

## UPDATE

### Diabetes and Cardiovascular Diseases (VI)

# Prevention and Treatment of Congestive Heart Failure in Diabetic Patients

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Diabetes mellitus is a strong risk factor for the development of cardiovascular disease, and is associated with a worse prognosis. The incidence of congestive heart failure is higher in diabetic patients, although the reasons for this increased rate are debated (higher incidence and severity of coronary heart disease and arterial hypertension, or a true «diabetic cardiomyopathy»). The treatment of heart failure in diabetic patients does not differ from that of non-diabetic patients, although recent studies of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers offer interesting new perspectives.

**Key words:** *Diabetes. Heart failure. Cardiomyopathy.*

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### Prevención y tratamiento de la insuficiencia cardíaca en los pacientes diabéticos

La diabetes mellitus se asocia con una elevada incidencia de patología cardiovascular y es también un factor de mal pronóstico en pacientes con enfermedades cardiovasculares. La incidencia de insuficiencia cardíaca está aumentada en pacientes diabéticos, aunque existe controversia sobre la causa real de este aumento (mayor incidencia y severidad de enfermedad coronaria e hipertensión arterial, o una verdadera «miocardiopatía diabética» independiente de otros problemas). El tratamiento de la insuficiencia cardíaca en pacientes diabéticos no difiere en términos generales del tratamiento habitual en pacientes no diabéticos, aunque estudios recientes con inhibidores de la enzima convertidora de la angiotensina y antagonistas del receptor de angiotensina II ofrecen perspectivas alentadoras.

**Palabras clave:** *Diabetes. Insuficiencia cardíaca. Miocardiopatía.*

## INTRODUCTION

Cardiovascular diseases are the most important complication, by far, of diabetes mellitus. Nowadays, cardiovascular complications are the major risk factor for morbidity and mortality in diabetic patients.<sup>1</sup> It is well known that the most frequent heart disease in diabetes is coronary artery disease, including the major epicardial arteries and microcirculation. Mortality from acute myocardial infarction is greater in diabetic patients in the short and long term.<sup>2</sup> Likewise, poorly controlled hyperglycemia is associated with a greater mortality in the acute phase of acute myocardial infarction.<sup>3</sup> However, it was not so long ago that there

was less information available on the association between diabetes mellitus and the other major cardiovascular complication, heart failure. Interest in heart failure has grown dramatically in the last decade for several reasons: *a)* increasing prevalence; *b)* poor prognosis (similar to that of common types of cancer); *c)* increased rate of hospital admissions; *d)* very high incidence (particularly in older persons), and *e)* high economic cost. Likewise, the development of new drugs capable of improving the prognosis and quality of life of patients with congestive heart failure has also helped to raise interest.

Although arterial hypertension and coronary artery disease are the fundamental causes of congestive heart failure in our geographic area, diabetes mellitus is also associated with a greater risk of developing heart failure, as well as with a worse prognosis. It is not known for sure if this increased incidence of heart failure in diabetes is due to the consequences of coronary artery disease associated to diabetes or if it

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is a direct consequence of diabetes that is independent of myocardial ischemia, the so-called «diabetic cardiomyopathy.» Although some authors believe that sufficient pathogenic and epidemiological evidence exists to support the presence of direct myocardial damage in diabetes,<sup>4</sup> it is probably closer to the truth to assume that the pathogenesis of heart failure in diabetes is multifactorial, and that myocardial ischemia and arterial hypertension have an important role in the condition. However, there are findings that support the idea that diabetes produces direct myocardial damage.

## **PATHOGENESIS OF DIABETIC CARDIOMYOPATHY**

It is an established fact that patients with diabetes mellitus develop coronary disease earlier, have a greater incidence of multivessel disease, and tend to suffer more severe and diffuse disease.<sup>5</sup> Microangiopathic changes in small vessels can also contribute to diabetic cardiomyopathy.<sup>6</sup> Likewise, it is known that a high percentage of diabetics, ranging from 28% to 68%, have associated arterial hypertension. This can explain in part the increase in left ventricular mass (ventricular hypertrophy) observed in diabetic patients. Nevertheless, experimental and clinical evidence exists that many of the functional and morphological disturbances associated with the heart in diabetic patients may be independent of the two factors mentioned above.

In experimental models of haloxane or streptozotocin-induced diabetes in pigs or rats,<sup>7,8</sup> various myocardial disturbances have been demonstrated, such as a reduction in stroke volume (in spite of normal ventricular filling pressures), increased ventricular rigidity, increased left ventricular mass, prolongation of the contraction and relaxation phases, extension of the isovolumetric relaxation time, elevation of the end-diastolic pressures and decreased shortening speed. These functional and morphological disturbances may have a biochemical origin. In diabetic rats, disturbances in the ATPase and myosin isoenzymes, impaired calcium transport, changes in membrane receptor function, and abnormalities in the metabolism of carbohydrates, lipids and adenine nucleotides have been described.<sup>7,8</sup> Likewise, an endothelial dysfunction exists in diabetes that may be important for the development of heart failure. The combination of arterial hypertension and diabetes mellitus in rats leads to a greater mortality, with a synergic effect, as also occurs in human clinical practice.

