In Brief

Cardiovascular disease (CVD) is a common complication of diabetes; nearly 80% of all people with diabetes will die from macrovascular complications. Dyslipidemia, hypertension, hypercoagulability, poor glycemic control, smoking, obesity, and lack of physical activity are just some of the multiple risk factors responsible for the increased risk of CVD in diabetes. A multi-pronged approach to address these risk factors is imperative. Although nonpharmacological therapy is the cornerstone of treatment, some pharmacological treatments are almost always warranted. These may include statins for dyslipidemia and their pleiotropic effects, tight blood pressure control (especially with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers), antiplatelet therapy, and appropriately tight glycemic control based on comorbidities. Evidence has shown that this approach can reduce the risk of CVD in diabetes but that these strategies continue to be underutilized.

Best Practices for Lowering the Risk of Cardiovascular Disease in Diabetes

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Nearly 80% of people with diabetes will die as a result of cardiovascular disease (CVD). Diabetes is an independent risk factor for CVD, with CVD death rates two to four times higher and stroke risk two to six times greater in adults with diabetes than in adults without diabetes.[1,2] Seven-year follow-up data have shown that people with diabetes but no CVD have the same risk as those who do not have diabetes but who have already had a myocardial infarction (MI). Alarmingly, for people with diabetes who have already had an MI, the risk of a recurrent event is nearly 50%.[3]

The cause of the increased risk of CVD in diabetes is multifactorial. Important factors include dyslipidemia, hypertension, hypercoagulability, poor glycemic control, smoking, obesity, and lack of physical activity, among others. Appropriate interventions to address each of these risk factors are imperative to lowering the risk of CVD in people with diabetes.

The Steno-2 trial, involving subjects with type 2 diabetes and microalbuminuria, randomized subjects to standard, at doctor's discretion, or intensive, with interventions to aggressively treat to goal cholesterol, triglycerides, blood pressure, and provide antiplatelet therapy. Through ~8 years of follow-up, a lower risk of retinopathy, nephropathy, and CVD was noted, and subjects in the intensive treatment group were more likely to meet goals for hemoglobin A_{1c}(A1C), cholesterol, and systolic blood pressure and to take aspirin.[4] At 13.3 years of follow-up, this resulted in a reduction in all-cause mortality, end-stage renal disease, and retinal photocoagulation.[5] Diet, exercise, smoking cessation, and obesity management are also crucial to

reducing the cardiovascular burden of people with diabetes, but the focus of this article is on current best practices with therapeutic drug modalities.

Cholesterol Treatment and Diabetes

Patients with diabetes have lipid abnormalities that place them at a high risk for cardiovascular and cerebrovascular events. Patients with either type 1 or type 2 diabetes have these abnormalities; however, the pattern differs between these populations. Patients with type 2 diabetes typically have elevated triglycerides and decreased HDL cholesterol concentrations, whereas patients with type 1 diabetes typically have triglyceride concentrations lower than those of patients with type 2 diabetes, and their HDL levels are average or even elevated.[6] LDL cholesterol concentrations in patients with diabetes are usually similar to those of the general population; however, the LDL particles in diabetes patients are smaller and more dense, making them more atherogenic than LDL particles in nondiabetic individuals.[7,8]

Research has shown that therapies that positively affect the lipid panel in patients with diabetes will reduce vascular events and mortality. The Multiple Risk Factor Intervention Trial (MRFIT), which involved ~ 360,000 men, showed that for every 38-mg/dl decrease in total cholesterol, there was a 50% decrease in death from cardiovascular causes.[9] A subset of 5,000 men with diabetes in MRFIT showed the same magnitude of benefit, although the absolute risk of coronary death was three to five times higher compared to nondiabetic subjects.[9] Moreover, data from the Cholesterol Treatment Trialists' (CTT) Collaboration have shown that a decrease in LDL of 38 mg/dl reduces the risk of major vascular events by 20% regardless of diabetes status.[10,11] Data from the U.K. Prospective Diabetes Study (UKPDS) also showed a direct relationship between LDL and CVD.[12] Furthermore, the UKPDS also discovered an inverse relationship between HDL and CVD in patients with diabetes.[12]

Hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, popularly known as statins, are associated with reduced vascular events in patients with diabetes (Table 1). The Scandinavian Simvastatin Survival Study (4S) was one of the first trials to show reduced rates of death and major coronary events.[13] The trial demonstrated that a 35% reduction in LDL, a 25% reduction in total cholesterol, and an 8% increase in HDL from baseline with simvastatin therapy reduced the rates of death by 30% when compared to placebo; however, only 5% of the sample in the 4S trial had diabetes.

