appeared at the end of the third decade or beginning of the fourth, independently of the age of onset of DM. The risk of CAD increased quickly after the age of 40 years. By age 55 years, 35% of subjects with type 1 DM had died of CAD.<sup>32</sup>

As in type 2 DM, the protection against CAD observed in menstruating non-diabetic women is lost in women with type 1 DM.<sup>33</sup>

The appearance of nephropathy in patients with type 1 DM also is associated to a considerable increase in the incidence of CAD; diabetic patients with persistent

proteinuria present a risk 8 to 15 times greater of CAD and a mortality due CAD 37 times higher than in the general population, whereas in patients without proteinuria cardiovascular mortality was only 4.2 times higher.<sup>34</sup> Therefore, microalbuminuria in type 1 DM is not only a marker of renal involvement, but also a powerful marker of risk of CAD and mortality due to CAD.

Diabetic nephropathy appears in 30% to 40% of the patients with type 1 DM. The risk of developing diabetic nephropathy is determined only partially by the control of blood glucose, since genetic predisposition has a strong influence. CAD is two times more frequent as a cause of death among the parents of diabetic patients with nephropathy than among parents of diabetic patients without nephropathy. Among diabetics with nephropathy, those that present a coronary event have a 6-fold greater possibility of having a family history of CAD than those without any such episode. A history of CAD in one or both parents of a patient with type 1 DM increases the risk of nephropathy in offspring by 10-fold and 3-fold, respectively. Therefore, there is a subgroup of patients with type 1 DM that has a special genetic predisposition to the development of kidney disease, AHT, and CAD.<sup>35</sup>

## PROGNOSIS AND TREATMENT OF ACUTE CORONARY SYNDROME IN DIABETIC PATIENTS

### Greater proportion of silent ischemia

The Framingham study demonstrated that diabetic patients present a higher proportion of silent and, therefore, undiagnosed AMI.<sup>1</sup> On the other hand, a large proportion of patients with DM presented atypical symptoms like confusion, dyspnea, fatigue, syncope, nausea, and vomiting as manifestations of AMI.<sup>36</sup> In addition, anginal pain is less intense in diabetic than in non-diabetic patients. On the other hand, in the diabetic patient precordial pain is more delayed with respect to the onset of ST-segment depression during the exercise stress test than in non-diabetics. All these disturbances can be secondary to functional autonomic nervous system disorders.<sup>37</sup> These facts can reduce the suspicion of AMI and delay its correct diagnosis and treatment, worsening the prognosis. Therefore, the presence of atypical symptoms in diabetic patients should serve as an alert to the possibility of an acute coronary syndrome.

### Less favorable prognosis of acute coronary syndrome

The overall intrahospital mortality of diabetic patients with AMI is 1.5 to 2 times greater than in non-diabetic patients. The prognosis is especially poor in women, who have an almost two-fold greater increase

in mortality than male diabetics. This risk is maintained in young patients. The factors that determine a worse prognosis are detailed in Table 3. Thirty percent of patients with DM who suffer an AMI die before arriving at the hospital. Diabetic patients present a 30-day mortality due to AMI of 11.3% versus 5.9% in non-diabetic patients. The one-year mortality from the first AMI in diabetic patients is close to 50%<sup>38</sup> and the diagnosis of DM is an independent predictor of greater long-term mortality for up to 12 years in patients with a first AMI<sup>39</sup> (Figure 2).

