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Approaches to Prevention of Cardiovascular Complications and Events in Diabetes Mellitus

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Contents

Abstract

Diabetes mellitus affects about 8% of the adult population. The estimated number of patients with diabetes, presently about 170 million people, is expected to increase by 50–70% within the next 25 years.

Diabetes is an important component of the complex of 'common' cardiovascular risk factors, and is responsible for acceleration and worsening of atherothrombosis. Major cardiovascular events cause about 80% of the total mortality in diabetic patients. Diabetes also induces peculiar microangiopathic changes leading to diabetic nephropathy conducive to end-stage renal failure, and to diabetic retinopathy that may progress to vision loss and blindness.

In terms of major cardiovascular events, coronary heart disease and ischaemic stroke are the main causes of morbidity and mortality in diabetic patients. Peripheral arterial disease frequently occurs, and is more likely to be conducive to critical limb ischaemia and amputation than in the absence of diabetes.

Although there are a number of differences in the pathogenesis and clinical features of diabetic macroangiopathy and microangiopathy, these two entities often coexist and induce mutually worsening effects. Endothelial injury, dysfunction and damage are common starting points for both conditions. Causes of endothelial injury can be distinguished into those 'common' to nondiabetic atherothrombosis, such as hypertension, dyslipidaemia, smoking, hypercoagulability and platelet activation; and those more specific and in some cases 'unique' to diabetes and directly related to the metabolic derangement of the disease, such as (i) desulfation of glycosaminoglycans (GAGs) of the vascular matrix; (ii) formation of advanced glycation end-products (AGE) and their endothelial receptors (RAGE); (iii) oxidative and reductive stress; (iv) decline in nitric oxide production; (v) activation of the renin-angiotensin aldosterone system (RAAS); and (vi) endothelial inflammation caused by glucose, insulin, insulin precursors and AGE/RAGE.

Prevention of major cardiovascular events with the antithrombotic agent aspirin (acetylsalicylic acid) is widely recommended, but reportedly underutilised in patients with diabetes. However, some data suggest that aspirin may be less effective than expected in preventing cardiovascular events and especially mortality in patients with diabetes, as well as in slowing progression of retinopathy.

In contrast, a recent study found picotamide, a direct thromboxane inhibitor, to be superior to aspirin in diabetic patients. Clopidogrel was either equivalent or less active in diabetic versus nondiabetic patients, depending upon different clinical settings.

Recent studies have shown that some GAG compounds are able to reduce micro- and macroalbuminuria in diabetic nephropathy, and hard exudates in

diabetic retinopathy, but it is as yet unknown whether these agents also influence the natural history of microvascular complications of diabetes. Lifestyle changes and physical exercise are also essential in preventing cardiovascular events in diabetic patients.

Available data on the control of the metabolic state and the main risk factors show that careful adjustment of blood sugar and glycated haemoglobin is more effective in counteracting microvascular damage than in preventing major cardiovascular events. The latter objective requires a more comprehensive approach to the whole constellation of risk factors both specific for diabetes and common to atherothrombosis. This approach includes lifestyle modifications, such as dietary changes and smoking cessation and the use of HMG-CoA reductase inhibitors (statins), which are able to correct the lipid status and to prevent major cardiovascular events independently of the baseline lipidaemic or cardiovascular status.

Tight control of hypertension is essential to reduce not only major cardiovascular events but also microvascular complications. Among antihypertensive measures, blockade of the RAAS by means of ACE inhibitors or angiotensin II receptor antagonists recently emerged as a potentially polyvalent approach, not only for treating hypertension and reducing cardiovascular events, but also to prevent or reduce albuminuria, counteract diabetic nephropathy and lower the occurrence of new type 2 diabetes in individuals at risk.

1. Introduction

Diabetes mellitus is a ubiquitous disease that affects about 8% of the adult population worldwide.[1] It has been calculated that in the year 2000, there were about 170 million individuals with diabetes all over the world.[2] This figure is bound to increase very rapidly as a result of the augmentation in real prevalence of type 2 diabetes in affluent societies, and increase in diagnosis both of type 1 and 2 diabetes in the developing world. It has been surmised that the number of diabetic individuals may increase up to about 300 million people in the next 30 years.[2]

The considerable life-threatening potential of diabetes is due to several factors.

- Diabetes is an important and independent risk factor[3] for the development of atherothrombosis and the related occurrence of major cardiovascular events.
- Diabetes must be seen within the context of 'common' risk factors for atherothrombosis along with hyperdyslipidaemia and hypertension, and potentiates their detrimental effects. Additionally, diabetes also confers more specific risk factors specifically relating to the metabolic derangement.
- The presence of diabetes within the constellation of atherogenic factors leads to accelerated and multifocal atherothrombosis processes, with an increased tendency to instability and vulnerability of plaques and hence to superimposed arterial thrombosis.
- Diabetes is characterised by specific changes in microvessels, thus causing diabetic microangiopathy, namely nephropathy, retinopathy, myopathy (including myocardiopathy) and neuropathy. Microangiopathic changes combine with macroangiopathy in worsening tissue response to ischaemia.

For example, the appearance of multiple silent ischaemic lesions in heart and brain during the course of diabetes suggests concomitant macro- and microvascular changes and the likelihood of a 'common ground' for diabetic macro- and microangiopathy, probably as a result of endothelial injury.

Thus, diabetes, as 'our mortal enemy',[4] deserves maximum recognition and dedication from clini-

cians, and is also of special interest for vascular medicine experts.

The aim of this article is to recall some of the complex pathogenic mechanisms and, in particular, to discuss the main approaches aimed at prevention of vascular complications of diabetes, with special regard to major cardiovascular events but not neglecting the main aspects of the microvascular conditions.

2. Diabetes Mellitus and Cardiovascular Disease: Size of the Problem

An interesting 'in the field' experience of the incidence of cardiovascular (both micro- and macrovascular) events and complications in type 2 and type 1 diabetes has been reported in a Scottish community.[5]

Type 1 diabetes was present in 88.4% of patients and type 2 in 11.6%. The figure for the cumulative rate of major cardiovascular events (acute myocardial infarction [MI], angina pectoris, stroke or transient ischaemic attack [TIA]) was 74.5 per 1000 patients per year in type 2 versus 18.5 patients per year in type 1 diabetes. For peripheral arterial disease (PAD), the corresponding rates were 13.6 for type 2 versus 5.5 for type 1 diabetes, but limb amputation rates were equivalent (3.1 vs 3.2). Severe outcomes related to microvascular complications, as for blindness (1.6 vs 1.1), and those for renal failure (5 vs 6.4), were approximately equivalent for type 2 and type 1 diabetes.

The prevalence of the main complications according to duration of type 2 diabetes[6] is represented in table I, showing that all complications clearly increase with time from diagnosis.

Table I. Prevalence of the main complications of type 2 diabetes mellitus in relation to time from diagnosis (reproduced from Guja and Ionescu-Tirgoviste,[6] with permission)

Complication	Time from diagnosis (%)			
	<5y	5–9y	10–19y	>20y
Cardiovascular disease	26	41	56	71
Retinopathy				
background	18	35	49	52
proliferative	4	6	8	10
blindness	1.5	2.5	5.5	8.5
Nephropathy	7	14	22	25
Neuropathy	15	25	48	65

2.1 Macrovascular Disease

2.1.1 Diabetes and Coronary Heart Disease

About 80% of all diabetic patients die from cardiovascular events. Seventy-five percent of such deaths are due to coronary heart disease (CHD), and the remaining 25% to cerebrovascular, peripheral or other macrovascular disease.[7] Age is a major adjunctive factor for cardiovascular risk,[8] and other main risk factors for cardiovascular morbidity and mortality are high total and low-density lipoprotein (LDL)-cholesterol and triglyceride levels, low high-density lipoprotein (HDL)-cholesterol,[9] in addition to fasting plasma glucose, proteinuria and the presence of nephropathy and/or retinopathy.[10]

The risk of developing an acute MI, as well as other acute coronary syndromes is increased 2- to 4-fold,[3] and in the Euro Heart Survey,[11] which involved 5000 coronary patients, 30% had confirmed diabetes. Many patients with acute MI or acute coronary syndromes may present without chest pain,[12] and silent myocardial ischaemia is found in as many as 33% of diabetic patients.[13] Early (in-hospital) mortality for coronary causes appears only moderately increased,[14] while 1-year mortality rates are elevated[15] because of the frequent occurrence of cardiogenic shock or heart failure. In the OASIS (see table II for list of acronym definitions) register,[16] diabetes increased the death rate of patients with unstable angina pectoris by 75%, and it is also noteworthy that coronary syndromes and acute MI are more frequent in diabetic women than men, and that the relative risk of fatal disease is much higher in women.[17,18]

Recently, previously unrecognised poor glucose tolerance emerged as a risk factor for severe outcome or death in patients with coronary syndromes.[19,20] In the GAMI study,[21] 67% of all acute MI patients considered had an altered glucose tolerance during and/or after the acute episode.