A subgroup analysis of the Heart Protection Study evaluated the efficacy of simvastatin in 5,963 diabetic adults in the United Kingdom.[14] When compared to placebo, simvastatin, 40 mg daily, decreased major coronary events by 27% ($P < 0.001$), stroke by 24% ($P = 0.01$), revascularization by 17% ($P = 0.02$), and major vascular events (i.e., major coronary events, stroke, and revascularization considered together) by 22% ($P < 0.0001$). All of these reductions in events were similar to the overall high-risk cohort. The benefits of HMG-CoA reductase inhibitors are apparent whether patients with diabetes are treated for primary or secondary prevention.

In a subgroup of the Long-Term Intervention with Pravastatin in Ischemic Disease trial, pravastatin was compared to placebo in 1,077 patients with diabetes and 940 patients with impaired fasting glucose (IFG).[15] All patients had a history of either MI or unstable angina. For the primary combined outcome of CVD death or nonfatal MI, the relative risk reduction (RRR) was 19% (23.4 vs.19.6%, $P = 0.11$). The RRR in the IFG group was 36% (17.8 vs. 11.8%, $P = 0.009$). Pravastatin reduced the risk of stroke by 39% ($P = 0.02$) in the cohort with diabetes and 42% ($P = 0.09$) in the IFG group.

Primary prevention of cardiovascular events with atorvastatin was evaluated in the Collaborative Atorvastatin Diabetes Study (CARDS).[16] A total of 2,838 patients with type 1 or type 2 diabetes were randomized to either atorvastatin, 10 mg daily, (average diabetes duration 7.8 years) or matching placebo (average diabetes duration 7.9 years). All study participants had no history of CVD, an LDL ≤ 157 mg/dl, a fasting triglyceride level ≤ 600 mg/dl, and one of the following: retinopathy, albuminuria, current smoking, or hypertension. This trial was terminated 2 years early because of the efficacy of atorvastatin over placebo. The median duration of follow-up was 3.9 years. Atorvastatin was associated with a 37% reduction in the overall primary outcome (composite of cardiovascular event, coronary revascularization, or stroke). There was a similar reduction in the overall primary outcome regardless of baseline LDL. Although not statistically significant, there was also a survival benefit for patients who received atorvastatin (hazard ratio [HR] 0.73; confidence interval [CI] 0.52–1.01; $P = 0.059$). Patients who received atrovastatin had LDL concentrations 40% lower than those taking placebo. The authors concluded that CARDS strengthened the evidence that use of statin therapy should be more widespread in patients with diabetes, particularly those with type 2 diabetes.

The efficacy of lipid-lowering therapies, particularly statins, in patients with diabetes has been further evaluated in meta-analyses. The CTT Collaboration reviewed 14 trials of statins that included 18,686 patients with diabetes.[11] The mean follow-up for patients in these trials was 4.3 years. The investigators found that for every 38-mg/dl decrease in LDL with a statin, there was a significant 9% ($P = 0.02$) reduction in all-cause mortality. There was also a significant reduction in MI or coronary death (22%; $P < 0.0001$), coronary revascularization (25%; $P < 0.0001$), and stroke (21%; $P = 0.0002$) with statin therapy. Another meta-analysis[17] that included 12 landmark trials of lipid-lowering therapy, mostly statins, evaluated patients with diabetes. The authors evaluated primary and secondary prevention trials in patients receiving statin therapy or gemfibrozil. In the primary prevention cohort, the risk reduction for major coronary events in patients with diabetes was 21% ($P < 0.0001$). In the secondary prevention cohort, the risk reduction for major coronary events in patients with diabetes was a significant 21% ($P < 0.0001$), similar to primary prevention trials.

The American Diabetes Association (ADA) recommends statin therapy for individuals with diabetes and CVD regardless of baseline cholesterol levels.[18] Statin therapy is also recommended for individuals without overt CVD who are > 40 years of age and have one or more other CVD risk factors. The recommended LDL goal for all diabetes patients is < 100 mg/dl. There is also an optional LDL goal of < 70 mg/dl for diabetes patients with overt CVD; however, the data sup-

Table 1: Relative Potencies of Different HMG Co-A Reductase Inhibitors*

Fluvastatin (mg)	Pravastatin (mg)	Lovastatin (mg)	Simvastatin (mg)	Atorvastatin (mg)	Rosuvastatin (mg)	Ezetimibe/ simvastatin (mg)	Approximate Percentage LDL Cholesterol Decrease (%)
20	10	10	—	—	—	—	15–20
40	20	20	5–10	—	—	—	21–29
80 XL	40–80	40	20	10	—	—	30–38
—	—	80	40	20	5–10	10/10	39–47
—	—	—	80	40	20	10/20	48–54
—	—	—	—	80	40	10/40	55–59
—	—	—	—	—	—	10/80	> 59

**Not based on head-to-head comparisons*

porting this optional goal are not as strong.