The left ventricular hypertrophy usually present in

diabetic patients could be due in part to the high prevalence of arterial hypertension or myocardial ischemia, as has been noted. However, there are data suggesting that it can be an independent phenomenon, as in experimental models. Several studies have shown that diabetics, particularly women, have a greater left ventricular mass due to the increased wall thickness and greater ventricular diameters.<sup>9</sup> Diabetes seems to be an independent factor in this hypertrophy.<sup>9</sup> Other anomalies found in diabetic human hearts include interstitial fibrosis, interstitial edema, and constrained microcirculation in the absence of hypertension or epicardial coronary disease.<sup>6</sup> As occurred in experimental animals, the association of hypertension to diabetes significantly increases morphological damage, originating a powerful substrate for the development of heart failure.

## **EPIDEMIOLOGICAL EVIDENCE**

Since the initial description by Rutler et al<sup>10</sup> of diabetic cardiomyopathy almost 30 years ago, based on the post-mortem study of 4 cases, much evidence has accrued of the association between diabetes mellitus and heart failure from clinical and epidemiological studies. Data from the Framingham study indicate that diabetic patients have a greater risk of developing heart failure than non-diabetics.<sup>11,12</sup> This risk is 2 and 5 times greater for men and women, respectively. The excess risk of heart failure persists after adjusting cases for age, the presence of arterial hypertension, obesity, hypercholesterolemia, and coronary heart disease.<sup>11</sup> Diabetes is also a risk factor for sudden death. More recent studies have demonstrated that the existence of ischemic heart disease, particularly in patients who have suffered myocardial infarction, is associated with a greater incidence of heart failure in diabetics than in non-diabetics.<sup>13</sup> The frequency and speed of the evolution from preclinical functional and morphological anomalies to symptomatic ventricular dysfunction are not known, or the role that the metabolic control of hyperglycemia can play in preventing this evolution. It is not known if correct metabolic control can make cause myocardial anomalies to remit. Recent data indicate that these disturbances can occur in both type 1 and type 2 diabetes mellitus.<sup>14</sup>

## PROGNOSIS OF HEART FAILURE IN DIABETIC PATIENTS

The rates of mortality and complications of heart failure are greater in diabetic patients than in non-diabetic patients. In a recent meta-analysis that included almost 13 000 patients with symptomatic or asymptomatic ventricular dysfunction after myocardial infarction, from the SAVE, AIR, TRQCE and SOLVD studies, the mortality was 36.4% and 24.7% in diabetics and non-diabetics, respectively,<sup>15</sup> although the relative roles of other concomitant factors was not well defined. Substudies from other more recent clinical trials also demonstrate a greater mortality in diabetic patients. Thus, in the MOCHA study with carvedilol (one of the trials in the Program USA of carvedilol), the mortality in the patients assigned to the placebo group was 30% in diabetics and 9% in non-diabetics.<sup>16</sup> In the ATLAS study, these rates were 49% and 42%, respectively,<sup>17</sup> as also occurred in the MERIT-HF trial with metoprolol.<sup>18</sup> A recent publication of data from the TRACE study (trandolapril postmyocardial infarction) showed that the negative impact of diabetes on the prognosis of patients with postinfarction ventricular dysfunction is inconstant, but increases progressively with time.<sup>19</sup>

## PHARMACOLOGICAL TREATMENT OF HEART FAILURE IN DIABETIC PATIENTS

The pharmacological treatment of heart failure is essentially similar in diabetic and non-diabetic patients, and it is based on the administration of diuretics, angiotensin converting enzyme inhibitors (ACEI), and beta-blockers, as well as digitalis, spironolactone and antagonists of the angiotensin II receptors (ARA II) in suitable cases. It should be noted that all the information available on the usefulness of these drugs in patients with heart failure derives from clinical trials carried out in patients with depressed ejection fraction (traditionally known as «systolic heart failure»). To date, there is no information on the prognostic effect of these drugs in patients with «diastolic heart failure» (or, as it is more correctly designated, «heart failure with conserved systolic function»). Studies are under way, fundamentally with ARA II, that should yield valuable information on the treatment of this problem, which represents a growing percentage of all cases of heart failure, particularly in older patients.<sup>20</sup>

The available information on the results of the drugs mentioned earlier in diabetic patients with heart failure and depressed systolic function has not been drawn from studies specifically designed in diabetics,

but from general clinical trials of heart failure, in which *post hoc* analyses have been made in the subgroups of diabetic patients. In addition, in all the cases, the diagnosis of diabetes was defined by the clinical history, without making distinctions between diabetes type 1 and type 2, which is much more frequent. The diuretics are the drugs that more rapidly and effectively improve congestive symptoms in patients with heart failure, although no clinical trials have studied their effect on prognosis and mortality. Since diuretics can raise glycemia values in patients with type 2 diabetes, particularly in high doses, careful dose titration is necessary in these patients, to determine the minimum effective dose.