A large Finland-based population study on long-term cardiovascular mortality in diabetic or non-

Table II. List of study/trial acronyms and definitions

Study/trial acronym	Study name
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ASPEN	Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus
BENEDICT	BErgamo NEphrologic DIabetes Complications Trial
CAPP	Captopril Prevention Project
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CARDS	Collaborative Atorvastatin Diabetes Study
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management, and Avoidance
DAIS	Diabetes Atherosclerosis Intervention Study
DAMAD	Dipyridamole, Aspirin, Microangiopathy of Diabetes
DAVID	Drug evaluation in Atherosclerotic Vascular disease In Diabetics
DIAD	Detection of Ischemia in Asymptomatic Diabetics
DiNAS	Diabetic Nephropathy and Albuminuria Sulodexide
DREAM	Diabetes REduction Assessment with ramipril and rosiglitazone Medication
ETDRS	Early Treatment Diabetic Retinopathy Study
EUROPA	European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease
FACET	Fosinopril versus Amlodipine Cardiovascular Events randomized Trial
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
GAMI	Glucose Abnormalities in Patients with Myocardial Infarction
HOPE	Heart Outcomes and Prevention Evaluation study
IDNT	Irbesartan type 2 Diabetic Nephropathy Trial
IRAS	Insulin Resistance Atherosclerosis Study
IRMA	Irbesartan Microalbuminuria trial
LIFE	Losartan Intervention For Endpoint reduction in hypertension study
MATCH	Management of Atherothrombosis with Clopidogrel in High-risk patients
MICRO-HOPE	MIcrovascular, Cardiovascular and Renal Outcomes in the HOPE study
OASIS	Organization to Assess Strategies for Ischemic Syndromes
PROactive	PROspective pioglitAzone Clinical Trial In macroVascular Events study
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan
TIMAD	Ticlopidine Microangiopathy of Diabetes
TNT	Treating to New Targets
UKPDS	UK Prospective Diabetes Study
VA-HIT	Veterans Affairs High-Density Lipoprotein Cholesterol Intervention TriaL
VYTAL	Vytorin vs Atorvastatin in Patients With Type 2 Diabetes Mellitus and Hypercholesterolemia
WESDR	Wisconsin Epidemiological Study of Diabetic Retinopathy

NIDDM = non-insulin dependent diabetes mellitus (type 2 diabetes).

diabetic patients with or without a previous acute MI[22] suggested that having diabetes could be considered an equivalent of a previous acute MI in a nondiabetic individual,[23] but this concept has recently been questioned.[23,24] Quite recently, even a higher than optimum fasting plasma glucose concentration without overt diabetes was found to be a leading factor for cardiovascular mortality.[25]

2.1.2 Diabetes and Cerebrovascular Disease

Diabetes greatly increases, by 1- to 4-fold, the risk for stroke and stroke-related disability and mortality that already exists in the adult or presenile age.[26,27]

In a large population database of unselected patients with type 2 diabetes from general practice in the UK, the absolute proportion of stroke was 11.9 per 1000 person-years versus 5.5 in age- and sex-

matched non-diabetic individuals, with a general hazard ratio (HR) of 2.19 (2.32 in females), declining with advancing age.[28] In patients with ischaemic stroke, diabetes has a prevalence of at least 15%[29] or even higher, and concomitant hypertension greatly enhances the related stroke risk.[30] Type 2 diabetes is also an important and independent predictor of stroke recurrences[31] and of long-term survival after carotid endoarterectomy.[32]

Atherothrombotic stroke due to plaques in the internal carotid and only occasionally in the intracranial arteries, also occurs more often in patients with diabetes, as instability and vulnerability of plaques in diabetes greatly favour detachment of arterial microemboli. Similar lesions can be found in the thoracic aorta (complicated aortic plaques) of diabetic individuals and are often undiagnosed or underestimated.[33]

The risk of cerebral cardioembolism is also greatly enhanced as diabetes is a strong, independent risk factor for the occurrence of atrial fibrillation[34] and is an adjunctive risk factor for stroke in this condition.[35] Other causes of cardioembolic stroke often found in diabetic individuals are heart failure and diabetic cardiomyopathy.[36]

Lacunar syndrome is a typical feature of silent cerebral ischaemia, which is common in diabetes and favoured by concomitant hypertension.[37] Lacunar syndromes are probably related both to diabetic macroangiopathy through arterial microembolism and to diabetic microangiopathy of cerebral small vessels.

Similarly to acute MI, hyperglycaemia after acute ischaemic stroke without known pre-existing diabetes has recently been recognised as an important factor in brain damage through inflammatory and oxidative mechanisms,[38] and insulin infusion has been advocated to counteract these detrimental effects. However, it should be noted that the effects of insulin on the atherothrombotic mechanisms can be beneficial or detrimental depending on different experimental and clinical conditions (see sections 2.7 and 2.11).

2.1.3 Diabetes and Peripheral Arterial Disease

Diabetes is one of the main risk factors for PAD: the attributable risk increases by 2- to 4-fold.[39] Major associated risk factors for the development of PAD during diabetes are smoking, hypertension and dyslipidaemia.[40] In the UKPDS 59,[41] a low HDL-cholesterol was the main lipidic risk factor involved.

Patients with PAD and diabetes carry a particularly high burden of polyfocal atherothrombosis[42] and are at a 4- to 6-fold increased risk of cardiovascular morbidity and mortality.[42] Infrapopliteal and, especially, tibial artery stenosis or obstruction are common in diabetes-associated PAD; asymptomatic forms with no claudication occur in about one-half of patients, some of whom will refer to their physicians with already severe ischaemic manifestations (ulcers, rest pain[39]). A typical feature is the 'diabetic foot' that may be frankly ischaemic (macro- and/or microvascular) or more frequently neuroischaemic or 'mixed'.[43]

Diabetic PAD is associated with accelerated deterioration of claudication: worsening of the limb condition is much faster and critical limb ischaemia occurs more often.[44] Among risk factors for progression of disease, diabetes appears most correlated with deterioration of small vessels.[45] In the large WESDR study, initiated in 1980–2 and primarily focused on diabetic retinopathy, the cumulative 14-year incidences of lower extremity amputations were 7.2% in younger-onset diabetes (onset age <30 years) and 9.9% in the older-onset (>30 years) group.[46] In the latter, the main risk factors for lower extremity amputations were high glycosylated haemoglobin (HbA_{1C}), high systolic and pulse pressure, and severe retinopathy, while smoking, high diastolic blood pressure and, again, high HbA_{1C} were the main risk factors for younger-onset patients, especially if receiving insulin treatment. Medial artery calcification in femoral arteries of diabetic patients with PAD was found to be a strong predictor of cardiovascular morbidity and mortality.[47] Mortality after amputation seems no different in diabetic and nondiabetic patients.[48]

2.1.4 Diabetes and Venous Thromboembolism

Investigations into the risk of venous thromboembolism in diabetes are surprisingly rare. In an early epidemiological study, the presence of diabetes did not seem to add further risk of deep vein thrombosis (DVT) to patients with predisposing conditions, such as acute MI, stroke or heart failure.[49] In another study during the 1980s, DVT risk was suggested to be higher in those with juvenile type 1 diabetes.[50] More recently, in a retrospective study,[51] a 2-fold elevation of the thromboembolic risk was attributed to diabetes; however, this study cannot be considered conclusive and needs confirmation from prospective trials.

It has to be noted that, in the large epidemiological studies on DVT or pulmonary embolism, diabetes is not identified and not even quoted as a risk factor either for a first venous thromboembolism episode or for recurrences.[52] However, obesity is a possible link between diabetes and DVT. In fact, a body mass index (BMI) >25 kg/m^2 seems to be an additional risk factor for DVT after hip arthroplasty[53] and is a worsening factor for the post-thrombotic syndrome.[54]

In summary, despite the existence of a prothrombotic state (see section 2.10), evidence for an increased risk of venous thromboembolism in diabetes is not yet conclusive.

2.2 Microvascular Disease

2.2.1 Diabetic Nephropathy

Diabetic nephropathy is a frequent complication of type 1 and type 2 diabetes and involves about 30% of all diabetic patients. The severity of renal damage is a strong predictor of end-stage renal failure[55] and is the second major cause of death during diabetes.[56]

Without specific intervention, 20–40% of diabetic patients with microalbuminuria will progress to overt nephropathy and, within 20 years, 20% of these will develop end-stage renal failure.[57] Albuminuria (microscopic and macroscopic) correlates not only with risk of renal failure, but unexpectedly also with cardiovascular events and mortality.[58,59] Diabetic patients with renal failure often require haemodialysis or transplant.[60] Apolipoprotein A, fibrinogen, age and history of stroke have been identified as important predictors of death during haemodialysis.[61]

Recently, new links have emerged connecting hypertension, diabetes and diabetic nephropathy, based on better knowledge of the mechanism of action of the renin-angiotensin-aldosterone system (RAAS). An increase in and activation of angiotensin II in diabetes causes vasoconstriction and vascular damage responsible both for hypertension and for glomerular damage inducing albuminuria and nephropathy.[62] In addition, the increase and activation of angiotensin may contribute to insulin resistance by hampering peripheral flow-mediated interactions between insulin and glucose; or by direct interference with insulin signalling mechanisms; or, again, through the damaging effect of a pancreatic RAAS system on β-cell structure and function; and finally by inhibiting recruitment and differentiation of adipocytes.[63]

These mechanisms, in part still speculative,[64] could offer a common platform to aspects such as the frequent association of diabetes and hypertension, the role of hypertension in diabetic nephropathy, and the onset of new cases of diabetes in certain high-risk conditions such as severe hypertension, cardiovascular disease and heart failure.[64]

2.2.2 Diabetic Retinopathy

Diabetic retinopathy is one of the main causes of progressive loss of vision and blindness in many geographic areas. In the large Wisconsin epidemiological study, WESDR,[65] the more advanced form of retinopathy, namely the proliferative type, was present at baseline or after a 4-year follow-up in 23% of younger-onset (aged <30 years) diabetic individuals, and in 10% of older patients receiving insulin and in 3% of those not taking insulin. However, type 2 diabetes finally accounts for the higher absolute number of cases of proliferative retinopathy.[65]

