Prevention of the Complications of Diabetes

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Abstract

For patients with diabetes mellitus (DM), chronic complications can be devastating. Cardiovascular illness, the major cause of morbidity and mortality among these patients, encompasses macrovascular disease, with heart attacks, strokes, and gangrene; and microvascular disease, with retinopathy, nephropathy, and neuropathy (somatic and autonomic). Macrovascular events occur earlier in individuals with DM than in people without DM, and the underlying pathologies are often more diffuse and severe. Diabetic arteriopathy, which encompasses endothelial dysfunction, inflammation, hypercoagulability, changes in blood flow, and platelet abnormalities, contributes to the early evolution of these events. Efforts are under way to determine interventions that may have the potential to prevent or halt the complications of DM. Tight glucose and blood pressure (BP) control is known to improve the vascular status of patients with DM by varying degrees. Use of anti-inflammatory drugs and lowering low-density lipoprotein cholesterol (LDL-C) levels are also useful. An emerging understanding of the importance of small, dense LDL-C and the anti-inflammatory effects of statins has provided new algorithms for primary prevention of macrovascular disease. Antiplatelet agents have also been shown to be effective in the secondary prevention of cardiovascular events. In the ideal world every risk factor would be addressed and each person with DM would have excellent glycemic control, low to normal BP, and a low LDL level, and would be taking an angiotensin-converting enzyme (ACE) inhibitor, together with a statin, aspirin, and clopidogrel. Under these near-perfect conditions, the emerging epidemic of macrovascular disease could be contained. Microvascular disease, however, is a consequence of hyperglycemia. For every 1% reduction in glycosylated hemoglobin it is possible to achieve a 22% to 35% reduction in the microvascular complications. BP control is vital and the liberal use of ACE inhibitors and angiotensin receptor blockers to slow the progression of renal disease should drastically reduce the incidence of blindness, dialysis, and amputations.

This article provides an overview of prevention of macrovascular disease such as stroke, myocardial infarction, and peripheral arterial disease and microvascular complications such as retinopathy, nephropathy, and neuropathy in patients with DM.

(Am J Manag Care. 2003;9:S63-S80)

The prevalence of diabetes mellitus (DM) worldwide has reached epidemic proportions. From recorded numbers of 120 million people with DM in 1997, estimates indicate an increase to >200 million by the year 2010. Indeed, in Asia every 1% increase in the prevalence of DM translates to 10 million new cases.[1] The dysmetabolic syndrome is an early and common manifestation preceding frank DM. The dysmetabolic syndrome includes central obesity, hypertension, insulin resistance (with or without diagnosed type 2 DM), atherogenic dyslipidemia, and a procoagulant state. According to the National Cholesterol Education Program (NCEP)[2] the dysmetabolic syndrome is characterized by 3 or more of the following findings:

Waist: men, >102 cm; women, >88 cm
Hypertriglyceridemia: ≥150 mg/dL
High-density lipoprotein (HDL):
men, <40 mg/dL; women, <50 mg/dL
Hypertension: ≥130/85 mm Hg
Fasting blood glucose level: ≥110 mg/dL.

Therapeutic efforts on behalf of such patients should be initiated well before their first major vascular event and before the

Table 1. Major CHD Event Reduction in Patients With Diabetes or the Metabolic Syndrome in the Scandinavian Simvastatin Survival Study

Patient Group	Placebo Event Rate (%)	Reduction in CHD Events (%)	n
All patients entered into study*	28	34	4444
Metabolic syndrome†	35.9	52	458
Diabetes‡	51	55	202

CHD indicates coronary heart disease.
**Source:* Reference 5.
†*Source:* Reference 6.
‡*Source:* Reference 7.

advent of DM. The Diabetes Prevention Program[3] and the Finnish Diabetes Prevention Study[4] established that a program consisting of dietary reduction of caloric consumption each day, a modest reduction of 5% to 7% of initial body weight, and exercising about 30 to 60 minutes 3 to 5 times per week prevents the progression from impaired glucose tolerance to DM. A subanalysis of the Scandinavian Simvastatin Survival Study (4S) clarified that the dysmetabolic syndrome is a forerunner to macrovascular disease and intervention at this stage yields a success rate equivalent to that with established diabetes (**Table 1**).[5-7]

Once DM is established, patients have a high frequency of atherosclerosis (macrovascular disease), leading to increased risk of stroke and/or heart attack. Individuals with DM are 2 to 4 times more likely to die from heart disease than people without DM, and cardiovascular disease is responsible for 80% of diabetes-related deaths; a person with DM is 2 to 4 times more likely to have a cerebrovascular accident than someone without DM.[1] These are not the only complications of DM. Diabetic microvascular complications are most commonly manifested in the eyes, kidneys, and nerves. Indeed, DM is the leading cause of new cases of blindness in adults between the ages of 20 and 74 years.[8] After 15 years of DM, 2% of patients become blind and 10% develop severe visual disability due to retinopathy and macular edema.[8,9]

DM is now the leading cause of nephropathy and end-stage renal disease (ESRD). It accounts for about 35% to 40% of new cases of ESRD. People with DM make up the fastest-growing group of renal dialysis and transplant recipients. DM is the leading cause of nontraumatic lower-extremity amputations, accounting for 50% of amputations in the United States. About 60% to 70% of people with DM have some degree of diabetic nerve damage.[9]

DM complications are costly. Whereas the cost of treating uncomplicated DM is >$6 billion per year in the United States, chronic complications comprise the largest portion of the economic impact of DM. The highest costs associated with DM result from treating the long-term chronic conditions associated with vascular complications. These serious disorders include retinopathy, nephropathy, peripheral neuropathy, and an increase in atherosclerotic disease, which is associated with an increased risk of stroke and heart disease. Altogether, these direct medical costs of DM totaled $44.1 billion in the United States in 1997; total annual expenditures amounted to $10 071 per person with DM.[10] According to the American Diabetes Association (ADA), "the economic burden of diabetes is substantial and disproportionate to the number of people affected." As a result, the group concluded in 1998 that "medical, technical, behavioral, and public health and policy changes and innovations that can delay the onset or slow the progression of diabetes have tremendous potential to mitigate the costs associated with the disease."[11]

