UPDATE

Diabetes and Cardiovascular Diseases (V)

Prevention and Treatment of Ischemic Heart Disease in Patients with Diabetes Mellitus

Héctor Bueno

Servicio de Cardiología. Hospital General Universitario Gregorio Marañón. Madrid. España.

The incidence of cardiovascular diseases among diabetic patients is so high that diabetes mellitus is currently defined as a cardiovascular disease equivalent. Furthermore, diabetic patients who develop acute coronary syndromes have a poorer short-term and long-term prognosis, so primary and secondary preventive measures are critically important in this population subgroup.

There is substantial evidence that pharmacological therapy for primary and secondary cardiovascular prevention is more effective in diabetic patients than in non-diabetics. This article reviews the evidence of the efficacy of pharmacological prevention therapies in diabetic patients in favor of an aggressive pharmacological preventive strategy. Every diabetic patient without known cardiovascular disease should be treated with angiotensin-converting enzyme inhibitors and statins. High-risk patients should also receive low-dose aspirin.

Compared with non-diabetics, diabetic patients who develop acute coronary events benefit more from the addition of intensive antithrombotic therapy to aspirin treatment. Diabetic patients presenting with non-ST segment elevation syndromes have better outcomes when treated with clopidogrel or glycoprotein IIb/IIIa inhibitors, and diabetics presenting with ST-segment elevation or left bundle-branch block have a greater survival benefit when given thrombolytic therapy compared with non-diabetic patients.

Unless formal contraindications are present, diabetic patients with ischemic heart disease, particularly those with previous myocardial infarction, should always be treated with aspirin, betablockers, angiotensin converting enzyme inhibitors, and statins, regardless of lipid levels, left ventricular systolic function or the presence of congestive heart failure.

Key words: *Diabetes. Ischemic heart disease. Myocardial infarction. Primary prevention. Secondary prevention.*

Correspondence: Dr. H. Bueno.
Servicio de Cardiología. Hospital General Universitario Gregorio Marañón.
Dr. Esquerdo, 46. 28007 Madrid. España.
E-mail: hecbueno@jet.es

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Prevención y tratamiento de la cardiopatía isquémica en pacientes con diabetes mellitus

La incidencia de enfermedades cardiovasculares entre los pacientes con diabetes mellitus es tan alta que actualmente se define como un equivalente de enfermedad cardiovascular. Además, los diabéticos que desarrollan episodios coronarios agudos tienen un riesgo mucho mayor tanto a corto como a largo plazo, por lo que las medidas de prevención primaria y secundaria son de importancia capital en este grupo de población.

Existe una amplia evidencia de que los tratamientos farmacológicos de prevención primaria y secundaria de la cardiopatía isquémica son mucho más eficaces en los pacientes diabéticos que en los no diabéticos. Este artículo revisa las evidencias que hay sobre la utilidad de los tratamientos farmacológicos de prevención cardiovascular en los diabéticos para defender una estrategia agresiva de prevención cardiovascular farmacológica. Todo diabético sin enfermedad cardiovascular conocida debe recibir tratamiento con inhibidores de la enzima conversiva de la angiotensina, estatinas y, en casos de riesgo, aspirina a bajas dosis.

Cuando desarrollan síndromes coronarios agudos, los diabéticos se benefician en mayor grado de un tratamiento antitrombótico intensivo asociado a la aspirina, con clopidogrel o inhibidores de la glucoproteína IIb/IIIa en los casos sin elevación de ST y con fibrinólisis cuando presentan elevación de ST.

Los diabéticos con enfermedad coronaria, particularmente aquellos con infarto de miocardio previo, deberían ser tratados siempre que no presenten contraindicaciones con aspirina, bloqueadores beta, inhibidores de la enzima conversiva de la angiotensina y estatinas, independientemente de los niveles de lípidos, la función ventricular izquierda o la presencia de insuficiencia cardíaca.

Palabras clave: *Diabetes. Cardiopatía isquémica. Infarto de miocardio. Prevención primaria. Prevención secundaria.*

ABBREVIATIONS

IHD: ischemic heart disease.
AMI: acute myocardial infarction.
NSTE-ACS: non-ST segment elevation acute coronary syndrome.
DM: diabetes mellitus.
HT: arterial hypertension.
ACEI: angiotensin-converting enzyme inhibitor.
CVRF: cardiovascular risk factors.

INTRODUCTION

Although I will use the term diabetes mellitus (DM) generically in this review, I should clarify that most of the evidence obtained in clinical research investigating the incidence of cardiovascular diseases, their evolution, prognosis, and prevention in relation to DM has been developed in patients with type 2 DM. Type 2 DM appears at an older age than type 1 DM and its prevalence is much higher, which is why it is the form of diabetes most commonly assessed in clinical cardiology. Nevertheless, it is important to note that most of the recommendations made for patients with type 2 DM are applicable to patients with type 1 DM.