The main risk factors for developing proliferative retinopathy reported in WESDR were longer duration of diabetes, high blood glucose and, in the younger-onset group, higher blood pressure at base-

line.[65] A role for certain types of dyslipoproteinaemia in the pathogenesis of retinal capillary injury was suggested by advanced lipoprotein analysis by means of nuclear magnetic resonance.[66] Namely, a positive correlation with small and medium LDL and related particles, a negative correlation with LDL size, and a possible but controversial role of oxidised LDL, were observed in type 1 diabetic patients with retinopathy.[66] The 10-year incidence of blindness was 1.8% in younger-onset and 4–4.8% in older-onset patients, respectively, receiving or not receiving insulin.[67] Smoking and systolic blood pressure were important adjunctive risk factors for blindness.[67] Macular oedema, a severe ophthalmic complication, heavily contributes to blindness, as its incidence over a 10-year period was 20–25% and was especially frequent in patients receiving insulin.[68,69] In a large observational 18-year cohort study in Finland, proliferative retinopathy was an independent predictor of total and cardiovascular mortality in both sexes.[69]

2.2.3 Diabetic Neuropathy

The mechanism of diabetic neuropathy is unclear; however, long-term hyperglycaemia and tissue ischaemia are considered the main pathogenic factors. Diabetic neuropathy of different degrees is thought to be present in as many as 60% of patients with diabetes and can be classified into prevalently motor, sensory or autonomic forms.[44]

Motor neuropathy mainly induces limb muscle atrophy and structural alterations in the feet. Sensory neuropathy alters the tactile, thermal and pain-related functions. Autonomic neuropathy mainly affects the microcirculation and the heart.[44]

Sensory neuropathy plays a crucial role in the pathogenesis of diabetic foot: 60% of cases are in fact due to neuropathy and other cases to coexisting neuropathy and macro- and/or microangiopathy.[44]

Among the autonomic forms, cardiac autonomic neuropathy is an often neglected entity[70] the features of which are (i) resting tachycardia, a recognised risk factor for cardiovascular events; (ii) loss of heart rate variability; postural hypotension and related heart rate changes; (iii) low tolerance to exercise; and (iv) silent myocardial ischaemia and hence propensity to sudden and unexpected death. The relationship between cardiac autonomic neuropathy and silent myocardial ischaemia has been extensively studied and confirmed in the DIAD study,[71] and patients with overt type 1 diabetes and symptomatic autonomic neuropathy show increased mortality rates.[72]

3. Diabetes and Vascular Damage: an Insight into the Mechanisms

3.1 Generalities

Vascular alterations are specific complications of diabetes, affecting patients with type 1 and type 2 diabetes. Usually, macrovascular involvement is considered separately from diabetic microangiopathy, because of differences in terms of natural history, pathogenesis and clinical aspects. A distinction between macro- and microangiopathy remains meaningful; however, the two forms have some common pathogenic mechanisms, often coexist and concurrently influence the clinical course of the patient.[73] Basically, endothelial dysfunction is the common starting point both for macro- and microangiopathy.[73] The main mechanisms responsible for endothelial damage and vascular complications in diabetes are represented in figure 1.

3.2 Endothelial Dysfunction

Injuring factors responsible for endothelial dysfunction and subsequent damage in diabetes can be either common to nondiabetic atherogenesis, or rather specifically related to the underlying metabolic derangement of diabetes. Injuring factors common to atherothrombosis (e.g. high total and LDL-cholesterol, hypertension, inflammatory reactants as fibrinogen and C-reactive protein [CRP] and homocysteinaemia) are potentiated in the presence of diabetes. Other endothelial damaging factors (e.g. hyperglycaemia, hyperinsulinaemia, insulin precursors and by-products, glycated proteins such as albumin, haemoglobin, insulin itself, the advanced end-products of glycation [AGE] with their receptors [RAGE][74,75] and the final products of lipoxida-

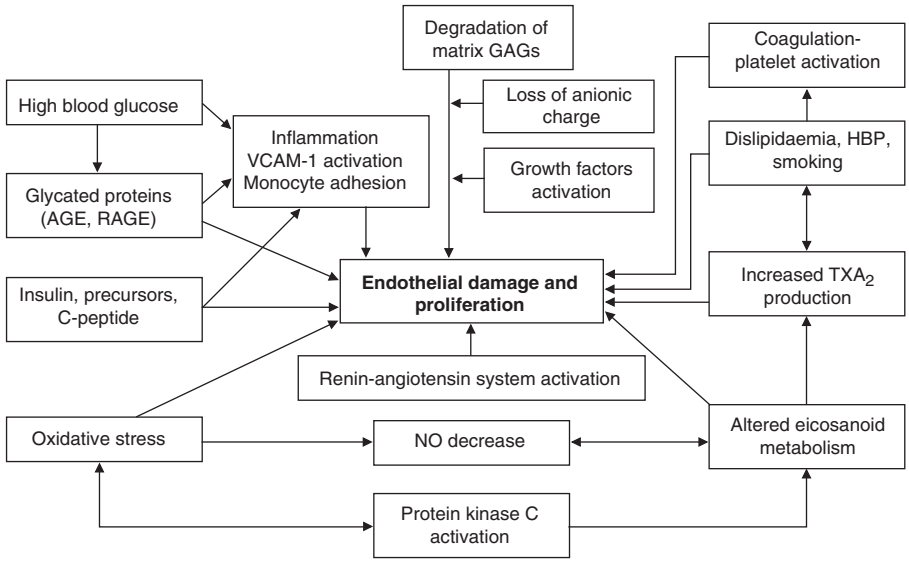

Fig. 1. Schematic representation of some of the main mechanisms of vascular complications in type 2 diabetes mellitus. **AGE** = advanced glycation end-products; **GAGs** = glycosaminoglycans; **HBP** = high blood pressure; **matrix** = intercellular group substance; **NO** = nitric oxide; **RAGE** = endothelial receptors of advanced glycation end-products; **TXA** = thromboxane; **VCAM-1** = vascular cell adhesion molecule-1.

tion[76]) are connected to the metabolic derangement and therefore appear 'unique' to diabetes.

Sensitivity of the endothelial lining to these injuring agents seems to be enhanced even prior to the onset of overt diabetes,[73,77] probably because of a congenital tendency to desulfation and degradation of proteoglycans, which are major components of the intercellular and basement membrane matrix of endothelial cells. These changes induce abnormal endothelial permeability and selectivity (perm-selectivity), and other reactive phenomena. This concept proposes a unifying interpretation of macro- and microvascular involvement in diabetes, indicating endothelial injury as the original starting event, and has been named after, the 17th century holistic scientist and Bishop Niels Stensen, to whom a Danish hospital and diabetes centre is dedicated.[73] Although not completely proven, the Steno hypothesis has inspired experimental and clinical work on the relationship between diabetic macro- and microangiopathy.[78]

The pattern of endothelial damage in diabetes can be described as a complex phenomenon of abnormal augmentation of vascular permeability, gradual change of endothelial cells towards a secretory phenotype and enhanced cell proliferation.[77] The anionic charge of the normal endothelium becomes gradually reversed, and reduction and patchy distribution of the anionic sites occur, more in arteries and capillaries than in the veins.[77] As the anionic endothelial surface charge counteracts attraction between endothelial lining and circulating cells, charge alterations will enhance cell-to-cell interactions, thus favouring endothelial damage.[79] Such endothelial changes are probably similar in diabetic macro- and microangiopathy.

3.3 Oxidative and Reductive Stress

Many concordant data show that a marked enhancement of oxidative processes occurs in diabetes. Circulating lipoperoxides and free fatty acids mainly deriving from oxidised LDL are produced by the action of free radicals from various sources and severely reduce the antioxidant potential of blood.[80] On the other hand, increased glucose flux via the sorbitol pathway[6] induces a 'reductive' stress (transformation of nicotinamide-adenine dinucleotide to the reduced form of nicotinamide-adenine dinucleotide phosphate), that in turn stimu-

lates a reactive increase in free radicals. In addition, AGE products and activation of protein kinase C contribute to free radical production and activity.[6]

3.4 Decline in Nitric Oxide Activity

A consequence of oxidative stress is a decline in nitric oxide synthesis and activity, due to decreased endothelial expression and accelerated inactivation of nitric oxide by free radicals.[6] In these conditions, failure of the normal balance between production of vaso-contracting and relaxant factors occurs, and an important mechanism of platelet aggregation inhibition is impaired.[81] Interestingly, it has been observed that particulate air pollution impairs endothelial nitric oxide-mediated vascular reactivity in diabetic patients and probably contributes to their cardiovascular risk.[82]

3.5 Protein Glycation and Advanced Glycation End-Products

AGEs, including glycated albumin, haemoglobin and insulin itself, may couple with tissue proteins and lipoproteins, producing abnormal compounds capable of damaging the endothelial lining.[74] The complexes between AGEs and their receptors, RAGEs, can inhibit tissue clearance of lipids, lipoproteins and cholesterol, and may impair permeability and finally disrupt the vessel wall.[83,84] These compounds also contribute to the oxidative stress by stimulation of free radical formation. Polymorphisms in RAGEs have been surmised to enhance or in turn attenuate their damaging effects on the vascular wall.[75]

3.6 Activation of the Renin-Angiotensin-Aldosterone System

Activation of the RAAS is linked to the formation of free radicals and reactive oxygen species, leading to oxidative stress, and also to a concomitant decrease in nitric oxide production and activation of protein kinase. Excess angiotensin II, a major product of the RAAS system, may induce vasoconstriction and vascular damage, and impaired delivery of glucose and insulin to the skeletal muscles, hence increasing insulin resistance.[64] Other angiotensin II-dependent mechanisms conducive to altered glucose metabolism and vascular damage concern the pathogenesis of diabetic nephropathy and are discussed in sections 1.2.1 and 4.1.