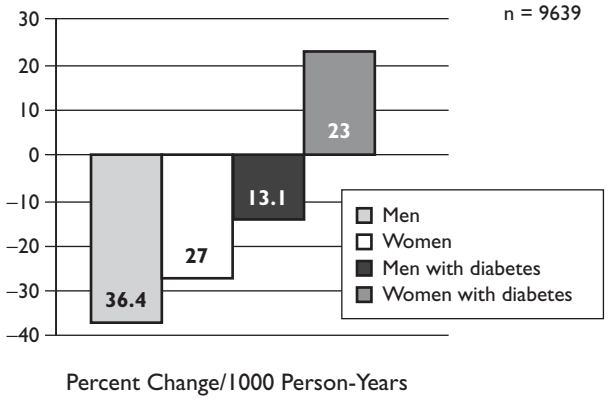
Epidemiology of Diabetic Complications

An estimated 17 million Americans have DM.[11] The majority of these (90%) have type 2 DM, and this proportion can be expected to rise.[12] Aging, obesity, and a sedentary lifestyle all synergize to increase insulin resistance. As the population ages and gains more weight, the prevalence of type 2 DM will rise. Perhaps the greatest explosion in the incidence of DM is the 300 000 new cases annually of type 2 DM in children and is our third leading cause of

death. Much of this mortality is related to macrovascular rather than microvascular disease, because in the United States renal dialysis is universally available. The First National Health and Nutrition Examination Survey (NHANES I) (**Figure 1**),[13] which has followed 9639 subjects for 30 years, has shown an overall decline in mortality from cardiovascular disease (CVD) of 36.4% in men without diabetes, whereas men with diabetes have enjoyed less than one third of this benefit. Even women without diabetes have had a decrease in CVD of about 27% in contrast to women with diabetes who had an increase of 23%.

Women with diabetes are at a higher risk for cardiovascular complications than those without diabetes. A man with diabetes has a 2.5-fold increased risk of a macrovascular event, but a woman with diabetes has a 5-fold increase.[14] The San Antonio Heart Study[15] too has shown that men with diabetes have a similar risk of having a myocardial infarction (MI) as men without diabetes who have already had an MI. Thus, all patients with diabetes ought to be treated as if they already had an MI when first seen. Emerging data from epidemiological studies regarding risk factors dictate an aggressive approach to prevention and management of this patient population.

Figure 1. Changes in Age-Adjusted Heart Disease Mortality in the 30-Year Follow-Up of NHANES I



NHANES I indicates the First National Health and Nutrition Examination Survey.
Source: Reference 13.

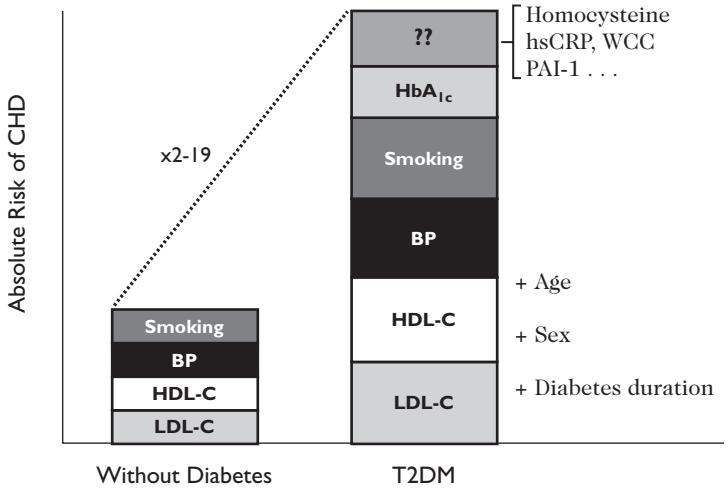
Macrovascular Disease

Risk Factors. The metabolic milieu of DM is particularly conducive to progression of accelerated atherosclerosis. This constellation of atherogenic dyslipidemia comprising oxidized and small, dense low-density lipoprotein (LDL), hypertriglyceridemia, and reduced HDL is a signature abnormality of DM. However, nearly half of all individuals with diabetes are also hypertensive, most are obese, have impaired glucose tolerance, and are insulin resistant. Although each risk factor conveys an increase in susceptibility to CVD, this overall constellation is particularly lethal (**Figure 2**). Each factor alone confers from a doubling to a 4-fold increase in risk; but the occurrence of multiple factors in the same individual increases the risk 19-fold.[16] Thus, the patient with diabetes is a walking time bomb for a heart attack. This situation is further compounded by the identification of new and emerging risk factors for CVD (**Table 2**).

Endothelial Dysfunction. Central to the barrier against atherosclerosis is the endothelium lining the blood vessels. The endothelium is equivalent in area to 3 tennis courts and is the largest endocrine organ in the body. It produces the important vasodilators nitric oxide (NO) and prostacyclin (also known as PGI_2), and is also a source of the most potent vasoconstrictors endothelin and angiotensin II.

Optimum dilation of the blood vessels is based on the balance between vasoconstriction and vasodilation. Cholinergic input into the endothelial cell activates NO synthase, increasing production of the vasodilator NO from its precursor arginine. Disordered endothelium allows acetylcholine to act on a smooth muscle muscarinic receptor causing vasoconstriction, thereby explaining the apparent paradox. Thus, the endothelial lining of blood vessels constitutes a barrier against atherosclerosis for a multitude of reasons including a smooth thromboresistant surface—one that discourages platelets and white cell adherence—and an impermeable layer that stubbornly rejects the transport of LDL-cholesterol and secretes

Figure 2. Risk Factors for Coronary Heart Disease



BP indicates blood pressure; CHD, coronary heart disease; HbA_{1c}, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PAI-1, plasminogen activator inhibitor-1; T2DM, type 2 diabetes mellitus; WCC, white cell count.

vasodilatory and antiplatelet humors, thereby combating the atherogenic process.

Functional changes occur earlier in the evolution of diabetic arteriopathy and are closely allied to dysregulation of endothelial NO.[17-19] NO is synthesized from l-arginine by NO synthase in all vascular beds and was more descriptively known as endothelial-derived relaxing factor. NO, as a direct vasodilator, exerts its effect independent of endothelial integrity. Indirect vasodilators, like acetylcholine, exert a paradoxical vasoconstrictor response when exposed to diseased endothelium. NO also inhibits platelet–vessel wall interaction, thereby functioning as an anticoagulant. Not only is endothelial NO expression and production reduced in diabetes but also in the setting of insulin resistance, before the development of diabetes. Thus in insulin-sensitive states, insulin is vasodilatory, probably related to NO production, whereas this fails to occur in the insulin-resistant state. Resistance to insulin impairs its ability to stimulate NO and prostacyclin production and action.