Diabetes mellitus and risk of coronary disease

The main cause of death in diabetics is cardiovascular disease, particularly ischemic heart disease (IHD). In fact, the risk of suffering cardiovascular complications of patients with DM is so high that its prognosis is equivalent to that of persons without diabetes who have suffered previous acute myocardial infarction (AMI).[1] For that reason, in many areas diabetes is considered equivalent to established cardiovascular disease.[2-5] For this reason, primary prevention interventions in diabetic patients are especially important, particularly measures to control the metabolic disorder in diabetes and those designed to control other cardiovascular risk factors that are frequently associated. Primary prevention measures must address health and diet (beginning with adequate control of diet and excess weight, frequent moderate physical exercise, and the absolute cessation of smoking)[6-9] and pharmacological treatment. Once non-pharmacological measures have been introduced, pharmacological treatment for the prevention of the development of cardiovascular diseases in diabetic patients must be weighed (Table 1).

PHARMACOLOGICAL TREATMENT OF DIABETIC PATIENTS WITHOUT CARDIOVASCULAR DISEASE (PRIMARY PREVENTION)

Control of glycemia

Although it has been demonstrated that strict control of glycemia improves microvascular disease, its effect on macrovascular disease is not so obvious. Several pharmacological intervention studies have failed to demonstrate a marked effect on the appearance of cardiovascular episodes.[10,11] In one of the most important of these studies, UKPDS (UK Prospective Diabetes Study), the intensive treatment of hyperglycemia with a sulfonylurea or insulin in 2729 patients with recently diagnosed type 2 DM only produced a non-significant reduction in the incidence of AMI (16%; *P*=.052), which was more marked in the 342 obese diabetics treated with metformin (39%; *P*=.01).[10] A recent meta-analysis estimated at 13% (95% CI, 1%-26%) the reduction in the risk of developing cardiovascular episodes (total mortality, cardiovascular mortality, non-lethal AMI, and stroke associated with pharmacological interventions to strictly control glycemia in diabetic patients.[12] Therefore, strict control of glycemia with multifactorial interventions is essential in the prevention of the microvascular complications of diabetes, including diet, physical exercise, and pharmacological treatment These measures are necessary but insufficient for preventing macrovascular disease.

Control of lipid values

The most frequent lipid abnormalities in diabetics are hypertriglyceridemia and low HDL cholesterol

TABLE 1. **Therapeutic objectives of preventive treatment in diabetic patients without cardiovascular disease**

Control of glycemia	HbA_{1c}<7%
	Posprandial glycemia 2 h<200 mg/dL
Suppression of smoking	
Control of obesity	
Control of BP	BP<135/85 mm Hg
	P<125/75 mm Hg if proteinuria >1 g/dL
Control of lipid levels	C-LDL<100 mg/dL
	Triglycerides <150 mg/dL

TABLE 2. **Current indications of preventive pharmacological treatment in diabetic patients without cardiovascular disease**

	Situation	Indication	Drugs	Observations
Antihypertensive treatment	Blood pressure >135/85 mm Hg	Always	ACEI	If proteinuria +
			Low-dose diuretic	If proteinuria –
Hypolipemic treatment	C-LDL≥130 mg/dL	Always	Statin	
	C-LDL 100-129 mg/dL	If >1 CVRF	Statin	
	Triglycerides >400 mg/dL	Always	Statin	If C-LDL>100 mg/dL
			Fibrate	If normal cLDL
	Triglycerides 200-400 mg/dL	If >1 CVRF	Statin	If C-LDL>100 mg/dL
			Fibrate	If normal C-LDL
Antithrombotic treatment	Age >55 years	If >1 CVRF	Aspirin	
			75-150 mg/day	Class IIA indication

CVRF indicates cardiovascular risk factor.

values (C-HDL). LDL concentrations do not usually differ in diabetics and non-diabetics, but non-HDL cholesterol (VLDL+LDL) values are usually high in diabetics. Glycemic control improves lipid values in the diabetic patient, but it does not always adequately control the lipid profile. Since, optimal control of glycemia is achieved in a minority of patients and the risk of developing macrovascular disease is high, one should not wait long to initiate the pharmacological treatment of hypercholesterolemia. Most of the information that we have about pharmacological primary prevention in patients with DM comes from the analysis *post hoc* of small subgroups of diabetics, including some of the major studies of primary prevention. The AFCAPS/TexCAPS study included 394 diabetics (6%) and was designed to confirm if the administration of lovastatin for at least 5 years could reduce the incidence of a first major coronary episode (non-lethal AMI, unstable angina, or sudden death) in individuals without known cardiovascular disease, intermediate total and LDL cholesterol values, and low C-HDL. The reduction in the incidence of coronary episodes was greater in diabetics (43%) than in overall group (37%), although it did not reach statistical significance.[13] In the Helsinki Heart Study, gemfibrozil treatment also was associated with a non-significant reduction in the incidence of IHD in diabetics.[14]