3.7 Inflammatory Changes

The impact of diabetes on the inflammatory component of atherothrombosis involves different mechanisms.[85-87] Insulin enhances vascular adhesive properties of monocytes by promoting vascular cell adhesion molecule-1 (VCAM-1) expression:[88] thus, hyperinsulinaemia associated with insulin resistance may be an important mediator for inflammation-linked atherosclerotic processes in diabetes. A cleavage product of pro-insulin, C-peptide, found in patients with insulin resistance or early type 2 diabetes, also shows pro-inflammatory properties by stimulating CD4+ lymphocyte and monocyte recruitment and chemotaxis.[89,90] These data implicate C-peptide as a factor possibly favouring transition from the 'metabolic syndrome' to type 2 diabetes, but this hypothesis needs further confirmatory studies.

Clinical data from the IRAS study showed that the levels of insulin and its precursors correlated with fibrinogen and plasminogen activator inhibitor-1 (PAI-1) and that insulin resistance correlated with CRP levels.[91] Recently it was also demonstrated that CRP directly promotes endothelial inflammation in type 2 diabetes, thus accelerating the atherosclerotic process.[92]

3.8 Eicosanoid Metabolism

Eicosanoids are a large family of autacoids of lipidic nature, generated by monocarboxylic polyunsaturated fatty acids and produced by different blood and vascular cells.[93]

The absolute amounts and proportions of different eicosanoids are profoundly altered both in atherogenesis and in diabetes. In patients with diabetes, synthesis of prostaglandins E_1 and E_2 and prostacyclin (PGI_2) is reduced, thus diminishing their inhibiting effects on aggregatory and vasoconstrictor stimuli.[93] In contrast, synthesis of thromboxane A_2 (TXA_2) is greatly enhanced;[94] an excess of TXA_2

amplifies platelet aggregation and endothelial-mediated vasoconstriction.[95]

Other eicosanoids, especially from the lipoxygenase or other non-enzymatic pathways, such as leukotrienes,[96] lipoxins[97] and isoprostanes,[98] increase in the diabetic condition and contribute to inflammatory, vasoconstrictive and endothelium damaging effects.

3.9 Platelet Function

Early findings *in vivo*[99] demonstrated an increased number of circulating platelet aggregates and aspects of 'spontaneous' platelet aggregation, and more recent studies showed an increase in platelet turnover,[100] circulating platelet microparticles[101] and large platelets.[102] Increased adenosine diphosphate (ADP) and TXA-induced aggregation was found in platelet-rich plasma of diabetic patients and attributed to enhanced expression of the glycoprotein receptor for the ADP pathway,[103] and to enhanced activation of phospholipase C for the cyclo-oxygenase (COX) pathway. In the latter conditions, excess of arachidonic acid availability from platelet membrane phospholipids occurs. COX and TXA-synthase activities are stimulated in diabetes, especially because of peroxide accumulation due to free radicals. Overproduction of TXA_2 through COX but also non-COX pathways, both in platelets and in vascular cells and monocyte/macrophages, is in fact an important feature of increased platelet activation in diabetes.[95]Aging was also found to be an important factor influencing platelet aggregation in diabetic patients.[104] In a recent review,[105] platelet abnormalities in diabetes were thoroughly discussed, with special regard to (i) glycation of membrane glycoproteins; (ii) peroxidation-induced formation of isoprostanes; and (iii) a "phenotypic switch" of endothelial cells conducive to increased platelet adhesion, and eventually a prothrombotic condition.

3.10 Blood Coagulation and Fibrinolysis

A number of coagulation factors were found altered in diabetic patients, and were influenced by the levels of both glucose and insulin.[106] Plasma fibrinogen levels, usually high, were found to decrease after insulin administration.[107] A fibrinogen breakdown product, fibrinopeptide A, was also increased and correlated well with high glucose levels.[107] High levels of coagulation factor VIII and VII and of soluble tissue factor have also been described.[108] Quite recently, statistically significant shortening of tests as simple as activated partial thromboplastin time (aPTT) and prothrombin time (PT) and elevated prothrombin levels have been described in patients with type 2 diabetes.[109] Regarding coagulation inhibitors, protein C decreases mainly in type 1 diabetes, while antithrombin tends to fall during acute hyperglycaemia.[110] These changes are reversed by insulin infusion, which also will abate the enhanced levels of von Willebrand factor.[111]

Important changes occur in the fibrinolytic system: an increase in PAI-1 antigen and activity is common,[112] and endothelial cells lose their ability to produce tissue plasminogen activator antigen.[113] The mechanisms responsible for PAI-1 increase include high glucose levels, hyperinsulinaemia[114] and elevated pro-insulin concentrations.[115] A recent study stressed the strict relationship between hypofibrinolysis and high levels of HbA_{1C} in type 1 diabetes, thus emphasising the importance of glycaemic control in the regulation of fibrinolysis.[116] An increase in D-dimer is often observed especially in diabetic patients with vascular complications.[117]

Thus, a hypercoagulable state with a tendency to the formation of fibrin and impairment of its removal by the natural fibrinolytic system typically occurs in diabetes, and may contribute to instability, vulnerability and dynamic features of the atherothrombotic plaques.[118]

3.11 Risk Factors and Predictors of Vascular Complications

As previously pointed out in the introduction, risk and pathogenic factors for vascular complications of diabetes should be separated into two distinct classes: (i) factors common to nondiabetes-associated atherosclerosis and atherothrombosis; and (ii) factors 'unique' to diabetes, as being specifi-

cally related to the metabolic derangement of the disease.

Among the 'common factors', high blood pressure is at least twice as frequent in diabetic as in nondiabetic individuals and, including isolated systolic hypertension, is associated with both macrovascular events and microvascular complications.[119] Type 2 diabetes mellitus was found, in a prospective study, to be a strong risk factor for onset of hypertension in post-menopausal women.[120] In addition, the recently defined criteria for pre-hypertension (systolic blood pressure 120–139mm Hg and diastolic 80–90mm Hg) are more prevalent in diabetic patients and increase their cardiovascular risk.[121] The impact of diabetes-associated hypertension on stroke and stroke mortality has already been stressed.[31] Dyslipidaemia is very common in patients with diabetes and may include lowered HDL-cholesterol and, often but not always, increased total and LDL-cholesterol.[9] Recently, based on studies on the metabolic syndrome and insulin resistance, the concept of a 'mixed dyslipidaemia', including high triglyceride levels, low HDL-cholesterol, presence of small and dense LDL particles and accumulation of apolipoprotein B, has emerged as a new lipidaemic risk factor.[122] Obesity is common in patients with diabetes, and visceral lipid accumulation seems a more sensitive indicator of risk than body mass index.[123] Smoking is a crucial risk factor for major cardiovascular events[124] and especially for critical limb ischaemia and amputation in diabetes-associated PAD.[45] The role of hyperhomocysteinaemia in atherogenesis with or without diabetes has recently been questioned.[125] Among clotting and related factors, high fibrinogen and D-dimer levels are associated with increased risk of events in diabetes-associated PAD,[126] and high levels of soluble tissue factor confer a 15-fold higher risk for diabetic microangiopathy.[108] Regarding platelets, no current platelet function test has a predictive power; however, large platelets[102] and especially platelet microparticles in the circulating blood, as well as the platelet-derived adhesive protein P-selectin,[101] have been proposed as indicators of risk for vascular complications. Several markers of inflammation are also predictive of CHD and more generally atherothrombosis, such as white blood cell number, erythrocyte sedimentation rate, C-reactive protein, von Willebrand factor, fibrinogen, PAI-1, various adhesion molecules, interleukins and others. However, a detailed discussion of these markers goes beyond the scope and limits of this article, and the reader may refer to specific reviews on the role of inflammation in atherosclerosis[87] and diabetes.[86]

Among factors specific for diabetes, hyperglycaemia *per se* is a risk factor for cardiovascular morbidity and mortality.[10] High fasting levels of insulin were found to be an important and independent risk factor for a first event of ischaemic heart disease.[127] More recently, insulin resistance and the insulin precursor pro-insulin were defined as predictive of myocardial ischaemia and coronary death.[128,129] C-peptide may have similar significance according to experimental studies,[91] but still needs clinical validation. Glycated proteins, AGE and RAGE, have a pathogenic role in the development of endothelial damage (see section 2.5), but in practice only HbA_{1C} is widely measured as an indicator of metabolic control and its levels are especially correlated with diabetic microangiopathy.[130] Quite recently, skin autofluorescence due to tissue accumulation of AGEs has been found to be strongly correlated with the presence of CHD and with cardiac mortality.[131] Microalbuminuria as well as overt proteinuria, besides being obviously related to renal function and diabetic nephropathy, are also important markers of macrovascular damage and predictors of cardiovascular events,[132] thus confirming the existence of a 'common ground' including macro- and microangiopathy.[77] In type 2 diabetic patients, cardiovascular complications are associated with an enhanced pituitary-adrenal activity, and cortisol secretion is strongly correlated with the presence and number of macro- and microvascular complications.[133]

Interestingly, a prolonged corrected QT interval associated with high heart rate predicted cardiovascular mortality in a study including 475 patients with uncomplicated diabetes,[134] thus suggesting a

role for the myocardial cell electrolyte balance, and relationships with the autonomic cardiomyopathy of diabetes (see section 1.2.3).