Table 2. Newly Recognized Risk Factors for Cardiovascular Disease

- Metabolic syndrome
- Endothelial dysfunction
  - —Enhanced vasoconstriction
  - —Defective vasodilation
  - —Prothrombotic factors
  - —Proinflammatory factors
  - —Oxidative stress
  - —Raised homocysteine levels
- Impaired fasting glucose
- Subclinical atherosclerosis

Hypercoagulability. Alterations in coagulation, fibrinolysis, and platelet function define the hypercoagulable state and are found in DM. Patients with DM have lower antithrombin III activity,[19,20] which would provide less of a mechanism to neutralize thrombin. Patients with DM have an acquired protein C deficiency, which, by not neutralizing activated factors V and VIII, would ensure hypercoagulability. Lastly, contact activation (intrinsic pathway) is enhanced in patients with DM with increased levels of kallikrein, factors XII, XI, and VIII, and von Willebrand factor.[21]

Fibrinolysis is stimulated by plasminogen activators and inhibited by antagonists, of which plasminogen activator inhibitor–1 (PAI-1) is the most important. PAI-1 is elevated both in states of insulin resistance and with hypertriglyceridemia and is a further reason for the hypercoagulable state of DM.[22] Platelets are small, anucleate, discoid cells that circulate in the bloodstream and participate in hemostasis.[23] Their main function is to plug holes in blood vessel walls. Platelets do this by undergoing a change in shape, adhering to subendothelial surfaces, secreting the contents of intracellular organelles, and aggregating to form a thrombus in response to stimuli generated in endothelia of damaged blood vessels. These proaggregatory stimuli include thrombin, collagen, and epinephrine (which are exogenous to the platelet) and agents such as adenosine diphosphate (ADP), which is secreted from platelet storage granules, and thromboxane A_2 (TxA_2),

which is synthesized by the platelets during activation.

DM is associated with miscellaneous platelet abnormalities, which act in concert to increase hypercoagulability. Both increased adhesion and spontaneous aggregation[24,25] are seen. Possible reasons include hypersensitivity to ADP and increased TxA_2 generation from arachidonic acid.[26,27] In addition, there is decreased membrane fluidity of platelets, perhaps related to glycation and perturbed lipid composition.[28,29]

Increased platelet activity and an increased tendency for thrombus formation occur in atherosclerosis, heart disease, hypertension, and DM. An evolving concept is that enhanced platelet activity may not only derive from procoagulant activity but also from unbridling platelet hyperfunction secondary to loss of the restraining action of the antiaggregatory mechanisms. It appears that central to this loss of containment of the platelet and its interaction with vessel endothelium is the resistance to the inhibitory action of insulin coupled with defective endothelial production of the antiaggregatory agents, NO and PGI_2.[8] Abnormalities may occur in potentially all the mechanisms regulating platelet function discussed above, involving platelet–agonist interaction, platelet–vessel wall interaction, platelet–platelet interaction, platelet secretion, and platelet–coagulant protein interaction.

Antiplatelet Drugs. Currently available antiplatelet drugs include aspirin, clopidogrel, dipyridamole, and ticlopidine. Although an effective drug, ticlopidine[30] has been associated with severe adverse effects, principally neutropenia and thrombotic thrombocytopenic purpura, thereby limiting its use. Dipyridamole, despite minimal side effects, has only marginal efficacy as monotherapy.[31] For this reason it is infrequently prescribed. The discussion of antiplatelet drugs, therefore, centers on aspirin and clopidogrel, as monotherapy or in combination.

Changes in Blood Flow. Increased fibrinogen and plasma globulins would be expected to increase blood viscosity and promote states of low flow. Immune system activation with increased expression of adhesion molecules further compromise blood flow by making leukocytes "stickier" to increase their binding to the endothelium.[32] Arterial narrowing and roughened intima further compound this DM complication.[33,34] Disturbances in blood flow appear to precede the development of hyperglycemia and are a central or cardinal defect in DM. Various means of studying blood flow have been used to demonstrate these abnormalities. Noninvasive techniques using laser Doppler and measurement of endothelial-dependent blood flow responses to acetylcholine or direct vasodilation using sodium nitroprusside have demonstrated a defect in vasodilation in DM[32,35] and recently in prediabetes and in family members of people with DM.[36,37] The defect may be part of the dysmetabolic syndrome and cosegregates with insulin resistance, hypertension, obesity, and dyslipidemia (**Table 3**).

Inflammation. Recent evidence has stressed the role of inflammation. Indeed, detection of elevated C-reactive protein (CRP) using a highly sensitive assay is a predictor of risk. Furthermore, in the West of Scotland Coronary Prevention Study (WOSCOPS), lipid lowering reduced events by only 25% in patients without inflammation but 54% in those with raised CRP.[38] Abnormalities in lipids (known as the lipid hypothesis) explain risk of CVD in only 25% of people affected. However, the gap may close as more risks are confirmed.

Treating the risk factors for macrovascular disease after devastating MI may appear to have little merit; however, such treatment is important for curbing future CVD events. Although these risk factors will be discussed sequentially, they should be assessed in parallel, because their associated morbidities are multiplicative rather than additive. The ADA and The American College of Cardiology suggest making the link between diabetes, heart disease, and strokes, and recommend keeping glycosylated hemoglobin (HbA_{1c}), blood pressure (BP), and cholesterol levels in the normal range; quitting smoking; being active most days; eating low-fat meals high in fruits, vegetables, and whole grains; and discussing with their healthcare

Table 3. Functional Abnormalities in the Endothelium in Diabetes: Mechanism, Pathogenesis, and Consequences

Function	Mechanism	Abnormality	Result
Permeability barrier	Tight cell junctions	↑ Permeability-delayed regeneration	LDL, mitogens reach subendothelial space
Thromboresistant surface	NO, PGI_2, tPA, heparin sulfate, thrombomodulin	↓ NO, ↓ PGI_2, ↑ PAI-1, ↑ TF	Enhanced thrombosis, impaired fibrinolysis
Block leukocyte adherence	NO	Induction of adhesion molecules (VCAM-1, E-selectin)	Recruitment of macrophages to vascular wall
Regulation of vascular tone	NO, PGI_2, bradykinin, ET-1, A-II	↓ NO, PGI_2, bradykinin ↑ ET-1 A-II, ↑ AGEs	Impaired vasodilation
Secretion of growth inhibitors/cytokines	NO, heparin sulfate, IL-6, TNF	Inactivation of NO, C-reactive protein	↑ VSMC, proliferative activity, ↑ inflammation

AGEs indicates advanced glycation end products; A-II, angiotensin-II; ET-1, endothelin type 1; IL-6, interleukin-6; LDL, low-density lipoprotein; NO, nitric oxide; PAI-1, plasminogen activator inhibitor type 1; PGI_2, prostaglandin (also known as prostacyclin); TF, TNF, tumor necrosis factor; tPA, tissue plasminogen activator; VCAM-1, vascular cell adhesion molecule-1; VSMC, vascular smooth muscle cell.

provider the use of aspirin and other medications to reduce heart attacks and strokes.