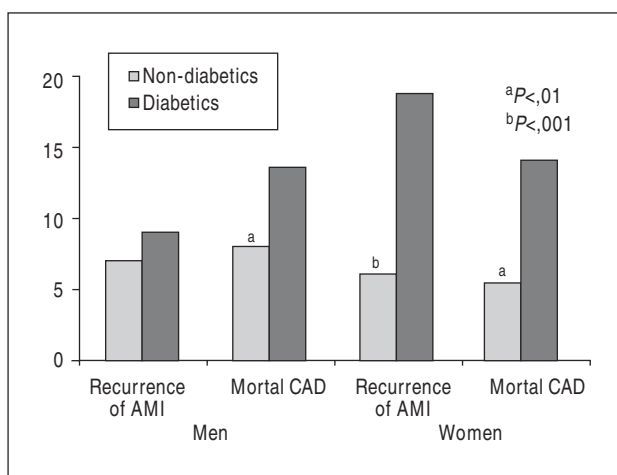
The DIGAMI study demonstrated that the excess intrahospital mortality among diabetics with AMI is related to the greater prevalence of congestive heart failure and cardiogenic shock in this group of patients.<sup>40</sup> Men with DM had a relative risk of developing heart failure 2.4 times greater in diabetics, this risk rising to 5.1 in the case of women, regardless of age, body weight, and other cardiovascular risk factors.<sup>41</sup> Nevertheless, no proof exists that diabetic patients present more extensive AMI than non-diabetic patients. Likewise, congestive heart failure is more prevalent in diabetics in spite of a similar left ventricular ejection fraction in both types of patients, although a worse ventricular function in non-infarcted areas is observed in diabetics.<sup>42</sup> The factor involved in the more frequent than expected presentation of heart failure is the presence of subclinical disease of the cardiac muscle of diabetics, in which abnormalities of coronary microcirculation and functional endothelial disturbances seem to have a determinant role.<sup>43</sup> Left ventricular diastolic dysfunction in the absence of another cause is considered the early phase of this cardiac disorder. It is important to emphasize that the presence of microalbuminuria is associated with diastolic dysfunction of the left ventricle.<sup>44</sup>

The fact that only one-third of diabetics develop this disease of the cardiac muscle and the absence of a clear relation with the degree of metabolic control suggests that there may be a genetic predisposition that

TABLE 3. Determinant factors and characteristics of the prognosis of coronary artery disease in the diabetic patient

Eliminates the protective effect of the menstrual hormonal cycle in women
Early involvement
Fast progression of coronary atherosclerosis
More extensive and diffuse involvement
Larger proportion of silent ischemia
Worse short and long-term prognosis of coronary syndrome
Greater proportion of heart failure
Greater proportion of sudden death
Worse results of fibrinolytic treatment
Worse results of revascularization techniques

Adapted from Scheid-Nave et al.<sup>36</sup>



**Fig. 2.** Prognosis of acute myocardial infarction in diabetic patients (adapted from Miettinen et al<sup>38</sup> and Room et al<sup>39</sup>). AMI indicates acute myocardial infarction; CAD, coronary artery disease.

favors the development of diabetic cardiac muscle disease and heart failure. It is especially important to identify diabetic patients with disease of the cardiac muscle soon, due to the especially poor prognosis that acute coronary syndrome has in these patients. In this sense, the quantifiable increase in myocardial echodensity should be emphasized, which could correspond to increased collagen deposits and in the future could be used as an early marker of diabetic disease of the heart muscle.<sup>45</sup>

Plasma glucose concentrations at the time of admission for acute coronary syndrome are an important prognostic factor, even in non-diabetic patients.<sup>46,47</sup> In the REGICOR study, the patients with a blood glucose level of more than 6.67 mmol/L (120 mg/dL) at the time of admission for AMI had a mortality in the first 28 days that was 4 times greater than that of the patients with lower levels, regardless of other cardiovascular risk factors and the history *per se* of diabetes.<sup>48</sup> The DIGAMI study<sup>40</sup> demonstrated that an optimal glucose control (<180 mg/dL) during the acute phase of AMI allowed a significant reduction of 30% in the mortality at one year and of 11% in the mortality at 3-4 years.