4. Antithrombotic Agents in the Prevention of Cardiovascular Events in Diabetes

4.1 Antiplatelet Drugs

4.1.1 Rationale

The rationale for antiplatelet therapy to prevent major cardiovascular events mainly due to macrovasculopathy in patients with diabetes corresponds to the rationale for prevention of atherothrombosis in nondiabetic patients.

On the other hand, the use of antiplatelets in diabetic microangiopathy, especially retinopathy, is based on the observed aspects of endothelial damage and platelet microthrombosis, and on the perspective of inhibiting the proliferative effects of the platelet-derived growth factor.[135]

4.1.2 Cyclo-Oxygenase Inhibitors: Aspirin (Acetylsalicylic Acid) Studies

Subgroup analyses of diabetic patients from major trials that included both diabetic and nondiabetic patients, provide unclear advice regarding the use of aspirin (acetylsalicylic acid), as do results from a small number of specific studies.[136-138]

A predefined *post hoc* analysis was performed within the Primary Prevention Project.[139] This was a study of 4500 individuals with no history of cardiovascular events but with at least one cardiovascular risk factor. In the 1031 diabetic patients included, the effects of aspirin were surprisingly poor: for example, major vascular events were reduced by only 10% in diabetic individuals versus 31% in nondiabetic individuals. These results were unlikely to be due to chance, as the predefined diabetic subgroup was separately enrolled in specialised diabetes clinics. These data, even if not conclusive, cast doubts on the efficacy of aspirin for primary prevention in diabetes.

Specific studies in patients with diabetes are also inconclusive. In the ETDRS,[140] which focused on the progression of retinopathy, long-term administration of aspirin (650mg) reduced the rate of MI by 28%, but not that of total cardiovascular events. Such events were even more frequent among treated patients versus controls (7.5% vs 5.1%) in another retinopathy trial, the DAMAD study assessing aspirin alone or with dipyridamole.[141]

It seems even more meaningful that the pooled results of nine specific trials of cardiovascular prevention with antiplatelet drugs (mainly aspirin) in diabetic patients, systematically reviewed in the Antithrombotic Trialist Collaboration Meta-Analysis,[142] showed a slight and nonsignificant odds reduction for cardiovascular events (7%, standard error = 8), a figure far smaller than those obtained for other high-risk categories, as for instance, post-infarction or post-stroke patients (in both groups, 22%, standard error = 4). The mentioned trials included a majority of patients who did not have a history of cardiovascular events, although they probably had other cardiovascular risk factors (e.g. hypertension, high cholesterol) besides diabetes.

Few data are available from trials of secondary prevention. The 5-year Veterans Administration Cooperative Study[143] followed a group of 231 diabetic patients with peripheral gangrene or amputation as a result of associated PAD, who were allocated to aspirin plus dipyridamole or placebo. No significant benefit of the study drugs on major cardiovascular events was seen. The addition of aspirin to clopidogrel-treated patients was examined in the MATCH study,[144] in patients with recent ischaemic stroke or recent cerebral ischaemic attack, with at least one additional risk factor, which in two-thirds of the cases was diabetes. The addition of aspirin to clopidogrel had no significant effect versus clopidogrel alone on an endpoint composed of ischaemic stroke, acute MI and hospitalisation for vascular causes. However, the risk of life-threatening major bleedings was increased with the combination, confirming that diabetic patients should not be exposed to an excessive risk of bleeding.[138]

Finally, in the more recent CHARISMA trial,[145] the group of patients with multiple risk factors reported no benefit from the combination of aspirin

and clopidogrel, and the overall risk of severe bleeding was increased by 25%.

In summary, some doubts are warranted about the real degree of efficacy of aspirin in patients with diabetes, and further research is needed to definitively assess aspirin efficacy and test other antiplatelet regimens or combinations in diabetic patients, although some recent trials have pointed out the bleeding risk of such combinations.

4.1.3 Recommendations on Aspirin

Despite the mentioned uncertainties, many official medical bodies maintain that aspirin is sufficiently effective in the prevention of cardiovascular events in diabetic patients.[146] The American Diabetes Association (ADA),[147] the American Heart Association (AHA),[148] the US Preventive Services Task Force[149] and the European Society of Cardiology (ESC)[150] all recommend regular use of aspirin in diabetic patients especially in the presence of other risk factors, according to the following criteria:

- ADA (1998–2004): diabetes (age >40 years) plus ≥1 cardiovascular risk factor;
- AHA (2002): diabetes and 10-year risk of first CHD event >10%;
- US Preventive Services Task Force (2002): diabetes and 5-year risk CHD >3%;
- ESC (2003): 'suggested' for diabetic patients with 1-year risk of CHD >1.5%.

The recommended dosages of aspirin in the above recommendations vary from 75 to 162 mg/day. The estimated risk of cardiovascular events in diabetic patients exceeds the quoted figures in most studies. In a recent contribution,[151] the mean 10-year risk of coronary events in a large cohort of type 2 diabetic outpatients from general practice was found to be as high as 21.5% in 10 years. Thus, according to the above indications, a high proportion (at least 65%) of all patients with type 2 diabetes are candidates for aspirin therapy.[146] On the other hand, data and comments from the ADA reprove the fact that aspirin is underused in diabetic patients.[152] This is probably because the prevailing care provided by the family doctor is in pursuing glycaemic control and counteracting the measurable risk factors rather than in administering an antithrombotic drug.

It is worth noting that by making the use of aspirin in diabetes dependent upon the presence of other associated risk factors, official recommendations elude the core of the problem, which is whether aspirin is really satisfactorily efficacious in diabetes.

4.1.4 Thromboxane Synthase and Receptor Inhibitors

The rationale for investigating direct inhibitors of TXA-synthase is based on the observation of an increased TXA_2 synthesis in diabetes.[94,95] However, relevant clinical data have become recently available only for picotamide, a dual inhibitor of TXA synthase and the TXA receptor. In the DAVID study,[153] >1200 patients with type 2 diabetes and established PAD were blindly allocated to picotamide (600mg) or aspirin (320mg). The trial was designed as a survival study, partly in view of the possible low efficacy of aspirin in preventing mortality, as recently suggested.[154]

In the DAVID study, picotamide almost halved general mortality compared with aspirin with a significantly lowered relative risk of death (0.55) [figure 2][153] and also reduced vascular deaths from 4.1% to 2.1%, although not significantly.

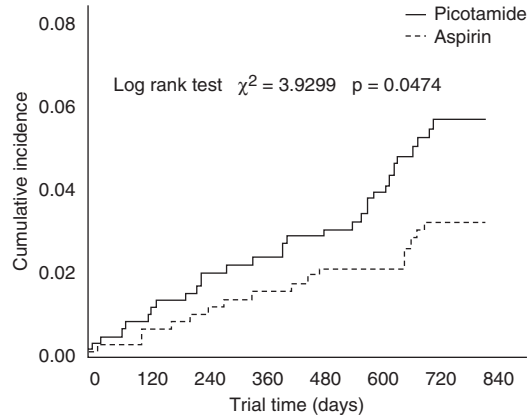

Fig. 2. Mortality in diabetes-associated peripheral arterial disease under aspirin (acetylsalicylic acid) or picotamide from the DAVID study: Kaplan-Meyer curves of time to death. Relative risk in picotamide vs aspirin is 0.55, significant (reproduced from Neri Serneri et al.,[153] with permission from the European Society of Cardiology).

Picotamide was associated with less bleeding and was better tolerated than aspirin.

The DAVID study suggests that dual inhibitors of TXA synthase and TXA receptors may have an advantageous pharmacological profile for cardiovascular prevention in diabetic patients. This study may pave the way to further trials both with picotamide and other agents of the same class, such as ridogrel and the recently studied terutroban sodium.

4.1.5 Thienopyridines

It is particularly noteworthy that in the CAPRIE study, the advantage of clopidogrel over aspirin observed in the total study population was maintained in the large diabetic subgroup (3866 patients). Indeed, the absolute risk reduction in cardiovascular events in diabetic versus nondiabetic individuals was a significant 2.1% and even greater (3.8%) in diabetic individuals receiving insulin. These results seem to be mainly linked to the higher absolute event rate occurring in diabetic patients as the relative risk reduction in favour of clopidogrel was similar in diabetic and nondiabetic individuals.[155] At variance with these data, resistance to the agent was observed in patients with diabetes receiving long-term treatment with clopidogrel, especially in patients also receiving insulin.[156] Resistance to clopidogrel in diabetic patients with acute coronary syndromes has also been described,[157] and, in the Optimus Study,[158] could partly be overcome by increasing the loading dose to 600mg.

4.1.6 Glycoprotein IIb/IIIa Inhibitors

Glycoprotein IIb/IIIa inhibitors include abciximab, a chimeric antibody against the fibrinogen platelet receptor, and peptides with similar properties (e.g. tirofiban, lamifiban and eptifibatide). They are generally used via the parenteral route within the multiple antithrombotic treatment panel for acute coronary syndromes. A pooled subgroup analysis of patients with diabetes from six trials of these drugs in patients with acute coronary syndromes suggested a 26% reduction in 30-day mortality versus placebo, which was greater than in nondiabetic individuals.[159] Moreover, in diabetic patients who also underwent percutaneous coronary interventions the benefit on mortality was even greater (70%).

Glycoprotein IIb/IIIa inhibitors seem highly effective in diabetes and are recommended in diabetic patients with acute coronary syndromes undergoing percutaneous coronary interventions.[160]

Unfortunately, these effective antiplatelet agents failed to show activity when administered orally, making them unsuitable for long-term prevention, as is desirable in a lifelong disease such as diabetes.