Safety with statin therapy is a controversial topic; since the voluntary removal of cerivastatin from the market in 2001, there have been concerns about the overall safety of statins. Cerivastatin was removed from the market because of reports of fatal rhabdomyolysis (destruction of skeletal muscle cells). The overall safety of statin therapy is well documented in large clinical trials that show adverse event rates, particularly myopathy, to be comparable to placebo.[14,16,19–22] Meta-analysis was performed on many of these landmark trials to determine the absolute risk of statin-induced adverse events.[23] The analysis included 18 trials with 71,108 patients. There were 36,062 people receiving a statin and 35,046 receiving a placebo. Statin therapy increased the risk of any adverse event by 40% (odds ratio [OR] = 1.4; 95% CI 1.09–1.80; $P = 0.008$) compared with placebo. This equates to treating 197 patients with statin therapy to observe one adverse event (number needed to harm [NNH] = 197). Statins were associated with a 26% reduction in the risk of a clinical cardiovascular event (OR = 0.74; 95% CI 0.69–0.80; $P < 0.001$). This equates to treating 27 patients with statin therapy to prevent one clinical cardiovascular event (number needed to treat [NNT] = 27). Looking at this clinically, a provider treating 1,000 patients with statin therapy would prevent 37 cardiovascular events, and five adverse events would be observed. Serious events (creatine phosphokinase > 10 times the upper limit of normal [ULN] or rhabdomyolysis) are infrequent (NNH = 3,400) and rhabdomyolysis, although serious, is rare (NNH = 7,428). However, many of these trials have a run-in phase in which patients who experience myalgias or adverse events during this time may not be reported.

This raises the question: what proportion of patients started on statin therapy experience myalgias/myopathies/rhabdomyolysis in clinical practice? Several studies have tried to answer this question using varying study designs. A study was performed that reviewed statin-associated rhabdomyolysis using the adverse event reporting system (AERS) employed by the U.S. Food and Drug Administration (FDA).[24] Investigators reviewed incidence rates with atorvastatin, simvastatin, pravastatin, and cerivastatin. Data included incidence rates of hospitalized rhabdomyolysis among statin users from a population-based study, as well as reported AERS cases and national estimates of statin use from an AERS analysis. It was found that the extent of reporting differed by statin (atorvastatin, 5.0%; cerivastatin, 31.2%; simvastatin, 14.2%; all four combined, 17.7%; and non-cerivastatin statins combined, 9.9%). The AERS cases for cerivastatin increased significantly from 14.8 to 35% after the release of a Dear Health Care Provider letter warning of the danger of fatal rhabdomyolysis. The authors concluded that incident reporting may have been influenced by publicity, particularly with cerivastatin.

Another study conducted by the FDA reviewed claims data from 11 managed care health plans across the United States.[25] The study objective was to estimate the incidence of rhabdomyolysis in patients treated with different statins and fibrates, alone and in combination, in the ambulatory setting. The investigators reviewed 252,460 patients treated with lipid-lowering agents and found 24 cases of hospitalized rhabdomyolysis that occurred during treatment. In absolute terms, the investigators found that, per year of therapy, the NNT to observe one case of rhabdomyolysis was 22,727 for statin monotherapy, 484 for older patients with diabetes who were on both a statin and fibrate, and between 9.7 and 12.7 for patients who were treated with cerivastatin plus fibrate. Rhabdomyolysis was found to be a rare occurrence in patients receiving statin monotherapy. Patients were at higher risk of rhabdomyolysis if they were on concomitant fibrate therapy or were older with diabetes.

The concerns regarding myopathy with statin therapy and the voluntary removal of cerivastatin from the market prompted the American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute Clinical Advisory to comment on the use and safety of statin therapy.[26] The Clinical Advisory recommends obtaining a baseline creatinine kinase (CK) level before statin initiation. Serial monitoring of CK levels in asymptomatic patients is not recommended and is of little value. CK measurements should be obtained if a patient complains of muscle weakness, pain, or tenderness. A thyroid-stimulating hormone level should also be obtained in any patient with muscle symptoms because patients with

hypothyroidism are predisposed to myopathy. It is recommended that statin therapy be discontinued if the CK level is > 10 times the ULN in patients with muscle symptoms. In patients who experience muscle symptoms but no CK elevation or moderate elevation (3–10 times the ULN), it is recommended that providers monitor symptoms and CK levels weekly until there is no longer medical concern or until symptoms worsen (which requires statin discontinuation). If a provider chooses to obtain serial CK values in asymptomatic patients and levels are elevated to > 10 times the ULN, strong consideration should be given to discontinuing therapy. After discontinuation, the provider should wait for symptoms to resolve and CK levels to return to normal before reinitiating statin or combination lipid therapy and should use a lower dose of the drug(s), if possible.