Cigarette Smoking. Cigarette smoking is one of the most powerful risk factors for macrovascular disease, and nicotine cessation must be regarded as a behavioral imperative. In epidemiological terms, nicotine should be regarded as the disease, the advertising and tobacco industry as the vector, and the patient as the host. In this model, blaming the patient for becoming "infected" would be futile, as well as implying moral culpability. Partnering the patient in a structured nicotine-cessation program, which includes nicotine substitution (gum or transdermal patches) and/or bupropion will yield the best results.

Hypertension. Hypertension is a well-established risk factor for stroke[39] and contributes to coronary heart disease (CHD) and peripheral vascular disease. The optimal BP in patients with DM is unknown, but both the ADA[40] and the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI)[41] recommend a BP of <130/80 mm Hg. A reasonable goal for BP in patients with DM is 120/80 mm Hg, but this may be difficult to accomplish in patients with critical vascular stenoses. Furthermore, the choice of antihypertensive medication may be of less importance than reaching the target BP.[42] An exception to this rule would be the use of β-blockers with CHD and angiotensin-converting enzyme (ACE) inhibitors with CHD, dilated cardiomyopathy, or proteinuria. The recently published Heart Outcomes Prevention Evaluation (HOPE) study[43] and the MICRO-HOPE substudy[44] make a case for prophylactic ACE inhibition in patients with DM at risk for CVD. Subjects randomly assigned to ramipril (10 mg per day) had a 25% reduction in the combined end points of stroke, MI, and death when compared with placebo. This effect persisted even after adjustment for the changes in BP in the ramipril group. Ramipril also lowered the risk of overt

nephropathy, renal failure, and laser therapy, making the drug ideal for middle-aged people with DM. Ramipril also decreased the rate of conversion of impaired glucose tolerance to DM. These effects were independent of the BP lowering, dictating a need for more aggressive antihypertensive therapy. In the Hypertension Optimal Treatment (HOT) trial the greatest reduction in macrovascular events was found with diastolic BP <80 mm Hg.[45] To achieve this in the population with diabetes requires 3 drugs.[46]

Glycemic Control. Both the Diabetes Control and Complications Trial (DCCT)[47] and the United Kingdom Prospective Diabetes Study (UKPDS)[42] have shown that relatively tight control of DM (HbA_{1c} of approximately 7%) mitigates the microvascular complications of DM. Unfortunately, these studies did not show statistical significance in reducing macrovascular complications, although there was a trend toward better outcomes. There was, however, a significant decrease in macrovascular events in the subset of obese patients receiving metformin.[48] Furthermore, in the Kumamoto study,[49] intensive glycemic control with insulin in Japanese patients with DM reduced the incidence of CVD. Lastly, the level of glycemia targeted may need to be revised. A reanalysis of the Cholesterol and Recurrent Events (CARE) study[50] showed that fasting blood glucose levels between 115 and 126 mg/dL, currently classified as nondiabetic, confer increased susceptibility to macrovascular disease. Separating microvascular from macrovascular complications is probably an artificial distinction as both are interlinked. Restated, renal failure (ie, microvascular disease) with its associated hypertension, dyslipidemia, and hyperhomocystinemia would put the patient at increased risk for macrovascular disease. Similarly, autonomic neuropathy increases cardiovascular mortality by inciting dysrhythmias. It would, therefore, be advisable to reduce HbA_{1c} to at least 7%, which would additionally treat the hypertriglyceridemia of uncontrolled DM.

Dyslipidemia. The NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults—Adult Treatment Panel III (ATP III) guidelines[51] target LDL as the prime culprit in atherogenesis. They strongly endorse lowering the LDL level below 100 mg/dL after MI, stroke, peripheral vascular disease, and in people with DM. The wisdom of this recommendation has been proved in large clinical trials,[52-55] particularly in those with DM. For example, the diabetic subgroup in the 4S study had an absolute risk reduction double that of the patients without DM.[6,56] Numerically, this translated to 8 fewer cardiovascular events per 100 patients over 5 years when patients with diabetes treated with simvastatin were compared with similarly treated patients without diabetes.

Although statins are regarded as the drugs of first choice to treat the dyslipidemia of DM, gemfibrozil was shown to be equally effective in one study. The cohort of patients with diabetes in the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention trial had a 24% reduction in cardiovascular events when gemfibrozil was compared with placebo. This study was a secondary prevention trial in patients with confirmed coronary artery disease (CAD), "normal" LDL cholesterol (<140 mg/dL) but low HDL cholesterol levels (<40 mg/dL).[57] Prevention and treatment of risk factors for macrovascular complications of diabetes are outlined in **Table 4.**[5,58,59]

Aspirin. The ADA position statement[60] recommends the use of 81 mg to 325 mg of enteric-coated aspirin for secondary prevention in all people with DM with established macrovascular disease. The ADA also gives consideration to using aspirin for primary prevention in people with DM at high risk for macrovascular disease. This recommendation may be too conservative, as all people with DM should be regarded as evolving vascular calamities. The rationale for using aspirin is firmly embedded in the literature. The Physicians Health Study[61] showed that aspirin reduced the risk of MI by 44% in those over the age of 55 years. Effects on stroke and cardiovascular death remain inconclusive. Both the Antiplatelet Trialists' Collaboration[62] and the Early Treatment Diabetic Retinopathy Study[63]

Table 4. Prevention and Treatment of Macrovascular Complications of Diabetes

Risk Factor	Prevention/Treatment Strategy
Smoking	Cessation
Hypertension	BP ≤130/80 mm Hg
Dyslipidemia	LDL <100 mg/dL HDL (men: >45 mg/dL; women: >55 mg/dL) Triglycerides <150 mg/dL
Hyperglycemia	HbA_{1c} <7%, or as low as possible without dangerous hypoglycemia
Hypercoagulability/ inflammation	Antiplatelet drugs (eg, aspirin, clopidogrel, combinations), statins
Dysmetabolic syndrome/obesity	Weight loss as indicated using diet and exercise
Micro- or macroalbuminuria	Lifestyle changes or ACE inhibitors and ARBs
Atherosclerosis/CAD	Angioplasty, CABG, transplant

ACE indicates angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Source: References 5, 58, 59.