4.1.7 Antiplatelet Agents in Diabetic Retinopathy

In the DAMAD study,[141] aspirin alone (330 mg/day) or in combination with dipyridamole (75mg × three times daily) was compared with placebo in 475 patients with early diabetic retinopathy and microaneurysms. Aspirin alone, and in particular with dipyridamole, significantly slowed down the rate of increase in microaneurysm count but with no other beneficial effect. A more marked preventive action was expected with ticlopidine, and the TIMAD study[161] evaluated ticlopidine 250mg twice daily in 435 patients with type 1 or type 2 diabetes and non-proliferative diabetic retinopathy over 3 years. Ticlopidine was associated with a reduction in microaneurysm progression, similar to that observed in the DAMAD study with aspirin, with a small limiting trend on neovascularisation. Adverse effects of ticlopidine (gastroenteric, haemorrhagic and haematological) led to discontinuation of treatment in 13.2% of patients.

The issue of aspirin treatment in diabetic retinopathy was again investigated in the ETDRS trial,[162] a far larger study than the previous ones, including 3711 patients with non-proliferative or early proliferative diabetic retinopathy. The primary endpoint was the development of high-risk proliferative diabetic retinopathy. Aspirin did not prevent the primary endpoint and did not reduce the risk of vision loss. A trend suggesting some benefit was seen only in a subgroup of patients with less severe baseline retinopathy.[162]

Thus, aspirin, together with other antiplatelet agents, has shown limited efficacy in halting progression of diabetic retinopathy. Positive effects

could be seen only in patients entering the trial with minimal background retinal changes.

Platelet function inhibition may not be sufficient to counteract the complex microvascular changes occurring in diabetic microangiopathy.

4.1.8 The Debate on Antiplatelet Agents in Diabetes

Several hypotheses have been put forward to clarify the possible mechanisms by which, in diabetes, aspirin may be less effective than expected and necessary.

The Primary Prevention Project investigators argue that, in diabetes, platelets may be activated through partly peculiar aspirin-insensitive mechanisms.[139] The marked inflammatory phenotype of diabetes-associated atherothrombosis may involve hyperproduction of TXA from cells and tissues through the aspirin-insensitive COX-2 pathway.[163] Alternative prostanoid producing mechanisms (e.g. lipid peroxidation) can be activated by hyperglycaemia[164] or by insulin and insulin resistance,[93] and hypercholesterolaemia may also play a role in limiting the aspirin effect.[165] Furthermore, the increased turnover of platelets in diabetes could suggest the need for doses of aspirin that are higher than usual.[100]

It has also been shown that after prolonged treatment with aspirin, some production of TXA_2 may re-emerge and this fact may be important in a chronic disease such as diabetes.[166] What is perhaps more relevant is a rather high prevalence of aspirin resistance found in patients with type 2 diabetes,[167-170] which was attributed in one study to HbA_{1C} or other glycated proteins.[171]

Focusing on the results of the DAVID study,[153] superiority of picotamide over aspirin was specifically seen for mortality, thus suggesting that direct intervention on TXA_2 could be particularly effective in prevention of severe events possibly bound to a sudden TXA 'outburst'.[172] This possibility fits well with some of the properties of picotamide, specifically, that it diffuses from plasma to vascular tissues more easily than aspirin, which may ensure more complete inhibition of the effects of TXA.[173]

Resistance to clopidogrel has been attributed to hypersensitivity of the diabetic platelet to aggregation agonists.[156]

However, none of the above considerations seem to completely explain the suggested lower efficacy of aspirin and also of clopidogrel in diabetes, and further studies are necessary to clarify these issues.

4.2 Heparin and Oral Anticoagulants

The use of unfractionated heparin (UFH) and low molecular weight heparins (LMWH) both in prophylaxis and therapy of diabetic vascular complications seems no different from what is common use in nondiabetic individuals.

Surprisingly, diabetes is not quoted as a risk factor for venous thromboembolism in a large epidemiological survey,[52] or in recent articles[174] and guidelines.[175] However, clinical experience and the presence of a hypercoagulable state suggest prophylaxis in diabetic patients during risk circumstances for DVT. No special recommendation is made for UFH and LMWH therapy in acute venous or arterial thrombosis. In the subject index of recent guidelines for antithrombotic therapy,[175] the word 'diabetes' is not even quoted.

There is no indication that the presence of diabetes should influence the duration of the oral anticoagulant coumarin treatment after DVT. In contrast, in patients with atrial fibrillation, the coexistence of diabetes confers additional risk for cardioembolic stroke.[176,177]

Diabetes appears in some lists of conditions allegedly favouring bleeding complications during treatment with oral anticoagulants, even if specific data are scanty.[178]

Finally, pharmacological interactions have been described in the past between coumarin drugs and sulfonylurea-type antidiabetic compounds and acarbose,[179] with potentiation of the anticoagulant effect. No interaction has been found with metformin and similar compounds.

4.3 Glycosaminoglycans (GAGs) and Related Agents in Diabetic Microangiopathy

4.3.1 GAGs in Diabetic Nephropathy

In order to understand the rationale of glycosaminoglycan (GAG) compound treatment in diabetic nephropathy, it should be recalled that the main pathological features of the condition include desulfation and degradation of the glomerular matrix, thickening of the basal membrane and mesangial proliferation, and extra- and intracapillary jalinosis. These alterations lead to fibrosclerosis of the glomerular unit which induces glomerular damage and finally renal failure. The proliferative aspects are attributed to the production of growth factors such as transforming growth factor-β (TGFβ) stimulated by high glucose and angiotensin II levels,[180,181] vascular endothelial growth factor (VEGF) and possibly platelet-derived growth factor.[135] Microalbuminuria may be considered a composite effect of intraglomerular hypertension and renal capillary damage due to production of angiotensin II,[182] associated with alterations of endothelial permeability due to the degradation of heparan-sulfate, a GAG component of the intracellular and basement membrane matrix.[183,184]

The first mechanism provides a rationale for the therapeutic role of ACE inhibitors and angiotensin receptor antagonists (angiotensin receptor blockers [ARBs]) in diabetic nephropathy, as demonstrated in a number of trials (see section 4.4) The second one introduces the use of agents involved in the GAG metabolism of the matrix, according to the quoted 'Steno' hypothesis.[77] In fact, both in animals and in human preliminary studies it was shown that low-dose heparin,[185] and mixed compounds of sulfated GAGs, such as danaparoid sodium[186] and sulodexide,[187] favourably modify several features of diabetic nephropathy such as mesangial matrix thickening, loss of anionic sites and associated albuminuria.

Special attention has recently been focused on sulodexide, a compound containing 80% slow-moving heparin and 20% dermatan sulfate, two agents shown to be active in preventing experimental diabetic nephropathy.[188] An advantage of sulodexide over heparins is a higher and more consistent activity by the oral route.

In the DiNAS study,[189] sulodexide was administered orally at different doses for a period of 4 months to patients with diabetic nephropathy and micro- or macroalbuminuria. The highest dose (200 mg/day) significantly reduced albuminuria by 43% versus baseline and the effect persisted at the 8-month follow-up with no major adverse events. Sulodexide was effective both in type 1 and type 2 diabetes and maintained efficacy during concomitant treatment with ACE inhibitors. In a further study,[190] even a moderate dose of sulodexide 50 mg/day administered for 1 year in type 1 and type 2 diabetic patients with nephropathy was able to significantly reduce albuminuria independently of diabetes type and baseline presence of micro- or macroalbuminuria.

Treatment with sulodexide has also been tested in vascular conditions other than diabetes. Sulodexide prevented cardiovascular events in survivors of MI[191] and, in a study by our group, improved the walking performance of patients with PAD, among whom 25% had diabetes.[192]

Therefore, GAGs offer a new perspective in the treatment of diabetic albuminuria, but confirmatory studies of larger size and longer follow-up are necessary in order to clarify whether and to what extent these agents influence the natural history of patients with diabetic nephropathy.

4.3.2 GAGs in Diabetic Retinopathy

Diabetic retinopathy is the result of reduced perfusion of the retinal microvasculature, with formation of microaneurysms and, eventually, obliteration of retinal capillaries with aspects of platelet microthrombosis.[193] As in diabetic nephropathy, the intercellular and basement membrane matrix of endothelial cells is damaged. Permeability of retinal capillaries is markedly altered and causes plasma protein exudation forming 'hard' and 'soft' exudates.[193] Proliferation of endothelial cells, neovascularisation and reduction of pericytes appear as reactive phenomena, finally leading to loss of vision.[65] As in glomeruli, the alteration of capillary permeability is likely to be the result of high glu-

cose-induced heparan-sulfate desulfation and degradation. Heparan-sulfate proteoglycans also regulate retinal endothelial proliferation, as a result of being constituents of the TGFβ[180] endothelial receptors, and contributors to expression of other growth factors as PGDF,[135] VEGF[194] and insulin-like growth factor-1.[195] This background, similar to that described for diabetic nephropathy, warrants therapeutic trials with GAGs in the prevention of diabetic retinopathy, with the final hope of averting blindness.

In a small pilot study in 30 patients treated for 16 weeks with sulodexide, a significant reduction of hard exudates, haemorrhages and other microvascular abnormalities was observed.[196] Similarly, another GAG compound, danaparoid sodium, induced corresponding morphological changes.[197]

In summary, the rationale and the first results of GAG therapy in diabetic microangiopathies are very promising, but leave important questions open to future research, especially regarding the prevention of the ultimate outcomes such as end-stage renal failure and blindness.