The most important evidence regarding primary prevention with hypolipemic drugs in diabetics comes from a recently concluded study. The HPS study (Heart Protection Study), the results of which were presented at the 2001 Congress of the American Heart Association (AHA), randomly distributed 20 536 patients at high risk of coronary artery disease and no clear indication for cholesterol-lowering treatment to receive simvastatin 40 mg, a cocktail of antioxidant vitamins, or placebo. A significant reduction of 12% was found in overall mortality (12.9% versus 14.6%) and 17% in cardiovascular mortality (7.7% versus 9.2%), as well as a reduction of 24% (19.9% versus 25.4%) in the incidence of acute cardiovascular episodes (coronary, stroke, and coronary revascularization) in the group of patients assigned to simvastatin. This benefit was maximal in patients who had previous coronary artery disease. Among patients without previous coronary artery disease, diabetics obtained the greatest benefit. A relative reduction in the risk of cardiovascular episodes similar to that seen in patients with known coronary artery disease was observed (R. Collins, unpublished data).[15]

Although the evidence offered in publications is scant to date, the consensus among the official recommendations of the main scientific societies is important. The present recommendations for the treatment of hyperlipidemia of the American Diabetes Association, AHA and the third report of the National Cholesterol Education Program (NCEP III) establish the common therapeutic goal for all diabetics of reaching C-LDL<100 mg/dL, and instituting health and dietary measures like diet, physical exercise, and weight control in all overweight patients.[3-5] The undisputed threshold for beginning pharmacological treatment in diabetic patients without cardiovascular disease is established at C-LDL 130 mg/dL,[3,4] whereas it is considered optional between 100 and 129 mg/dL[3,5] (Table 2). The priorities in the treatment of dyslipidemias in diabetics must be: *a)* to reduce high LDL values; *b)* to raise HDL values, and *c)* to reduce triglyceride values.[4] Pharmacological treatment should begin with statins in moderate doses as the drug of first choice. Secondly, the use of fibrates or bile acid sequestering agents is recommended, and combined treatment when monotherapy fails to control dyslipidemia.[3-5]

The effect of treating hypertriglyceridemia is not well known, although pharmacological treatment of diabetics without cardiovascular disease is recom-

mended if they present severe hypertriglyceridemia (>400 mg/dL), in the absence of other associated risk factors, and if they present moderate hypertriglyceridemia (>200 mg/dL) with another risk factor. A statin is the drug of choice if high C-LDL values are associated, and a fibrate if only triglyceride values are raised (Table 2).[4]

Treatment of arterial hypertension

The pharmacological treatment of arterial hypertension (HT) prevents the appearance of cardiovascular disease in the general population. The decrease in blood pressure in hypertensive individuals is associated with a reduction in mortality and the incidence of cardiovascular episodes. Numerous studies have demonstrated that the benefit of treatment is superior in hypertensive diabetics than in non-diabetics, an observation that has been made with different regimens and therapeutic groups like diuretics, calcium antagonists, and angiotensin-converting enzyme inhibitors (ACEIs).[16-18] In the Systolic Hypertension in Europe (Syst-Eur) Trial, treatment with nitrendipine produced a reduction of 41% (95% CI, 9%-69%) in total mortality and of 70% (95% CI, 19%-89%) in cardiovascular mortality in 492 diabetics with systolic hypertension, whereas the reduction was 8% and 16%, respectively, in non-diabetics (*P*=ns).[17] The SHEP study (Systolic Hypertension in the Elderly Program), based on the treatment of systolic HT with chlorthalidone at low doses in 4736 patients over 60 years, showed a reduction of 34% at 5 years in the incidence of major cardiovascular episodes of similar magnitude in diabetics and non-diabetics, with no significant effect on total mortality. Nevertheless, a more marked reduction in coronary ischemic episodes (56%) and AMI (54%; *P*<.05 in both) was observed in 583 diabetic patients than in the non-diabetics (19% versus 23%; *P*=ns in both).[16]

Studies that have evaluated the importance of the intensity of antihypertensive treatment by comparing more or less aggressive therapeutic options for the control of blood pressure have demonstrated that strict control of blood pressure produces more benefits than less strict control.[17-19] The HOT study (Hypertension Optimal Treatment) randomly distributed 18 790 hypertensive patients to three progressively stricter strategies of control, based on diastolic blood pressure (≥90, ≥85 and ≥80 mm Hg, respectively). Among 1501 diabetic patients included, a progressive reduction in major cardiovascular episodes was observed with stricter control of diastolic blood pressure. In addition, diabetics assigned to the group of stricter control of blood pressure (diastolic ≥80 mm Hg) had a cardiovascular mortality three times lower than the other two groups.[18] The UKPDS, in HT control branch of the study, demonstrated a significant reduction in the combined endpoints of mortality and diabetes-related complications (24%), as well as diabetes-dependent mortality (32%), stroke (44%), heart failure (56%), and microvascular complications (37%), in the group of strict blood pressure control versus the group of less strict control. This benefit was obtained even in ranges of blood pressure considered normal.[20]