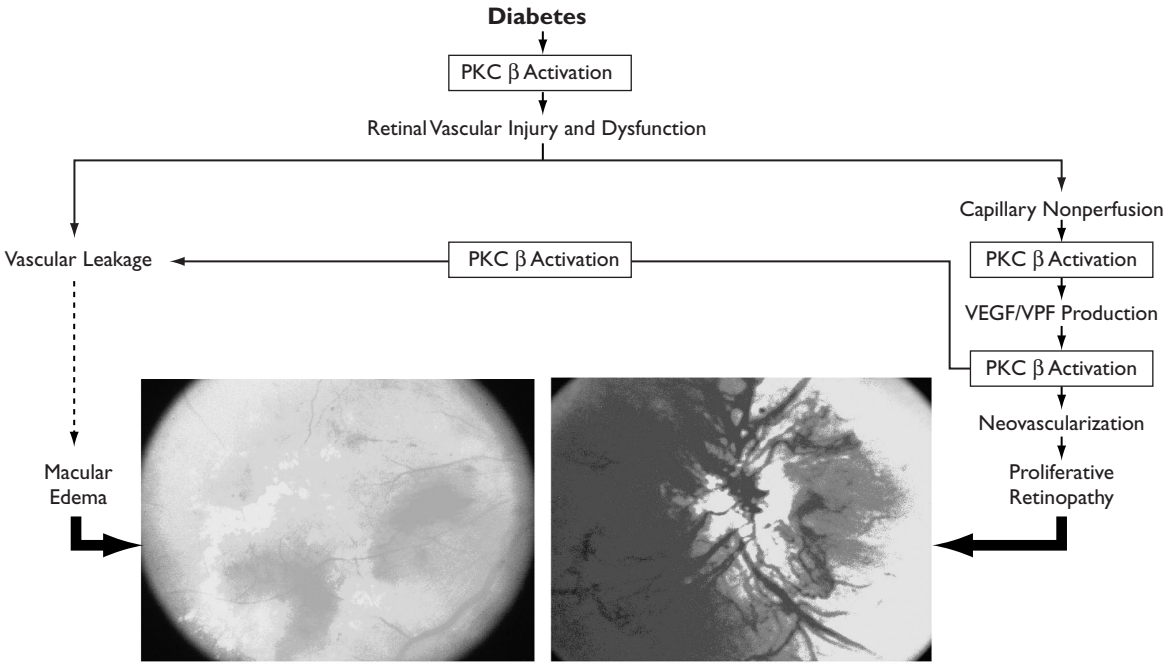
found that patients with DM using aspirin either had a reduction in the incidence of MI or reduced the risk of having a vascular event to levels approaching those of patients without DM. Although the benefits of aspirin are almost common knowledge, it is still underutilized. Studies[64,65] estimate that between 25% and 75% of patients at risk for ischemic events are not taking the drug. In the setting of MI, aspirin decreases mortality by about 25%, which is similar to the benefit obtained from thrombolytic agents. It should be regarded as a serious clinical omission for individuals with chest pain not to have aspirin prescribed. Nearly 50% of patients with angina are not being prescribed aspirin.[66] The use of aspirin has no real limitations other than allergy. Although certain investigators[65] have shown that patients having coronary events while on aspirin have worse outcomes than those not receiving the drug, this finding should not dissuade physicians from its use. Reasons for the unfavorable outcomes are uncertain, but the most likely explanation is that if aspirin cannot prevent an MI, CAD is severe and widespread. Adverse drug reactions to aspirin are well known and mostly related to excess bleeding.

Clopidogrel. Clopidogrel is a thienopyridine derivative that irreversibly inhibits platelet aggregation induced by ADP and is the only drug approved for use in all 3 vascular beds as secondary prevention in high-risk patients, including patients with DM. The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study showed that clopidogrel was safer and more efficacious than aspirin.[67] Overall, there was a relative 8.75% risk reduction for the combined end points of stroke, MI, or vascular deaths.

In the cohort of patients with diabetes in CAPRIE, the investigators noted a nonsignificant trend toward improved macrovascular end points (P = .042).[68] Side effects were less common with clopidogrel than with aspirin. Significantly less gastrointestinal bleeding was seen with clopidogrel (1.99% vs 2.66%; P < .002). Clopidogrel is more expensive than aspirin.

Combination Antiplatelet Therapy. A uniting principle in contemporary drug therapy is to sequentially target pathophysiological derangements with drugs in submaximal dosages rather than to use maximally tolerated monotherapy. Combining a drug that inhibits cyclooxygenase (aspirin) with one that inhibits ADP (clopidogrel) could be expected to give additive results. Both in animal and human models, in vivo and in vitro aspirin and clopidogrel have been shown to have synergistic effects.[69-72] Quantitatively, a meta-analysis of randomized trials found a 77% reduction in platelet thrombosis (P < .001) when this combination was compared with aspirin alone.[73] The Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS),[72] which compared clopidogrel and aspirin with ticlopidine and aspirin, found the former combination of clopidogrel and aspirin to be safer. Adverse drug reactions occurred more commonly with ticlopidine than with clopidogrel (9.1% vs 4.6%; P = .005).

Figure 3. Pathogenesis of Diabetic Retinopathy



PKC indicates protein kinase C; VEGF, vasoactive endothelial-derived growth factor; VPF, vascular permeability factor.

Major cardiac events were similar in both groups, although this study was not powered to detect differences in efficacy.[74]

Another vindication for combination therapy is the European Stroke Prevention Study-2 (ESPS-2),[75] which concluded that the additive benefit of dipyridamole (200 mg bid) and aspirin (25 mg bid) was synergistic in preventing stroke, producing highly significant benefits.

Microvascular Disease

Retinopathy. Today diabetes is the leading cause of blindness in the developed world. The pathogenesis of retinopathy has become better understood in recent years and is shown in **Figure 3,** which illustrates the pathogenesis and changes in the retina that comprise diabetic retinopathy. Diabetic eye disease, caused by retinal vascular damage, is the leading cause of new blindness in adults aged 20 to 74 years (up to 24 000 new cases annually). It is typically categorized as follows:

- *Nonproliferative retinopathy*—Microaneurysms and other retinal lesions.
- *Proliferative retinopathy*—Growth of abnormal blood vessels and fibrous tissue from optic nerve head or inner retinal surface.
- *Macular edema*—Fluid leakage from blood vessels that causes macular swelling.[76,77]

Retinopathy is strongly related to diabetes duration: after 20 years, almost all patients with type 1 DM have retinopathy, as do ~60% of patients with type 2 DM (about one fifth of type 2 DM patients have some degree of retinopathy at diagnosis).[77-79]