Diabetic patients that survive the immediate complications of acute coronary syndrome suffer recurrent AMI, both mortal and non-mortal, more frequently than non-diabetics. In addition, the 28-day mortality of non-Q wave AMI was 14% and 9%, and 22% and 8% in diabetic and non-diabetic men and women, respectively.<sup>49</sup>

Likewise, diabetic patients hospitalized for unstable angina have a one-year mortality greater than that of non-diabetics, with figures of 25% and 10%, respectively.<sup>50</sup>

In our setting, the main independent predictors of mortality at 90 days of patients with unstable angina

included in the RESCATE and PEPA studies were DM, the presence of heart failure at the time of admission, and deviation of the ST segment.<sup>20,21</sup>

### Less favorable results of thrombolytic treatment

Initially, the ISIS-II study (Study of Infarct Survival-II) demonstrated that diabetic patients treated with streptokinase had a 31% better survival from AMI than patients treated with placebo *versus* 23% observed in the non-diabetic population.<sup>51</sup> However, some findings indicate that fibrinolytics are administered less frequently to diabetic than non-diabetic patients with AMI.<sup>52</sup>

On the other hand, in the TAMI study the intrahospital and 6-weeks mortality was greater in diabetic patients undergoing fibrinolysis than in non-diabetics.<sup>52</sup> In the GISSI-2 study, satisfactory reperfusion was achieved less frequently in diabetic than in non-diabetic patients. The intrahospital mortality in patients treated with rt-PA was 7.4% in patients without DM, 15.4% in patients with type 1 DM, and 12.4% in type 2 DM. In patients treated with streptokinase, the respective mortality rates were 7.2%, 17.4%, and 10.9%. No significant differences in mortality were observed in relation to the type of fibrinolytic used.<sup>42</sup>

Anomalies of the fibrinolytic system, such as high PAI-1 concentrations, together with more extensive coronary artery disease in diabetic patients and states of insulin resistance can explain the lower rates of reperfusion.<sup>53</sup>

Diabetic patients with AMI must be considered high risk. Early fibrinolytic treatment should be performed and a more aggressive therapeutic approach should be considered, with early revascularization in patients who have a suitable anatomy.

### Less favorable results of coronary revascularization procedures

Aortocoronary bypass surgery and angioplasty are both effective techniques for coronary revascularization in diabetic patients. Coronary surgery does not have a greater postoperative mortality in diabetic patients, but the long-term results are worse, fundamentally due to the persistence of risk factors, particularly dyslipemia.<sup>54</sup>

The immediate results of angioplasty in diabetic patients are similar to those obtained in non-diabetics, although at 6 months the percentage of restenosis is higher.<sup>55</sup> Restenosis in diabetics is due to exaggerated intimal hyperplasia.<sup>56</sup> Various studies, like STRESS I and II, have demonstrated that the use of stents in diabetic patient reduces the rate of restenosis.<sup>57</sup> It should be noted that the inhibitors of IIb/IIIa glycoprotein platelet receptors have improved the results of coro-

nary angioplasty with and without stenting in diabetic patients.<sup>58</sup> Independently of the greater incidence of restenosis, it is important to consider that coronary involvement in diabetic patients is usually more extensive and diffuse and, therefore, the possibility of achieving complete revascularization with angioplasty is lower.<sup>59</sup> It is necessary to consider that the mortality in the first 2 years in diabetic patients undergoing angioplasty is four times greater than in non-diabetics; in addition, they present a higher percentage of coronary events in the long term and require 35% more revascularization procedures than non-diabetics.<sup>60</sup>

The BARI study (Bypass Angioplasty Revascularization Trial), in which the effect of angioplasty was compared to aortocoronary bypass surgery, demonstrated that the 5-year mortality for both techniques was higher in diabetic versus non-diabetic patients, and greater in the group of patients that underwent angioplasty.<sup>61</sup> Nevertheless, there were fewer initial complications (mortality or AMI) with angioplasty than with surgery. Therefore, it seems reasonable to indicate angioplasty in patients with DM, especially type 2 DM, with one or two-vessel disease, who do not present some of the factors favoring restenosis, such as arteries less than 3 mm in diameter, long lesions, lesions for which residual restenosis is expected, or those considered to have an unacceptable risk of surgical complications.<sup>60</sup>