5. Pharmacological and Non-Pharmacological Measures to Reduce Cardiovascular Risk

5.1 Lifestyle and Physical Exercise Counselling

Two recent sets of guidelines on the vascular complications of diabetes, one published by the AHA and the ADA,[198] and one by the ESC and the European Association for the Study of Diabetes (EASD),[199] placed special emphasis on the preventive value of nutritional and lifestyle measures as being capable of reducing cardiovascular endpoints in diabetic individuals.

The AHA-ADA guidelines[198] recommend weight control by reducing fat intake to <30% of daily energy with a prevalence of mono- or polyunsaturated fatty acids. To reduce LDL-cholesterol, the daily intake of saturated fat should be <7% of the energy intake, and that of trans-fats <1%, while cholesterol intake should drop to <200 mg/day. Other advice includes ample intake of dietary fibres, limitation of alcoholic beverages, moderate reduction of salt in the presence of hypertension to 3000–6000 mg/day, and cessation of smoking. Physical activity is recommended both to improve glycaemic control and to prevent cardiovascular events. Moderate intensity aerobic physical activity for 150 minutes, or vigorous aerobic exercise for 90 minutes per week are recommended, distributed over at least 3 days, with no more than 2 close days of inactivity.

The European ESC-EASD guidelines[199] recommend restriction of caloric intake to about 1500 kcal/day, restriction of fat intake to 30–35% of daily energy intake with 10% reserved for mono-unsaturated fatty acids, avoidance of trans-fats and of liquid mono- and disaccharides, adequate fibre intake and abstention from smoking. The European guidelines recommend 30 minutes of physical aerobic exercise at least five times a week, which was also found to be associated with reduced cardiovascular mortality in diabetic individuals.

To summarise, the US guidelines are stricter in terms of total caloric reduction and place more emphasis on alcohol restriction, while the European guidelines stress the importance of monounsaturated fatty acids (olive oil). The advice regarding physical activity is similar in both.[198,199]

5.2 Glycaemic Control and Antidiabetic Drugs

Although diabetes is a highly multifactorial metabolic disease, careful control of blood glucose levels obviously remains an essential part of diabetes care. Control of blood glucose with dietary and pharmacological measures seems especially effective in slowing progression of microangiopathy, rather than the course of atherothrombosis and the incidence of major events. In fact, in the UKPDS study,[130] for each 1% reduction in HbA_{1C} (the main marker of diabetic control), the occurrence of microvascular disease was reduced by as much as 35%, while death was reduced by 22% and acute MI only by 13%. In contrast, in the subgroup with diabetes-associated PAD, the combined endpoint of

death plus amputation was significantly lowered by 45%. Moreover, in a subgroup of patients treated with metformin, death and acute MI in obese diabetic patients were significantly less frequent compared with those receiving conventional or intensive treatment with sulfonylureas or insulin.[200]

The author of this review shares the opinion that a more comprehensive intervention on the global risk factors, rather than the mere adjustment of glycaemic levels, is necessary to obtain improvement in the course of atherothrombosis and the rate of major cardiovascular events. Similarly, the Steno 2 study[78] provides an example of an integrated and intensive pharmacological and behavioural therapy of diabetes, targeted on the whole constellation of risk factors, and capable of reducing by about 50% the main macro- and microvascular outcomes.

Glitazones are a recently developed class of drugs acting as agonists of the peroxisome proliferation activated receptors (PPARs)[201] which regulate glucose control, lipid metabolism, insulin sensitivity and inflammatory responses. In the recent PROactive study[202] pioglitazone, an agonist of PPARγ, that lowers blood glucose levels and improves insulin resistance, was partially effective in preventing cardiovascular events as it reduced a secondary endpoint composed of all-cause mortality, nonfatal acute MI and stroke by 16% versus conventional treatment. Despite these results, the general benefit-risk ratio of pioglitazone is still debated.[203] Moreover, beneficial results on cardiovascular events with another PPAR agonist, rosiglitazone, were not confirmed and the onset of new cases of diabetes was not prevented.[204]

5.3 Control of Lipid Alterations

Rigorous control of lipidaemic changes and normalisation of the altered lipid profile is an important approach in the programme of prevention of cardiovascular complications of diabetes. It is not established whether low-fat and low-cholesterol dietary regimens alone are effective in reducing the risk for cardiovascular complications in these patients.[205] The combination of lipid-lowering drugs and dietary measures seems to be necessary to obtain significant levels of event reduction. In any case, LDL-cholesterol targets as low as 70–100 mg/dL (1.8–2.6 mmol/L) have recently been recommended in official guidelines for diabetic individuals at risk or very high risk.[198,199,206]

A meta-analysis of 14 trials of lipid-lowering drugs in diabetic individuals showed a similar risk reduction in primary as in secondary prevention trials (22% and 24%, respectively). However, the absolute risk reduction over 4–5 years was 2- to 3-fold higher in secondary versus primary prevention trials as a result of the higher baseline risk of diabetic patients with a previous event. The benefit was also seen in patients with LDL-cholesterol levels as low as 100–115 mg/dL (2.6–3.0 mmol/L).[207]

Recent studies have further confirmed these data. In a subgroup of the Heart Protection Study, which included about 6000 patients with diabetes with total cholesterol >135 mg/dL (3.5 mmol/L), treatment with simvastatin was associated with a 28% reduction in ischaemic strokes and a 22% reduction in other major cardiovascular events.[208] In a recent specific study of primary prevention of cardiovascular events in type 2 diabetes, the CARDS study,[209] low-dose atorvastatin (10mg) given to patients with normal LDL-cholesterol reduced coronary events by 36%, stroke by 48% and death by 27%. However, some results of further trials were at variance. In the ASPEN study,[210] the effects of low-dose atorvastatin could not be confirmed and, in the TNT study,[211] superiority of atorvastatin (80 vs 10mg) was directly demonstrated: thus, the ideal doses of statins and particularly of atorvastatin are still unclear. It may be advisable to personalise the dose, with the goal of obtaining levels of LDL-cholesterol as low as 70–80 mg/dL (1.8–2.0 mmol/L).

A latest-generation HMG-CoA reductase inhibitor (statin), rosuvastatin, recently showed a high specific activity in reducing LDL-cholesterol and the apolipoprotein-B : apolipoprotein-A1 ratio in patients with type 2 diabetes.[212] These results were confirmed in a recent study[213] in which a more pronounced reduction of LDL-cholesterol was ob-

tained with rosuvastatin versus equivalent doses of atorvastatin.

Thus, statins are first-choice agents in the prevention of major events in diabetic patients, and the data discussed in this section postulate a widespread use of these drugs in diabetic patients >40 years of age, regardless of baseline cardiovascular or lipid status. In the recent VYTAL study,[214] the combination of ezetimibe, an inhibitor of cholesterol absorption, with simvastatin, provided additional benefits in comparison with atorvastatin alone with special regard to further reduction of LDL-cholesterol and triglyceride levels.

Combination therapy with atorvastatin and rosiglitazone, (see section 4.2), was associated with decreased levels of inflammatory biomarkers such as CRP, metalloproteinases and soluble CD40 ligand:[215] this observation indicates possible advantages of combinations of agents from the two classes.

Interest in fibric acid derivatives (fibrates) has been re-awakened by the well known links between the metabolic syndrome, insulin resistance and type 2 diabetes mellitus. These views, in fact, stimulated clinical use of fibrates and also a number of formal clinical trials,[122] although often flawed by the inclusion of an admix of patients with metabolic syndrome, dyslipidaemia alone and type 2 diabetes mellitus, or by add-in statin treatment. The readers especially interested in fibrate studies such as the VA-HIT, the Helsinki Heart Study and the Bezafibrate Infarction Prevention Study, may refer to the meta-analysis of Allemann et al.[122] However, one large trial deserves specific mention here (the FIELD study),[216] as it included about 10 000 patients with type 2 diabetes, 80% of whom were without previous cardiovascular events. Patients were randomised to fenofibrate or placebo, and in the treatment group the primary endpoint of fatal and nonfatal coronary events was only marginally and not significantly reduced; however, a significant decrease of 24% was seen for nonfatal MI and revascularisation procedures. Also of special interest is the DAIS study, in which treatment with fenofibrate reduced angiographic progression of coronary artery disease in type 2 diabetic patients.[217] In a recent review,[218] it is suggested that fenofibrate may be especially effective in the primary prevention of cardiovascular complications of type 2 diabetes. Some unexpected adverse effects, such as a reduction in microalbuminuria and a benefit in retinopathy, need further confirmation. Thus, fenofibrate can be seen as a 'reasonable second-line' therapy for dyslipidaemia in diabetes,[219] although the agent is probably less effective than statins in the prevention of cardiovascular events.

5.4 Control of Hypertension

Hypertension, as mentioned previously in this review (see sections 1.1 and 2.11), is a major comorbid condition for diabetes, especially type 2 diabetes, and greatly contributes to both macrovascular events and microvascular complications. Therefore, rigorous control of blood pressure down to targets as low as 130/80mm Hg is strongly recommended in diabetic patients,[220] and it seems noteworthy that even a moderate difference in reduction of blood pressure can make a great difference in reducing events and saving lives.