Prevention of diabetic retinopathy no doubt rests with tight glycemic control. The DCCT[80,81] and UKPDS[42] demonstrated that lower HbA_{1c} levels reduce retinopathy risk and slow its progression. The major finding of the DCCT showed that a >27% reduction in the progression of diabetic eye complications could be achieved with intensive glycemic control.[80,81] This intensive therapy decreased the progression of retinopathy by 34% to 76%, depending on disease severity. The decrease in relative risk among patients in the UKPDS undergoing intensive treatment was 21% at 12-year follow-up.[42]

Table 5. Recommended Eye Examinations for Patients With Diabetes

Patient Group	Recommended First Exam	Minimum Routine Follow-up*
Type 1	3-5 years after diabetes diagnosis, once patient is ≥10 years old	Yearly
Type 2	At diabetes diagnosis	Yearly
Pregnancy in preexisting diabetes	Before conception and during first trimester	As indicated, pending results of first-trimester exam

*Abnormal findings dictate more frequent follow-up.
Source: Reference 79.

New data implicate the benefits of protein kinase C (PKC) and vasoactive endothelial-derived growth factor. Clinical trials are in progress on the use of an inhibitor of PKC. Nonetheless prevention of progression to blindness still rests with aggressive laser therapy carried out by an ophthalmic surgeon.

Because photocoagulation surgery is so effective at preventing vision loss, it is essential—and cost effective—that patients with diabetes should have at least an annual dilated eye exam by an ophthalmologist or optometrist.[40,77,82] Recommendations for eye examinations are outlined in **Table 5.**

In addition to glycemic and BP control, surgical procedures also help prevent vision loss (**Table 6**).

Nephropathy. DM is the leading cause of renal failure and transplantation nationwide; 46% of patients with type 1 DM and 10% to 30% of patients with type 2 diabetes will develop microalbuminuria, proteinuria, and ESRD secondary to diabetes.[9] The major pathogenetic factors are hyperfiltration thought to be due to the increased osmolar load, hypersecretion of glucagon and other vasoactive peptides, and intrarenal hypertension. These features result in basement membrane thickening, mesangial proliferation, and glomerulosclerosis. Central to the development of intrarenal hypertension is the action of angiotensin.

Figure 4 summarizes the multiple mechanisms by which hypertensive and nonhypertensive insults lead to renal scarring, resulting in loss of nephrons and ultimately to renal failure.[83] Both systemic hypertension and nonhypertensive injury that causes loss of single nephron units result in hypertension in the remaining glomeruli (glomerular hypertension). Glomerular hypertension can lead to injury to the glomerular basement membrane, causing it to leak plasma proteins into the urine. Attempts by the proximal tubules to reabsorb this filtered protein cause injury to the tubular cells, activate an inflammatory response, and are associated with the development of lipid metabolic abnormalities that create further oxidative stress on the already compromised glomerulus. The

Table 6. Surgical Procedures to Prevent Vision Loss

Treatment	Indication
Laser photocoagulation therapy	Severe nonproliferative diabetic retinopathy
Panretinal photocoagulation laser surgery	Eyes approaching high-risk characteristics
Focal photocoagulation laser surgery	Significant macular edema
Vitrectomy	Blood leakage causing vitreous clouding

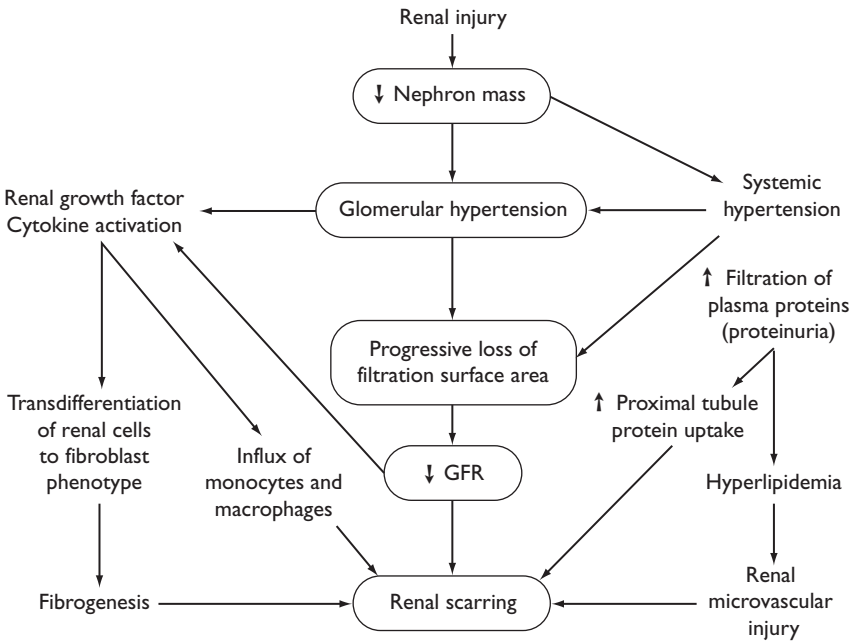
Source: Reference 79.

resultant tubular inflammatory response and renal microvascular injury activate pathways that lead to fibrosis and scarring of both glomerular and tubular elements of the nephron. An additional consequence of glomerular hypertension and resultant reduction in glomerular filtration rate (GFR) activates growth factors and cytokines that promote an influx of monocytes and macrophages into the vessel wall and into the renal interstitium, and also causes the differentiation of renal cells into fibroblasts. Monocytes, macrophages, and fibroblasts are capable of producing those growth factors and cytokines that activate pathways leading to expansion of extracellular matrix, fibrosis, and loss of both tubular and glomerular structures.