The ACEIs are the drugs that first demonstrated an improvement in the survival of patients with heart failure and a depressed ejection fraction, as well as cases of asymptomatic ventricular dysfunction. These findings are also applicable to diabetic patients, as shown by a subanalysis of the SOLVD study, where it was found that the ACEIs were as effective in diabetics as in non-diabetics in reducing mortality and the rate of readmission.<sup>21</sup> In the meta-analysis mentioned previously,<sup>15</sup> the absolute benefit was greater for diabetic patients (36 lives saved per 1000 patients treated with ACEIs in non-diabetics versus 48 per 1000 in diabetics). As far as the most effective dose of ACEI, whether high or low, the data of the ATLAS study, which compared lisinopril in doses of 35 mg versus 5 mg, demonstrated a greater reduction of the risk relative of mortality with the high dose as opposed to the low dose in 611 diabetic patients (of a total of 3164 included in the trial) than in non-diabetics (14% and 6%, respectively). The tolerability of the high dose of lisinopril was good and similar in diabetic and non-diabetic patients.<sup>17</sup> Although the results did not reach the level of conventional statistical significance, the maximum tolerated dose of ACEIs seems to be the most appropriate option in diabetic patients.<sup>17</sup>

In just a few years the beta-blockers have passed from being contraindicated in heart failure to being drugs of choice due to their very favorable prognostic effect in patients with heart failure and systolic dysfunction. Traditionally, diabetes was considered a relative contraindication for their use, but beta-blockers currently have a favorable effect in diabetic patients with arterial hypertension or ischemic heart disease, as well as heart failure. In the MOCHA study<sup>16</sup> the greatest reduction in mortality took place in the subgroup of diabetic patients treated with carvedilol; the 6-month mortality was 6% in these patients, compared with 30% in the control group. In

contrast, in the MERIT-HF study a slightly less beneficial effect of metoprolol was observed in diabetic patients than in non-diabetic patients.

In relation to ARA II, studies with irbesartan indicate that these drugs can increase the ejection fraction in diabetic patients with heart failure.<sup>22</sup> In the ELITE 1 study, the mortality in the subgroup of diabetic patients over 65 years old was less with losartan than with captopril (4.6% vs 13.6%).<sup>23</sup> Recently, the results of the Val-HeFT study, which compared the association of valsartan and captopril to captopril alone in patients with moderate heart failure, have become known. The addition of valsartan to ACEI produced a decrease in readmissions and a greater symptomatic improvement, although it did not reduce mortality. We still do not have an analysis of the subgroup of diabetic patients in this study. Other studies in course with ARA II, such as CHARM with candesartan, or others with losartan or irbesartan, will help to better know the role of these drugs in the treatment of heart failure with both conserved and depressed systolic function.

### Prevention of heart failure in diabetic patients

Prevention of the development of heart failure in diabetic patients requires, in first place, the prevention of coronary artery disease and, in second place, adequate control of arterial hypertension (the recommended figures of arterial tension must be lower than 130/85 mm Hg). As was commented previously, it is still not known if the metabolic control of diabetes can prevent or make the disturbances of the myocardium and coronary microcirculation remit. Nevertheless, some important clinical trials have contributed data on the utility of certain drugs (ACEI and ARA II) in the primary prevention of the failure in diabetic patients. Since the publication of the HOPE study, it is known that treatment with an ACEI, ramipril, significantly reduces the appearance of cardiovascular events in high-risk patients without known heart disease.<sup>24</sup> This beneficial effect was also observed in the subgroup of diabetic patients (Micro-HOPE).<sup>25</sup> Nevertheless, and although ramipril showed a beneficial effect in relation to the symptoms of heart failure, it did not significantly reduce the number of admissions. On the contrary, in the RENAAL study, which compared losartan with placebo in patients with type 2 diabetes and nephropathy, losartan produced a reduction in the risk of a first admission for heart failure of 32% ( $P=.005$ ).<sup>26</sup> A subanalysis of the HOPE study in patients with kidney failure showed no differences

in admissions for heart failure between ramipril and placebo.<sup>27</sup> Therefore, it seems that ARA II can have a protective effect against the development of heart failure in diabetic patients with nephropathy, and that this effect has not been found with ACEIs. Future studies should confirm these findings and determine if this favorable effect also takes place in diabetic patients without kidney failure.

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