In the UKPDS study,[221] patients with a tight control of blood pressure (resulting in mean levels of 140/80mm Hg) with an ACE inhibitor (captopril) or a β-adrenoceptor antagonist (β-blocker [atenolol]) versus patients at less tight control (resulting in mean levels of 155/85mm Hg), had a 44% lower incidence of stroke, a 32% diminution in all diabetes-related deaths, and a 37% amelioration in surrogate microvascular endpoints as albuminuria and retinal photographic imaging. Moreover, after 9 years of follow-up, a 47% reduction in deterioration of visual acuity was seen in the tight-control patients.[221]

These data were confirmed, in particular the major cardiovascular events data, in some study subgroups and specific studies with ACE inhibitors, among which are the diabetic subgroup of the CAPP study with captopril[222] and the specific study in diabetic patients with fosinopril (FACET).[223] However, a large study on hypertension treatment, ALLHAT and the related substudy[224] of hypertensive

patients with diabetes, failed to detect superiority of an ACE inhibitor (lisinopril) over amlodipine or chlortalidone in the prevention of cardiovascular events. In fact, chlortalidone showed a better therapeutic profile, being associated with fewer cases of heart failure than amlodipine, and with a lower number of global cardiovascular events than lisinopril. Based on the ALLHAT results, thiazide diuretics seemed to become first-choice treatment of hypertension in nondiabetic patients as well as in diabetic patients.

However, studies with ACE inhibitors continued with success. In the diabetic subgroup (MICRO-HOPE, 3577 patients) of a large study of cardiovascular prevention, (the HOPE study), ramipril clearly reduced cardiovascular events, and the effect was only in part due to lowering of blood pressure.[225] More recently, in the context of a large study with perindopril (the EUROPA study), performed in patients with stable coronary disease, prevention of the primary endpoint (death, nonfatal acute MI and resuscitated cardiac arrest) in a large diabetic subgroup,[226] although not reaching significance, was similar to the 20% reduction obtained in the whole study population.

Other similar studies have focused on the relationships between inhibition of the RAAS, cardiovascular events and renal function. In a recent trial with trandolapril[227] in patients with stable coronary disease, efficacy of the agent was seen only in patients with reduced renal function who experienced a 27% significant reduction in total mortality.

In BENEDICT, trandolapril was re-examined, both alone or in combination with the calcium channel antagonist verapamil, and was found able to prevent or delay the onset of persistent microalbuminuria in normoalbuminuric, hypertensive diabetic individuals.[228]

A systematic review[229] considered 16 trials with ACE inhibitors versus placebo (six trials) or active drugs (ten trials) in diabetic patients with normoalbuminuria and with or without hypertension. ACE inhibitors significantly inhibited the onset of albuminuria by about 40% compared with either placebo or calcium channel antagonists, apparently with no relationship to baseline blood pressure and renal function. Outcomes directly related to progression of renal damage, such as doubling of serum creatinine and others, did not reach statistical significance, probably because too few trials were available to such evaluation.

The problem of preventing or reducing albuminuria and protecting renal function as well as the cardiovascular system in patients with type 2 diabetes with or without hypertension, was further investigated with a novel class of RAAS inhibitors, namely the ARBs. These agents have been found effective in several trials: some of them such as the IRMA, the IDNT, the RENAAL and the LIFE study are reported and commented upon in a paper by Deferrari et al.[230] to which the interested reader is referred.

As a class, ARBs given to patients with type 2 diabetes with overt nephropathy were more effective than conventional antihypertensives in preventing or reducing proteinuria, slowing down progression towards end-stage renal failure and lessening cases of severe heart failure. In one of the trials (LIFE), the ARB losartan significantly reduced cardiovascular events and mortality in diabetic patients with hypertension and left ventricular hypertrophy compared with atenolol.[231] Some differential effects of the two main classes of RAAS inhibitors on mortality and renal outcomes in diabetic nephropathy have emerged from a large, although nonselective systematic review of 43 trials, 36 of them with ACE inhibitors, 4 with ARBs and 3 directly comparative. All-cause mortality was significantly reduced by 21%, only by ACE inhibitors and not by ARBs, while the two types of agents had similar effects on renal outcomes.[232]

Finally, a further application of drugs inhibiting the RAAS is prevention of type 2 diabetes itself as a basis for reducing related cardiovascular events. Traditional antihypertensive drugs such as diuretics or β-blockers may impair glucose tolerance and induce or worsen insulin resistance, although with the exception of carvedilol and nebivolol whose metabolic profiles appear acceptable.[233,234] In contrast, RAAS inhibitors show favourable effects on

diabetes onset.[62] In a systematic review of ten trials in patients with hypertension or congestive heart failure (two trials), both conditions conferring a high risk of developing diabetes, ACE inhibitors and ARBs were associated with an average reduction of 22% of new cases of type 2 diabetes, a figure that was highly significant given the large number of patients involved (>36 000).[235] These data were confirmed in a further, recent meta-analysis[236] that identified 13 eligible trials including >31 000 patients. The relative risk of new-onset diabetes was reduced significantly by 20% in patients treated with an ACE inhibitor or ARB, and the results were consistent in all studies. Finally, in the recent ASCOT study,[237] the combination of amlodipine plus perindopril was associated with fewer cases of new-onset diabetes than the combination atenolol plus a thiazide drug.

The impact of these observations has only in part been attenuated by the less assertive results in the ACE-inhibitor arm of the recent DREAM study: in >5000 individuals without cardiovascular history but with impaired glucose tolerance, ramipril did not reduce onset of new cases of diabetes and did not prevent death from any cause. However, patients in the ramipril group who were moderately hyperglycaemic were more likely to regress to normoglycaemia.[238] A recent systematic review including 22 trials with 143 000 participants showed that given the odds ratio (OR)[4,239] for incident diabetes during diuretics, the lowest ORs are those for sartans (0.57) and ACE inhibitors, while the ORs for calcium channel antagonists and β-blockers are intermediate.

In summary, antihypertensive drugs are an essential component of the therapeutic management of the patient with diabetes, especially of type 2 diabetes. The goals of antihypertensive treatment are as follows:

1. Lowering blood pressure down to levels close to 130/80mm Hg to obtain a meaningful reduction of major cardiovascular events and to inhibit evolution of microvascular changes. This goal can be achieved, essentially with ACE inhibitors or ARBs, but use of thiazide diuretics and/or carvedilol or nebivolol is acceptable, especially in initial phases or special circumstances.
2. Prevention and delay of progression of microalbuminuria and renal damage in diabetic patients, pursued independently of baseline albuminuria, blood pressure and renal function. These goals can also be achieved with ACE inhibitors and ARBs, although the effects of these agents on albuminuria are more robustly supported than those on renal damage. In diabetic nephropathy, a reduction in mortality has been attributed to ACE inhibitors in a meta-analysis,[232] although this has not been reproduced overall in trials.
3. Prevention of onset of new cases of type 2 diabetes in conditions at high risk of developing this metabolic disturbance, such as severe hypertension, heart failure and other cardiovascular conditions. This action is also validated by a meta-analysis and by many, but not all, related clinical trials.[236]

5.5 Perspectives on New Drugs

Novel agents with original mechanisms of action are being developed and tested, in particular, in the prevention and treatment of diabetic nephropathy.[240] Among them, pyridoxamine, a vitamin B_6 derivative, is an inhibitor of AGE formation; another compound, alagebrium chloride, works by breaking down AGE cross-links. Ruboxistaurin acts as an inhibitor of protein kinase C with the aim of preventing protein kinase-induced tissue injury and proliferative changes. These agents demonstrated renal protective properties in experimental models and in phase II clinical studies, and will soon undergo phase III trials with clinical endpoints such as renal failure, cardiovascular events and mortality.[240]

A metabolic drug, propionyl-carnitine, under specific investigation for the treatment of type 2 diabetes-associated PAD, could induce amelioration of the oxidative stress profile, and improvements in walking distance and the ankle-brachial index.[241] Quite recently, long-term C-peptide administration in patients with type 1 diabetes and early peripheral neuropathy was found to significantly improve sensory nerve function.[242]

6. Conclusions

Prophylaxis of cardiovascular complications and events is obviously one of the primary goals of diabetes care.

As most major cardiovascular events in diabetes are atherothrombotic in nature, the use of antithrombotic and especially antiplatelet agents deserves high consideration. Aspirin, although recommended by official bodies, seems to be less effective in diabetic than in nondiabetic patients. Some recent data suggest that a direct TXA inhibitor such as picotamide may be more effective than aspirin, and further studies with agents of this class are warranted. Among thienopyridine compounds, clopidogrel showed partly conflicting results according to different clinical settings and was not always able to effectively control platelet hyperactivity in the diabetic patient.

Recent data suggest that some GAG compounds, such as sulodexide, are able to reduce albuminuria in diabetic nephropathy and exudates in diabetic retinopathy; however, no data are available on their effect on the natural history of renal and retinal damage.

Regarding abatement of risk factors, dietary measures are effective in counteracting the transition from obesity to metabolic syndrome and type 2 diabetes. However, the efficacy of diet alone in the prevention of cardiovascular events in patients with overt diabetes is doubtful. Among lifestyle modifications, physical exercise and cessation of smoking have a crucial role, especially in prevention of stroke and critical limb ischaemia and amputation, in diabetic as well as in nondiabetic patients.

Control of hyperglycaemia is essential in limiting the severity of microangiopathy, but does not seem sufficient to induce a reduction of major vascular events. The latter goal requires a global approach to the complex of diabetes-associated risk factors.

In the control of hyper- or dyslipidaemia, statins have gained a central role in preventing major cardiovascular events regardless of baseline lipid levels and cardiovascular status. A new class of agents acting on insulin resistance, the glitazones, may have an auxiliary role in this respect.

Tight control of hypertension is essential in preventing macro- and micro-vascular events and complications, and some drug classes such as ACE inhibitors and ARBs are also effective in preventing and reducing albuminuria, limiting renal damage and the occurrence of new cases of diabetes in patients at risk.

Further case studies with current and novel agents and combinations are warranted in the search for an effective way of counteracting fatal and non fatal cardiovascular complications, and the severe outcomes of diabetic nephropathy and retinopathy, such as end-stage renal failure and blindness.

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