Angiotensin II plays a pivotal role in pathological processes in hypertension that ultimately lead to renal glomerular and tubular destruction and renal failure. Angiotensin II, acting either through signal-transducing mechanisms or directly on cells to stimulate the production or activation of mediators, causes infiltration of inflammatory cells and increased production of mesangial and interstitial matrix with resultant glomerular and tubular injury and destruction (ie, nephron loss). The remaining normal nephrons are forced to compensate by increasing filtration rate which, in the presence of greater angiotensin II, increases glomerular capillary pressure and perpetuates this progressive spiral of deteriorating renal function (**Figure 5**).[84]

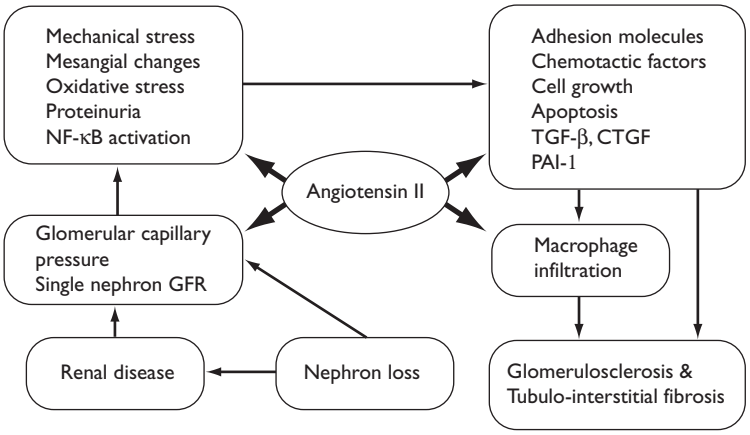
Nephropathy develops in about 20% to 30% of patients with type 1 or type 2 diabetes according to the ADA, but a much smaller number of patients with type 2 diabetes progresses to ESRD.[5] Therapy for diabetic nephropathy is not curative; renal disease may progress despite current, adequate management. Microalbuminuria, the earliest clinical evidence of diabetic nephropathy, is associated with a 10-fold increase in the risk of progression to overt nephropathy and eventual ESRD. More than 50% of patients starting dialysis have type 2 DM. Unfortunately, the prevalence of DM is increasing at an alarming rate. Therefore, new therapeutic advances in the prevention

Figure 4. Pathways Leading to Progressive Renal Failure



GFR indicates glomerular filtration rate.
Source: Reference 83.

Figure 5. Role of Angiotensin II in Chronic Renal Disease



CTGF indicates connective tissue growth factor; GFR, glomerular filtration rate; NF-κB, nuclear factor kappa B; PAI-1, plasminogen activator inhibitor-1; TGF-β, transforming growth factor-beta.
Source: Reference 84.

and treatment of diabetic nephropathy are needed.

ACE inhibitors have been shown to[85,86]:

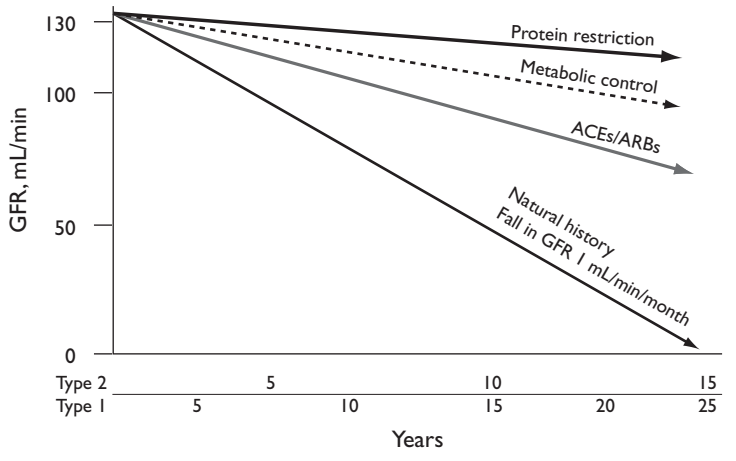
- Decrease the production of angiotensin II
- Decrease intraglomerular pressure by dilating the efferent arteriole
- Prevent glomerular hypertrophy
- Reduce proteinuria and microalbuminuria
- Slow rate of decline of GFR

ACE inhibitors have been studied extensively in humans with diabetes and animal models. Accumulated data indicate that ACE inhibitors have no adverse effects on glucose control, insulin sensitivity, or lipid metabolism.

Ravid and colleagues[87] were the first to observe that ACE inhibitors could stabilize microalbuminuria and prevent the progression of renal disease in patients with diabetes. Viberti et al[88] conducted a double-blind, placebo-controlled trial on 408 patients with type 1 diabetes with proteinuria of >500 mg/day; 206 were given captopril and 202 were given placebo and were followed for 3 years. Captopril protected against deterioration of renal function in type 1 diabetes and the effect was greater than that achieved by placebo. Captopril slowed the increase in creatinine and the decrease in creatinine clearance. The Euclid study[89] was a randomized, placebo-controlled trial of lisinopril in normotensive patients with type 1 diabetes and normoalbuminuria or microalbuminuria. Lisinopril slowed the progression of renal disease in normotensive type 1 diabetes patients with little or no albuminuria. The greatest effects were seen in patients with microalbuminuria. Three major studies—the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study,[83] the Irbesartan Microalbuminuria Type 2 Diabetes in Hypertensive Patients (IRMA II) study,[90] and the Irbesartan in Diabetic Nephropathy Trial (IDNT)[91]—were all published in the September 20, 2001, issue of *The New England Journal of Medicine.* Each trial of 2 to 3 years' duration showed that selective angiotensin receptor blocker (ARB) type 1 is effective in reducing the progression of renal disease in patients with type 2 diabetes and high BP. Standard care for diabetes was maintained. Using conventional high BP therapy such as diuretics, β-blockers, and calcium channel blockers (but no ACE inhibitors or other ARBs), BP control was similar in the placebo and in the ARB-treated groups. Thus, the concept has emerged from these 3 trials that ARBs protect the kidney independent of BP reduction.

It has now been established that the combination of an ACE and an ARB yields

Figure 6. Slowing Progression of Diabetic Nephropathy



ACEs indicate angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; GFR, glomerular filtration rate.

Table 7. Steps for Preventing Renal Disease

Treatment Goal	Strategy	Special Considerations
Optimize glycemic control (target HbA_{1c} <7%)	Lifestyle modifications, oral agents, insulin	Adjust glycemic targets for the individual patient.
Optimize blood pressure control (target 130/80 mm Hg); treat microalbuminuria irrespective of hypertension	Lifestyle modifications, ACE inhibitors and/or ARBs	ACE inhibitors are initial choice in type 1 patients; ARBs are the initial choice in type 2 patients. Combination therapy may decrease albuminuria more than either drug used alone. In some patients (or for those in whom these drugs are contraindicated) β-blockers, calcium channel blockers, or diuretics may be added alone or in combination.
Restrict protein intake	No more than 0.8 g/kg body weight per day (or ~10% of daily calories)	Further restriction may help slow GFR decline in some patients.
Correct dyslipidemia (target LDL <100 mg/dL)	Lifestyle modifications, pharmacotherapy	This factor appears more closely related to overall metabolic control than to nephropathy risk per se, but is linked to CV risk.