All these findings indicate that the reduction in blood pressure *per se* improves the cardiovascular prognosis of the diabetic patient and the benefit is greater with stricter control of blood pressure. For this reason, the threshold of blood pressure for initiating pharmacological treatment is lower in diabetics than in non-diabetics (Table 1). The present recommendations of the sixth report of Joint National Committee (JNC-VI) indicate that diabetics with blood pressure figures >130/85 should receive pharmacological treatment.[21] Nevertheless, it must be asked if the beneficial effect is the same with all antihypertensive drugs. In the ALLHAT study (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) the doxazosine treatment arm was discontinued because it was associated to a more than two-fold increment in the incidence of heart failure and a 24% increase in cardiovascular episodes in comparison with chlorthalidone-treated group in diabetic and non-diabetic patients.[22] In the ABCD study (Appropriate Blood Pressure Control in Diabetes), which randomly assigned 470 non-insulin-dependent diabetics with HT to nisoldipine or enalapril treatment, the nisoldipine arm was interrupted prematurely because of the higher incidence of lethal and non-lethal AMI in this group of patients (adjusted RR=4.2; 95% CI, 1.8%-10.1%).[23,24] A recent meta-analysis has confirmed these results and demonstrated that the use of calcium antagonists in diabetic patients, compared with other antihypertensives, is associated with a significant increment of 55% in the incidence of AMI and 44% in major cardiovascular episodes.[25] In the CAPPP study (Captopril Prevention Project), in which the treatment of HT with captopril was compared to conventional therapy in 10 985 patients, 572 of them diabetics, captopril produced no benefit in non-diabetic patients, but was associated with a reduction of 46% in total mortality (95% CI, 4%-54%) and 66% in the incidence of AMI (95% CI, 33%-83%) in diabetic patients.[26] In the LIFE study (Losartan Intervention For Endpoint reduction in hypertension), which specifically analyzed the evolution of 1195 hypertensive diabetic patients with electrocardiographic signs of left ventricular hypertrophy treated with losartan o atenolol during an average of 4.7 years, a 27% reduction (95% CI, 5%-43%) was found in the primary endpoint (cardiovascular death, AMI or stroke) in patients treated with losartan com-

pared with those who received atenolol, mainly due to a reduction of 38% (95% CI, 8%-59%) in cardiovascular mortality, together with a non-significant reduction in the incidence of stroke (22%) and AMI (19%), in addition to a significant reduction of 40% in total mortality and 43% in the incidence of heart failure.[27] Therefore, it seems that the use of ACEIs and, probably, angiotensin II receptor antagonists, is associated specifically in diabetics with more benefits than other antihypertensive agents. Nevertheless, it should be noted that in the studies cited a large proportion of the patients received concomitant treatment with diuretics, and that in clinical practice most hypertensive diabetics require two or more antihypertensives to control the condition.

In accordance with the JNC-VI, type 1 or 2 diabetics with BP>130/85 and proteinuria must receive pharmacological treatment with an ACEI, whereas the use of low-dose diuretics is recommended in type 2 diabetics without proteinuria (Table 2). The use of beta-blockers and high-dose diuretics must be avoided.[21] Nevertheless, studies published after 1997, when these recommendations were prepared, suggest that ACEIs also benefit patients without proteinuria. In the Micro-HOPE study,[28] a predefined substudy of the HOPE study (Heart Outcomes Prevention Evaluation Study Investigators), 3577 diabetic patients without clinical proteinuria, heart failure, or left ventricular systolic dysfunction were randomly distributed to receive placebo or ramipri l10 mg/day. The treated group had a significantly lower incidence of the combined endpoint (25% risk reduction) and each of its components, myocardial infarction (22%), stroke (33%), and cardiovascular death (37%). A significant reduction in total mortality (24%), heart failure of any degree (20%), and frank nephropathy (24%) was also observed. This beneficial effect was observed with a reduction at the end of the study of only 1.9 mm Hg in systolic pressure and 3.3 mm Hg in diastolic pressure. All the subgroups of diabetic patients showed some degree of reduction, although it was more marked in patients with dietary control of hyperglycemia and microalbuminuria present at the beginning of the study and in those that had previous cardiovascular disease (secondary prevention). The maximum benefit was observed in patients with type 1 diabetes, although the differences did not reach statistical significance because the group of patients was very small.[28] A recent meta-analysis confirmed that ACEI treatment of type 1 normotensive diabetics with microalbuminuria reduces the progression to macroalbuminuria and increases the probability of regression to normoalbuminuria independent of the control of blood pressure.[29] The IRMA II study (Irbesartan in Patients with type II Diabetes and Microalbuminuria Study) demonstrated in 590 hypertensive patients with type 2 diabetes and microalbuminuria that treatment with irbesartan 300 mg/day was capable of slowing the evolution of renal dysfunction in comparison with placebo or irbesartan at lower doses, although without affecting mortality or cardiovascular complications.[30] In diabetic patients with proteinuria, two recent studies – RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) made with losartan, and IDNT (Irbesartan Diabetic Nephropathy Trial) with irbesartan – have demonstrated that angiotensin receptor antagonists have a protective effect on the kidney, although, again, there was no evidence that they produced benefits in terms of mortality or cardiovascular complications.[31,32] These findings suggest that drugs that block the renin-angiotensin-aldosterone axis are superior to other antihypertensives in the prevention of renal dysfunction as well as cardiovascular morbidity and mortality in patients with DM. Therefore, it is very likely that the treatment of choice in diabetics with a blood pressure above the threshold value (130/85 mm Hg) should always include an ACEI, regardless of the presence of proteinuria. Nevertheless, in light of the results of the Micro-HOPE study, the indication for ACEIs must be extended to all diabetic patients with another risk factor, regardless of blood pressure values.