## RECOMMENDATIONS TO IMPROVE THE PROGNOSIS OF CORONARY ARTERY DISEASE IN DIABETIC PATIENTS

### Control of factors associated with cardiovascular risk in diabetic patients

Because the risk of cardiovascular death and CAD is significantly increased in DM, the impact of changes in conventional cardiovascular risk factors can have much greater effects on diabetic patients. Cardiovascular risk factors must be dealt with promptly and aggressively in diabetic patients. It has been calculated that for each level of abnormality of each risk factor, diabetics have a risk of CAD 2 to 4 times greater. This increased risk is more pronounced in women<sup>62</sup> (Figure 3).

On the other hand, it noteworthy that a low percentage of diabetics with CAD in Spain reach recommended target blood pressure and plasma lipid values (Table 4). The CARDIOTENS study demonstrated that less than 30% of diabetics with CAD had an adequately controlled blood pressure (less than 130/85 mm Hg) and only 12% of the patients with DM and CAD had a cholesterol and low-density lipoprotein (LDL) level of less than 100 mg/dL.<sup>63</sup>

## Arterial hypertension

Arterial hypertension (AHT) occurs 2-3 times more often in diabetics than in the general population, especially in men under the age of 50 years, black race, and lower socioeconomic level. This association between DM and AHT is due possibly to the situation of insulin resistance and hyperinsulinism in persons with diabetes and states of glucose intolerance. AHT seems to be present in more than 85% of diabetic patients with cardiovascular events.<sup>64</sup>

The HOT study (Hypertension Optimal Treatment) demonstrated a large reduction in cardiovascular events in the group with lower diastolic blood pressure, below 80 mm Hg. The number of events was approximately half that found in the group with blood pressures over 90 mm Hg.<sup>65</sup>

The Micro-HOPE and UKPDS studies have demonstrated that an optimal control of blood pressure in diabetic patients decreases the risk of CAD and increases survival in this group of patients. The goal of antihypertensive treatment must be to obtain blood pressure levels <130/80 mm Hg and, if proteinuria >1 g/24 h exists, the target figures must be lower than 125/75 mm Hg. The drugs of choice are ACEI, although ARA II, beta-blockers (considering their glucose-lowering effect), diuretics or calcium antagonists can also be used and, often, a combination of several antihypertensive drugs.<sup>66,67</sup>

## Dyslipidemia

Dyslipidemia is one of the main factors implicated in the increased cardiovascular risk associated with DM. In contrast with what occurs in type 1 DM, the lipid disorders present in type 2 DM, although they improve, do not disappear with the optimization of glucose control.<sup>68</sup> Around 40% to 50% of diabetic patient present C-LDL values over 130 mg/dL.<sup>69</sup>

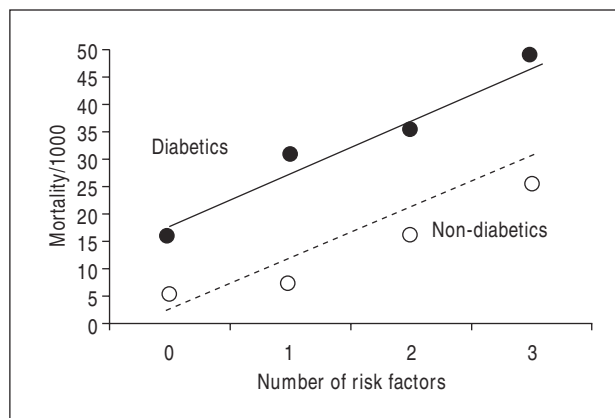


Fig. 3. Synergic effect of diabetes mellitus associated to other cardiovascular factors (adapted from Assmann and Schulte<sup>62</sup>).