ACE indicates angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CV, cardiovascular; GFR, glomerular filtration rate; HbA_{1c}, glycosylated hemoglobin; LDL, low-density lipoprotein.

greater effects on proteinuria than either agent alone and that these can be used in incipient renal failure with creatinine levels as high as 3.0 mg/dL.[92]

The normal rate of decline of creatinine clearance is 1 mL/min per month (**Figure 6**). With a combination of an ACE inhibitor and an ARB, control of BP, and appropriate intake of protein, this rate can be slowed to around 0.2 mL/min per month and 80% reduction in the rate of progression of renal disease. Despite all this knowledge, attempts at slowing the progression of diabetic nephropathy using established treatments for maintaining renal function remain woefully underutilized. Clinicians and healthcare systems should be encouraged to make use of the treatments and drugs that inhibit the renin-angiotensin-aldosterone system to slow the progression of renal disease. Recommendations for the prevention of renal disease are presented in **Table 7.**

Neuropathy. Diabetic neuropathy is a heterogeneous disease with many subtypes. It is the most common complication of diabetes and affects up to 70% of patients with diabetes.

The following list outlines strategies for the diagnosis of neuropathy:

- *Comprehensive foot exam*—Assess the patient's skin, circulation, and sensation, at least once a year; more frequently when ulcers occur.
- *Physical exam*—Test the patient for muscle strength; reflexes; and sensitivities to vibration, temperature, and touch. Nerve-conduction studies and quantitative sensory and autonomic function tests should be done at the clinician's discretion as symptoms dictate, for research, and as end points in clinical studies.
- *Electromyography*—To determine how well muscles respond to electrical signals from nearby nerves; often done concurrently with nerve-conduction studies.
- *Heart-rate variability*—To assess the heart's response to deep breathing and changes in BP and posture.
- *Ultrasound*—To evaluate the status of internal organs—eg, whether the bladder empties completely with urination.

Table 8. Neuropathy Categories

Neuropathy Type	Body Parts/Systems Usually Affected	Symptoms
Peripheral	Toes, feet, legs, hands, arms	Numbness or insensitivity to pain or temperature Tingling or burning sensations Extreme sensitivity to touch Loss of balance and coordination Muscle weakness
Autonomic	CV system, digestive system, genitourinary system, glycemic regulation, sweat glands, eyes	Postural hypotension and dizziness Increased risk of CV disease and (sometimes silent) MI; cardiac arrhythmias; lack of heart-rate variability; resting tachycardia Fluctuation in blood glucose levels and unawareness of hypoglycemia Sensitivity to temperature extremes Constipation/gastroparesis Diarrhea Difficulty swallowing Decreased sexual response Bladder infections/incontinence Nephropathy Abnormal sweating Difficulty seeing in low light
Proximal	Thighs, hips, buttocks	Pain, weakness in the thighs
Focal	Facial muscles, hands, and feet; pelvis and lower back; thighs; abdomen	Muscle weakness; cranial nerve, median, ulnar, peroneal, and medial plantar nerve pain and palsies; entrapment syndromes (nerve compression) such as carpal tunnel syndrome

CV indicates cardiovascular; MI, myocardial infarction.

Table 9. Treatments for Conditions Related to Diabetic Peripheral Neuropathy

Symptom	Treatment Options
Foot ulcers	Off-loading; debridement; antibiotics; oxygenation; surgery
Pain	NSAIDs; topical capsaicin creams; antidepressants; anticonvulsants; nerve stimulation/electrotherapy; acupuncture
Entrapped nerves	Neutral splinting and rest; NSAIDs; surgery

NSAIDs indicates nonsteroidal anti-inflammatory drugs.
Source: References 59, 93, 94, 96, 97.

- Special tests of autonomic function are carried out in specialized units.

Table 8 lists the body parts or systems affected and the symptoms of neuropathy.[93,94]

Treating diabetic neuropathy, as with most complications of the disease, begins with overall metabolic—and particularly glycemic—control. For example, the DCCT[95] showed that the difference in mean HbA_{1c} between treatment groups (7% vs 9%) slowed the onset and progression of neuropathy by ~60% in patients with type 1 diabetes. However, education and hygienic measures are the single best methods to prevent foot ulcers and amputations.

Peripheral Neuropathy and Foot Care. About 86 000 amputations—half the national total—are performed each year on patients with diabetes due to peripheral neuropathy, and up to 75% of these could be prevented with better foot care.[93] **Table 9** outlines the primary treatment options related to peripheral neuropathy.[59,93,94,96,97]

CONCLUSION

Perhaps the single most important message from this article is that no single component in our treatment arsenal can prevent the complications of diabetes (**Table 10**).[98] This was best exemplified in the Steno-2 intervention study,[98] in which the practitioners attempted to prevent the diabetes complications by controlling BP, lipids, and glycemia, and prescribing liberal use of an ACE inhibitor. What was the result? Nephropathy was reduced by 73%, retinopathy by 55%, autonomic neuropathy by 68%, and cardiovascular events by 46%.[98] The odds ratio of progressing to one of these complications is shown in **Table 11.** A follow-up study was recently published.[99]

Nonetheless, few people follow these treatments, and these reductions are not enough. Huge advances can still be made in preventing macrovascular disease in patients with DM. The literature describes proven therapies that significantly improve both morbidity and mortality in the patient with diabetes-associated vascular compromise. Although for didactic purposes it is convenient to compartmentalize the various therapies, each specialist caring for patients with diabetes should consciously address every risk factor. In the ideal world, each patient with diabetes would have excellent glycemic control, a normal BP, a low LDL-cholesterol, and be prescribed an ACE inhibitor, a statin, aspirin and/or clopidogrel. This strategy is our best hope to contain the emerging epidemic of complications of diabetes.

Table 10. Intensive Multifactorial Intervention in Type 2 Diabetes

Treatment Goal	Standard	Intensive
Systolic BP	<160 mm Hg	<140 mm Hg
Diastolic BP	<95 mm Hg	<85 mm Hg
HbA_{1c}	<7.5%	<6.5%
Triglycerides	<2.2 mM	<1.7mM
TC	<6.5 mM	<5.0 mM
ACE inhibitor regardless of BP	No	Yes
Aspirin with CVD	Yes	Yes
Vitamins C and E	No	Yes

ACE indicates angiotensin-converting enzyme; BP, blood pressure; CVD, cardiovascular disease; HbA_{1c}, glycosylated hemoglobin; TC, total cholesterol.
Source: Reprinted with permission from Gaede P, et al.[98]

Table 11. Odds Ratio of Progression to Complications Associated With Type 2 Diabetes

Complication	Odds Ratio
Nephropathy	0.27
Autonomic neuropathy	0.32
Retinopathy	0.45
Cardiovascular events	0.54

Source: Reference 98.

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