Antithrombotic treatment

In the Physicians´ Health Study, the use of 325 mg of aspirin on alternating days did not reduce mortality, but it did produce a more important reduction in the risk of AMI in diabetics (61%) than in non-diabetics (40%).[33] The HOT study randomly distributed the addition of low-dose aspirin in each one of three strata of blood pressure control. Aspirin treatment prevented the appearance of 2.5 AMI per 1000 patients/year (1.5 in the overall group) in diabetics.[18] The results of a recent meta-analysis confirm the beneficial effect of using of platelet antiaggregant drugs in diabetic patients, which produced an absolute reduction of 1% in the incidence of vascular episodes (RR=7±8%)[34] without increasing retinal or vitreous hemorrhage.[35] The authors conclude that «it may be appropriate to consider antiplatelet treatment in diabetic patients at high risk of suffering a first vascular episode (such as those with proteinuria).»[34] The recommendation for using aspirin in primary prevention in diabetics is type 2A in patients over 50 years without contraindications, according to the sixth ACCCP Consensus Conference on antithrombotic therapy,[36] whereas the American Diabetes Association recommends the use of low-dose aspirin in type 1 or 2 diabetics over the age of 30 years at high risk (with a family history of IHD, another risk factor, albuminuria, or obesity).[37]

SPECIFIC ASPECTS OF THE PHARMACOLOGICAL TREATMENT OF ACUTE CORONARY SYNDROMES IN DIABETICS

Non-ST-segment elevation acute coronary syndrome (NSTE-ACS)

There are no findings that suggest that antiaggregation with aspirin or heparin of patients with NSTE-ACS has a different effect on diabetic and non-diabetic patients. In the CURE study (Clopidogrel in Unstable angina to prevent Recurrent Events), which revealed an early benefit of the addition of clopidogrel to treatment with aspirin and heparin, a smaller relative benefit was observed in diabetics, but a greater absolute benefit compared to non-diabetics.[38] An analysis of the PRISM-PLUS study (Platelet Inhibition Receptor in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms) indicated that the addition of tirofiban to aspirin and heparin treatment reduced the incidence of death or AMI, particularly in diabetics,[39] a benefit that had been suggested previously for treatment with abciximab in diabetic patients treated with angioplasty with or without coronary stent.[40] A recent meta-analysis that evaluated the effect of treatment with glycoprotein IIb/IIIa inhibitors on NSTE-ACS found no benefit in the primary endpoint of these studies (non-fatal death and AMI at 30 days) in treated diabetics. However, a reduction in mortality was observed (4.6% versus 6.2%) at the expense of a lower number of deaths in the group that underwent percutaneous coronary intervention.[41] With respect to coronary revascularization strategy, the FRISC-2 study showed a similar relative reduction in the incidence of death or AMI in diabetic and non-diabetic patients (25% and 27%, respectively) who underwent invasive treatment, but a greater absolute reduction of episodes in diabetics than in non-diabetics (6.2% and 2.3%, respectively).[42] The TACTICS-TIMI study [18] demonstrated an absolute reduction of 7.6% in the primary endpoint (death, AMI, rehospitalization for ACS) in diabetics treated with an early invasive strategy preceded by the administration of tirofiban, whereas the reduction observed in non-diabetics (2.2%) was not statistically significant.[43] It is important to note that the results presented in all these studies are not adjusted for other risk factors, which are more frequent in diabetics and influence both the prognosis of patients with NSTE-ACS and the results of treatment with glycoprotein IIb/IIIa inhibitors and an invasive strategy, which is why it is not possible to establish definitive recommendations for all diabetics. However, patients with DM seemed to benefit more from these treatment options.