**TABLE 4. Therapeutic objectives for each cardiovascular risk factor in patients with diabetes mellitus**

Factor	Objective
Smoking	Complete withdrawal
Regular physical exercise	Whenever no contraindications exist
Body mass index	<27 kg/m <sup>2</sup>
HbA <sub>1c</sub>	<7% (if feasible <6%)
LDL	<100 mg/dL (2.6 mmol/L)
C-HDL	
Female	>45 mg/dL (1.15 mmol/L)
Male	>35 mg/dL (0.9 mmol/L)
Triglycerides	<150 mg/dL (1.7 mol/L)
Blood pressure	<130/85 mm Hg if proteinuria <1 g/24 h <125/75 mm Hg if proteinuria >1 g/24 h Age >60 years <140/90 mm Hg Isolated systolic arterial hypertension If SBP>180: target SBP<160 mm Hg If SBP>160 and <179: target SBP <140 mm Hg
Acetylsalicylic acid	80-325 mg/day if other risk factors or microalbuminuria present and contraindications absent
Beta-blockers	Always in secondary prevention if no contraindications present
ACEI or ARA II	If arterial hypertension or microalbuminuria is present, or after acute coronary syndrome

ACEI indicates angiotensin-converting enzyme inhibitors; ARA II, angiotensin II receptor antagonists (adapted from González-Juanatey et al<sup>63</sup>).

The benefit of statin treatment in diabetics with AMI included in the 4S, CARE, and LIPID studies was significantly greater than that observed in non-diabetics. These studies indicate that the reduction of cholesterol reduces by more than 70% the risk of death and recurrences of coronary events in diabetic patients.<sup>70</sup>

In patients with DM, the cardiovascular risk is equivalent to that of the patients who have already presented a CAD episode. According to the criteria of the American Diabetes Association and the third report of the National Cholesterol Education Program, the objectives in diabetic patients suggest that the target C-LDL should be 100 mg/dL or less.<sup>71,72</sup> It is advisable to maintain triglyceride concentrations below 150 mg/dL, especially in patients with CAD or several risk factors.<sup>73</sup>

Health and dietary measures and the optimization of glucose control are the basis of treatment of diabetic dyslipidemia, but pharmacological intervention with statins, fibrates or both often will be necessary.<sup>74</sup>

### Smoking

Tobacco has a procoagulation effect, which favors the appearance of acute events, and a proinflammatory

effect, which accelerates the arteriosclerotic process, especially in women, as well as a synergic effect with DM. The MRFIT Study demonstrated that, with the increase in smoking, the risk of cardiovascular death among diabetic patients was 3-4 times greater than among non-diabetics.<sup>75</sup> It is thus fundamental to emphatically advise diabetic patients to stop smoking.

### Healthy lifestyles (physical exercise, weight control, and diet)

Numerous studies indicate that obesity and insulin resistance are the main risk factors for type 2 DM. On the average, type 2 diabetics are more obese and have a more central or android obesity than non-diabetic subjects.<sup>76</sup> A recent study has shown that obese children and adolescents present a high prevalence of glucose intolerance and insulin resistance.<sup>77</sup> For that reason, it is especially important to avoid obesity beginning at an early age and to educate diabetics to exercise regularly and practice healthy habits.

Regular physical activity improves sensitivity to insulin,<sup>78</sup> reduces plasma glucose concentrations,<sup>79</sup> decreases body fat,<sup>80</sup> improves the lipid profile,<sup>81</sup> and decreases the probability of developing DM.<sup>82</sup>

All diabetic patients should be aware of the need to adopt healthy lifestyle, and diabetics with CAD should be preferred candidates for inclusion in cardiac rehabilitation programs.

### Control of blood glucose and insulin resistance

There seems to be a direct relation between blood glucose values and cardiovascular risk. In the UKPDS study, the improvement in blood glucose control (reductions of 0.9 points of HbA<sub>1c</sub>) was associated with a 10% decrease in overall mortality and a 16% reduction in AMI.<sup>83</sup> Epidemiological studies consistently suggest that the prevention of macrovascular disease in diabetic patients requires maintaining HbA<sub>1c</sub><6% for as much time as possible.<sup>84</sup>

Independently of the diabetic state, there is a clear relation between risk of CAD and plasma glucose values 2 h after an oral glucose tolerance test and baseline glycemia.<sup>85</sup> The threshold at which cardiovascular risk increases is as low as 5.5 mmol/L fasting and 6.5 mmol/L at 2 h in an oral glucose tolerance test.<sup>86</sup>

In all diabetic patients, the best metabolic control should be maintained to prevent late complications, without forgetting that the initial measures must always include changes in living habits.<sup>74</sup>

### Platelet antiaggregant treatment

The results of a meta-analysis of 145 prospective studies allow aspirin treatment (80-325 mg/day) to be

recommended in all patients with DM and cardiovascular disease and in primary prevention in diabetics with another cardiovascular risk factor.<sup>87</sup>

### Treatment with angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists

Various studies have demonstrated that angiotensin-converting enzyme inhibitors (ACEI) and, more recently, some angiotensin II receptor antagonists (ARA II), are useful in the control of blood pressure in both diabetic and non-diabetic patients. On the other hand, these drugs have a protective effect on the kidney in patients with microalbuminuria, improve sensitivity to insulin, decrease the incidence of heart failure in acute coronary syndrome, and reduce cardiovascular mortality in diabetic patients.<sup>88-91</sup> The GISSI-3 study demonstrated that the use of ACEI in AMI reduced the 6-month mortality only in diabetic patients (12.9% in the patients with treated DM versus 16.1% in patients randomized to placebo).<sup>92</sup> The results of the HOPE study have contributed new evidence for the use of ACEI by diabetic patients with CAD.<sup>66</sup>

The results of the CARDIOTENS study demonstrate that hardly 50% of diabetic patients with ischemic heart disease received an ACEI and only 14% of diabetics treated with ACEI also received a concomitant beta-blocker.<sup>63</sup>

### Treatment with beta-blockers

Sufficient information exists to affirm that the use of beta-blockers in the post-infarction period is also beneficial to diabetic patients, possibly more than to non-diabetics. The use of beta-blockers reduces coro-

nary mortality by 37% in the diabetic patient, whereas in the overall group of patients with CAD, it produces a reduction of 13%, a benefit that is maintained for reinfarction.<sup>93</sup>

It is especially remarkable that the CARDIOTENS study disclosed that only 26% of diabetic patients with CAD received beta-blockers and only 39% of these were treated simultaneously with a statin.<sup>63</sup>

### EARLY DETECTION OF ARTERIOSCLEROTIC DISEASE IN DIABETIC PATIENTS. FUTURE PERSPECTIVES IN THE FIELD OF PREVENTION

The detection of asymptomatic CAD in diabetic patients will allow the application of prevention programs, early antianginal treatment, and treatment with early revascularization techniques in high-risk patients.<sup>94</sup> The consideration of DM itself as a CAD equivalent, although there has been no history of coronary events, must translate into stricter control of these patients and their cardiovascular risk factors, considering secondary prevention criteria.<sup>2</sup>

Age, blood glucose concentrations, presence of hypertension,<sup>95</sup> smoking habit, and microalbuminuria are considered major predictors of macrovascular disease in diabetic patients.<sup>96</sup> These findings make it necessary to review the present indications for cardiological study in patients with DM (Table 5).<sup>97</sup> Age, triglyceride and apoprotein A-I concentrations, the duration of DM and blood glucose control are considered determinants of the extension and severity of CAD in diabetic patients.<sup>98</sup> High blood concentrations of reactive protein C and interleukin<sup>6</sup> also seem to behave like markers of risk for the development of DM.<sup>99</sup>

On the other hand, methods for the early diagnosis of early arteriosclerotic disease in diabetic patients are being developed, such as echo-Doppler of the brachial artery<sup>100</sup> or the detection of calcifications in the coronary arteries by electron-beam computed tomography,<sup>101</sup> which will help to improve the prognosis of vascular disease associated with DM.