Acute coronary syndromes with ST-segment elevation (AMI)

Although diabetes is associated with a worse prognosis in patients who undergo fibrinolysis than in those who do not,[45] the FTT meta-analysis (Fibrinolysis Therapy Trialists) concluded that the benefit of fibrinolysis in absolute terms is much greater in diabetics than in non-diabetics. Whereas the administration of fibrinolytic treatment to 1000 diabetic patients with AMI can save 37 lives at 35 days of evolution, this figure decreases to 15 in non-diabetics.[46] In spite of these findings, diabetics systematically receive reperfusion treatment less frequently than non-diabetics.[47] This paradox is due in part to fear of inducing intraocular hemorrhage, particularly in patients with retinopathy. However, the analysis of more than 40 000 patients included in the GUSTO study revealed no case of ocular hemorrhage[48] in 5995 diabetics treated with thrombolysis, which is why the option of fibrinolytic treatment should not be refused to diabetic patients with AMI simply because they are diabetic. Unless a diabetic has some of the contraindications for fibrinolysis commonly accepted for patients without diabetes, he or she should always receive reperfusion treatment. Primary angioplasty has not been shown to be superior to fibrinolysis in patients with DM, but it is equally safe and effective.[49] Consequently, it is an alternative therapy to fibrinolysis that can be considered when an experienced team is quickly available.

With respect to the coadjuvant treatment of reperfusion therapy, diabetics seem to benefit at least as much from aspirin treatment as non-diabetics.[50] Nonetheless, the early administration of beta-blockers and ACEIs has been shown to be much more beneficial in patients with DM than in non-diabetics. The use of intravenous atenolol in the first ISIS study (International Study of Infarct Survival) was associated with a greater reduction in mortality at 14 days in diabetic than in non-diabetic patients in relative (20% versus 14%) and absolute terms (1.6% versus 0.6%).[51] In the MIAMI study (Metoprolol In Acute Myocardial Infarction), the reduction in mortality with metoprolol at 15 days was 4 times greater in diabetics than in non-diabetics.[52] In the Norwegian study of timolol, while the mortality of diabetics with placebo was twice that of non-diabetics with placebo, the mortality of diabetics and non-diabetics treated with beta-blockers was similar.[53] In the third GISSI study (Italian Gruppo per lo Studio della Sopravivenza nell´Infarto Miocardico), a reduction in mortality was observed at 40 days of evolution with lisinopril administered

from the first day of AMI. This survival benefit in the overall group was due to a reduction in mortality in diabetic patients[54] (Table 3).

PHARMACOLOGICAL TREATMENT OF DIABETICS WITH CORONARY ARTERY DISEASE (SECONDARY PREVENTION)

Diabetics who survive an AMI present an incidence of complications and long-term mortality that is much higher than in non-diabetics,[55] which explains the special attention that secondary prevention deserves in these patients.

Antithrombotic therapy

Diabetics treated with aspirin seem to benefit as much as non-diabetics,[51] but they seem to benefit more from more potent platelet antiaggregation treatment. Thus, in the CAPRIE study (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events), treatment with clopidogrel produced a reduction of 9 ischemic episodes per 1000 non-diabetic patients with respect to aspirin therapy. In treated diabetics, 21 episodes were prevented per 1000 diabetics treated with oral antidiabetics and 37 episodes in diabetics treated with insulin.[56] In patients with NSTE-ACS, the CURE study demonstrated that the addition of clopidogrel to treatment with aspirin and heparin produced an absolute reduction of 25 episodes (death, AMI, and stroke) in 9 months of treatment per 1000 diabetic patients treated (incidence with and without clopidogrel of 14.2% versus 16.7%) and 20 episodes in non-diabetics (7.9% versus 9.9%, respectively).[38]

Beta-blocker therapy

Among patients who have suffered AMI, there is not much information from randomized studies on differences in the utility of long-term beta-blocker treatment between diabetic and non-diabetic patients, aside from the benefit observed with early oral beta-blocker treatment.[50,52,53] However, several observational studies suggest a much greater benefit in patients with DM,[57,58] particularly in older patients.[59] In spite of the beneficial effect of beta-blockers in diabetic patients with IHD, they are used much less often than recommended,[60] due in part to fear of producing or obscuring serious hypoglycemias. Nevertheless, it is currently known that the use of beta-blockers does not increase the incidence of serious hypoglycemia associated with insulin or sulfonylureas.[61,62]