We must not forget that effort myocardial perfusion studies by single-photon emission computed tomography (SPECT) radionuclide scan allow the prognosis to be stratified in both diabetic and non-diabetic patients, but that the grading of hypoperfusion is associated to greater severity in diabetics.<sup>102</sup>

In recent years the study of certain genetic polymorphisms, such as polymorphism in position -308 of TNF as risk markers for the development of insulin resistance and, therefore, the development of DM and cardiovascular complications, is acquiring increasing importance.<sup>103</sup> More recently, the function of peroxisome proliferator-activated receptors (PPAR) has been studied. These receptors are members of a superfamily of nucleic receptor of transcription factors ac-

TABLE 5. Indications for cardiological study in diabetic patients

1. In the presence of symptoms that suggest ischemic heart disease
2. Electrocardiogram at rest with signs indicative of myocardial infarction or ischemia
3. Peripheral arteriopathy
4. Carotid disease
5. Abdominal aneurysm of arteriosclerotic origin
6. Sedentary patients or patients over 35 years who wish to begin vigorous exercise
7. Presence of two or more risk factors:
  - Total cholesterol >240 mg/dL; LDL>160 mg/dL or C-HDL<35 mg/dL
  - Blood pressure >140/90 mm Hg
  - Smoking
  - Family history of premature death due to coronary artery disease
  - Microalbuminuria (some authors always recommend cardiological study)

Adapted from American Diabetes Association.<sup>97</sup>



tivated by ligands. In particular, PPAR $\gamma$  (which exists as a heterodimer associated to the retinoid X nuclear receptor, or RXR, bound to the promoter region of several target genes) seems to be related to the inhibition of transcription of the target genes or, in the presence of certain heterodimer activator proteins (ligands), to its activation.<sup>104</sup> The activity of the PPAR $\gamma$ -RXR heterodimer has been related to an increase in insulin resistance and its deactivation by ligands with improvement in the action of insulin. PPAR $\gamma$  agonists, such as the new oral antidiabetics of the glitazone class, have been shown to increase peripheral sensitivity to insulin and to improve the state of insulin resistance in type II diabetic patients.<sup>105</sup> In addition to controlling blood glucose, diabetic patients treated with glitazones showed improvement in all the components of the metabolic syndrome,<sup>105</sup> and a study has even shown a certain regression of atherosclerosis.<sup>106</sup> This knowledge will undoubtedly lead to a better management of insulin resistance and prediabetic and diabetic states by means of the development of new drugs that improve sensitivity to the action of insulin.<sup>107</sup> Some genetic variants of PPAR $\alpha$ , another receptor of the superfamily described previously, have been related to states of insulin resistance or enhanced sensitivity to environmental factors related to the appearance of DM.<sup>108</sup>

On the other hand, another remarkable finding is the result of a substudy of WOSCOPS that demonstrates that pravastatin reduces by 30% the possibility of developing DM, which can probably be explained by the capacity of pravastatin to reduce the concentrations of proinflammatory cytokines and improve endothelial function.<sup>109</sup>

Studies like the ACCORD trial presently under way will surely provide information on the benefits of intensive treatment, both in controlling diabetes and the hypertension and dyslipidemia found in patients with DM.<sup>110</sup>

## CONCLUSIONS

DM, a simultaneously endocrine and metabolic disease, is an especially aggressive process leading to vascular lesions. Therefore, its treatment must include all the measures that contribute to reducing its high morbidity and mortality. In addition to hyperglycemia and insulin resistance, in these patients detecting and intensively treating the main cardiovascular risk factors, particularly hypertension, must be considered high-priority. It is necessary to modify the attitudes of diabetic patients to favor the acquisition of healthy living habits. The goals of prevention must be maximal and equivalent to the secondary prevention measures applied in non-diabetic persons who already have CAD.

In order to reduce the high morbidity and mortality due to cardiovascular disease in diabetic patients, an

aggressive multidisciplinary approach and effort are needed. In the near future there will be enough genetic information for orienting and guiding therapy optimally.

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