Hypolipemic therapy

Solid evidence exists about the effectiveness of interventions to reduce lipid concentrations in secondary prevention in diabetics with known cardiovascular disease. In the LIPID study (Long-Term Intervention with Pravastatin in Ischaemic Disease), pravastatin treatment had a favorable effect on the incidence of death due to coronary artery disease and non-lethal AMI in both diabetic patients with IHD and cholesterol concentrations of 155 to 271 mg/dL and in non-diabetics.[63] In contrast, in the 4S (Scandinavian Simvastatin Survival Study), in which only 202 of 4444 patients were diabetics (4.5%), the reduction in the 5-year mortality was much greater in absolute terms (10.4%) in diabetics than in non-diabetics (3%). The reduction of both non-lethal coronary episodes and other cardiovascular episodes showed a pattern parallel to that of mortality, with the exception of stroke, the only event not reduced in a statistically significant way in diabetics.[64] It is important to note that the divergence between the mortality and survival curves in diabetics began between the fourth and fifth year of treatment. The CARE study (Cholesterol and Recurrent Events Trial), which examined the use of pravastatin in 4159 patients <76 years with previous myocardial infarction, total cholesterol <240 mg/dL, and C-LDL<175 mg/dL, included a larger proportion of diabetics (14%). The relative reduction in the incidence of accumulated coronary episodes (death due to coronary artery disease, non-lethal AMI, coronary revascularization surgery, and PTCA) was similar in diabetics (25%) and non-diabetics (23%). Nevertheless, since the number of episodes was approximately two times greater in diabetics, the benefit was also much greater in absolute terms. In this study it was also observed that the curves began to diverge in the fourth year of treatment in patients with DM.[65] A recent analysis of the Pravastatin Pooling Project, which centered on the 20% of patients with C-LDL values <125 mg/dL included in the CARE and LIPID studies, has shown that treatment with pravastatin for 5.5 years did not produce any beneficial effect in patients without DM. An incidence of coronary episodes of less than 44% (95% CI, 17%-63%) was observed in diabetics treated with pravastatin (22%) compared with placebo (34%).[66] However, a reduction in the incidence of adverse episodes in patients with DM has been demonstrated not only with statins. The VA-HIT study (Veteran Affairs High-Density Lipoprotein Cholesterol Intervention Trial), made in patients with known coronary disease, intermediate LDL concentrations (<140 mg/dL), and low C-HDL concentrations (<40 mg/dL), treatment with gemfibrozil 1200 mg/day caused a relative reduction of 24% in the primary endpoint (death due to coronary artery disease or non-lethal AMI or confirmed stroke) in both groups, but the absolute reduction

TABLE 3. **Effectiveness of ACEIs in secondary prevention in diabetic and non-diabetic patients**

Study drug	Group	Follow-up	Placebo Mortality	ACEI mortality	Absolute reduction	Relative reduction	95% CI
PGISSI-3		6 weeks					
Lisinopril	DM		12.4	8.7	3.7	32	14-47
	Non-DM		5.9	5.6	0.3	5	–9-17
TRACE		26 months					
Trandolapril	DM		61	45	16	36	9-55
	Non-DM		39	33	6 1	8	3-31
SMILE*		6 weeks					
Zofenopril	DM		16.5	7.2	9.3	61	16-82
	Non-DM		9.0	7.1	.9	23	–17-0
HOPE		5 years					
Ramipril	DM		14.0	10.8	3.2	24	8-37
	Total		12.2	10.4	1.8	16	5-25

*Death+severe IHD.

in episodes was greater in diabetics (8%) than in non-diabetics (5%).[67]

The present recommendations indicate that in diabetics with macrovascular disease (IHD, cerebrovascular or peripheral), pharmacological treatment should begin with statins in moderate doses[5] when C-LDL values reach >100 mg/dL.[4] The effect of treating hypertriglyceridemia is not well known, although pharmacological treatment is recommended with values above 400 mg/dL if there is no cardiovascular disease or other risk factors, above 200 mg/dL when other risk factors coexist, and 150 mg/dL in patients with known cardiovascular disease (Table 2). In principle, a statin is recommended, particularly when cholesterol values are high. When more medication is required, a fibrate should be added, although attention should be given to side effects like hepatic rhabdomyolysis and toxicity.

ACEI therapy

One of the beneficial effects of secondary prevention most consistently documented is the reduction of mortality with ACEIs in diabetic patients with previous myocardial infarction.[8,54,68-70] All the randomized, placebo-controlled studies that have analyzed the influence of diabetes on the effectiveness of ACEIs in this context have shown similar results, a significant reduction of mortality in the overall group, mainly at the expense of a reduction in the mortality of diabetics (Table 3). In addition, decreases in the incidence of heart failure[28,54,68] and AMI[28] have been observed.

PHARMACOLOGICAL CARDIOVASCULAR PREVENTION AND NEW DIAGNOSES OF DIABETES

An interesting aspect of the relation between cardiovascular prevention and diabetes is the finding that several preventive pharmacological interventions applied to the non-diabetic population cam reduce the incidence of type 2 DM of new appearance.

The study of ARIC cohorts (Atherosclerosis Risk In Communities) carried out on 12 550 individuals without diabetes evaluated the relation between antihypertensive treatment and risk of developing DM in a 6-year follow-up. In this study it was observed that the beta-blockers were only the antihypertensives associated with a greater risk of presenting diabetes but, regardless of treatment, the presence of HT was the main determinant of the risk of developing diabetes.[70] In the LIFE study (Losartan Intervention For Endpoint reduction in hypertension) newly diagnosed DM was observed in less than 25% of patients treated with losartan than in those treated with atenolol, although both groups showed a similar reduction in blood pressure.[71] In the CAPPP study, among hypertensive patients who received antihypertensive treatment with captopril an incidence of less than 14% (95% CI, 1%-26%) of newly diagnosed DM was observed among patients that received conventional therapy.[26] In the HOPE study (Heart Outcomes Prevention Evaluation Study Investigators) the incidence of DM development (diagnosed after the study began) was lower than 30% in patients treated with ramipril than in those that took placebo.[72] These studies suggest that there is a pathophysiological and etiological relation between HT and type 2 DM and that the pharmacological treatment of HT can modify its incidence, in such a way that the drugs that block the renin-angiotensin-aldosterone axis seem to prevent or

delay the development of type 2 DM and beta-blockers favor it. The mechanism involved in the protective effect of ACEIs and angiotensin II receptor antagonists is their capacity to improve insulin resistance in many hypertensive patients, whereas the opposite effect is associated with the use of beta-blockers.[73]

Nevertheless, not only antihypertensive drugs but also statins have been observed to prevent the appearance of type 2 DM. Thus, in the WOSCOPS study (West Of Scotland Coronary Prevention Study) it was observed that the incidence of DM development diagnosed after beginning the study was lower than 32% in patients treated with pravastatin than in those that took placebo.[74] The mechanism of this protective effect is not known, but it has been attributed to the anti-inflammatory effect of the statins.[75] Insulin resistance has been related to the concentrations of reactive protein C,[76] a mediator of inflammation. The mechanism by which the statins can reduce reactive protein C values[77,78] could be the same by which they can reduce insulin resistance, although other mechanisms have been proposed, like the improved capacity for physical activity of patients treated with statins[79] due to the reduction in the incidence of angina associated with their use.[80]

These findings not only open new paths for investigation of the pathophysiological etiology and relation between cardiovascular risk factors, their prevention and treatment, but also reinforce the evidence supporting aggressive treatment with these drugs in diabetic patients, whether or not they have cardiovascular disease.

CONCLUSIONS

The diabetic is a high-risk patient for the development of cardiovascular disease, particularly coronary artery disease, which is not reduced by health and dietary measures designed to control glycemia. For this reason, in addition to non-pharmacological prevention measures and control of glycemia, the strict application of effective pharmacological measures of primary prevention is particularly important. At present, there is enough evidence to recommend treatment with statins and ACEIs in all diabetic patients, regardless of their lipid profile and blood pressure levels. Hypertensive diabetics should have strict blood pressure control with a treatment that always includes an ACEI (or an angiotensin II receptor antagonist if they have proteinuria). In diabetics with other risk factors or a high probability of developing cardiovascular disease, the association of low-dose aspirin to preventive treatment should also be weighed (Table 4).

Diabetic patients with acute coronary syndromes benefit more than non-diabetics from intensive antithrombotic treatment with clopidogrel or glycoprotein IIb/IIIa inhibitors added to aspirin and heparin treatment in episodes without ST-segment elevation, and fibrinolytic treatment in cases of ST-segment elevation or left bundle-branch block.

TABLE 4. **Future of preventive pharmacological treatment in patients with type 2 diabetes (view of author)**

Primary prevention	
Statin	Always*,[a]
ACEI	Always*,[b]
Aspirin	Patients with other risk factors and low risk of bleeding
Secondary prevention (coronary artery disease)	
Aspirin and/or clopidogrel	Always*
Beta-blocker	Always*,[b]
ACEI	Always*,[b]
Statin	Always*,[a]

*Except for contraindications.
[a]Regardless of total cholesterol or LDL concentration.
[b]Regardless of the presence of left ventricular systolic dysfunction or heart failure.

Diabetics with coronary artery disease have a very high risk of presenting serious new cardiovascular episodes in the future, but they also benefit more than the general population from all secondary prevention interventions, regardless of their clinical characteristics (lipid profile, left ventricular systolic function, etc). For this reason, all diabetics with known coronary artery disease, and probably carotid artery disease or peripheral arteriopathy, must be treated with aspirin (75-150 mg/day), beta-blockers, an ACEI and a statin whenever there are no contraindications (Table 4).

In spite of the magnitude of the benefits achieved in diabetic patients with primary and secondary prevention measures, they are unfortunately underused at present. This unfavorable reality must be viewed as an opportunity for improvement. It is essential to develop information and awareness-raising programs about the importance of cardiovascular prevention in diabetics that target not only cardiologists, but all physicians who care for diabetic patients before and after presenting cardiovascular complications, such as endocrinologists, diabetologists, primary care physicians, internists, and geriatricians.

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