Although much of the focus for reducing coronary events is on LDL and statin therapy, ADA also recommends other goals and treatments. Patients with type 2 diabetes typically display the pattern of "diabetic dyslipidemia" in which HDL is decreased and triglycerides are increased. ADA recommends lowering triglycerides to < 150 mg/dl and increasing HDL to > 40 mg/dl in men and > 50 mg/dl in women.[18]

Fenofibrate is an agent in the fibrate class of lipid-lowering drugs that decreases LDL and total cholesterol by 15%, decreases triglycerides by 30%, and increases HDL by 10–15%.[27] Given the typical lipid profile in patients with diabetes, this agent was thought to be ideal. Fenofibrate was evaluated in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study,[28] a multinational, randomized controlled trial in 9,795 patients with type 2 diabetes (median duration 5 years). Patients were randomized to receive either micronized fenofibrate, 200 mg daily, or matching placebo. The primary outcome was coronary events (coronary heart disease death or nonfatal MI). The investigators found that 5.9% of patients on placebo and 5.2% of those on fenofibrate had a coronary event (nonsignificant relative reduction of 11%; HR 0.89; 95% CI 0.75–1.05; $P = 0.16$). Total mortality was 6.6% in the placebo group and 7.3% in the fenofibrate group ($P = 0.18$).

The results of this study—the first randomized controlled trial of fibrates in patients with type 2 diabetes—showed that fenofibrate is not efficacious in reducing mortality or coronary events. This was a disappointing finding considering several subgroup analyses with gemfibrozil[29,30] and bezafibrate,[31] which were associated with some benefit. The FIELD trial did show that fenofibrate was associated with overall reduction in microvascular events (progression to albuminuria and fewer laser treatments for retinopathy). Furthermore, fenofibrate does not interact with statin therapies to the same degree as gemfibrozil. (Fenofibrate does not block glucuronidation of statin agents, a step that is required for elimination of statins.) This was apparent in the FIELD trial; no reports of rhabdomyolysis occurred in patients on concomitant statin and fibrate therapy.

Niacin has also been investigated in patients with diabetes. There were concerns with the use of niacin in diabetic patients because it was thought that niacin worsened glycemic control. However, several recent studies have determined the utility of niacin in patients with diabetes. Extended release (ER) niacin was studied in patients with type 2 diabetes in a 16-week, double-blind, placebo-controlled trial.[32] A total of 148 patients were randomized to placebo ($n = 49$) or 1,000 ($n = 45$) or 1,500 mg/day $n = 52$) of ER niacin. Dose-dependent increases in HDL levels (+19 to +24% [$P < 0.05$] vs. placebo for both niacin dosages) and reductions in triglyceride levels (–13 to –28% [$P < 0.05$] vs. placebo for the 1,500 mg ER niacin dosage) were observed. Baseline and week 16 values for A1C level were 7.13 and 7.11%, respectively, in the placebo group; 7.28 and 7.35%, respectively, in the 1,000 mg ER niacin group ($P = 0.16$ vs. placebo); and 7.2 and 7.5%, respectively, in the 1,500 mg ER niacin group ($P = 0.048$ vs. placebo). Flushing was the only significant adverse event apparent with niacin over placebo. The HDL Atherosclerosis Treatment Study (HATS) evaluated the combination of simvastatin and nicotinic acid against placebo. HATS was a 3-year double-blind study of 160 patients with coronary artery disease, 25 of whom also had diabetes. At 3 years, combination therapy significantly improved the lipid profile compared to placebo (LDL decrease 43 vs. 8.7%; triglyceride decrease 37.6 vs. 3.4%; and HDL increase 26 vs. 6%, respectively).

Bile acid resins are often a forgotten class of medications for lipid management. The Glucose-Lowering Effect of WelChol Study evaluated colesevelam in a placebo-controlled trial in patients with diabetes.[33] This study evaluated the ability of colesevelam to lower A1C in patients with type 2 diabetes not controlled on oral antidiabetic agents. The primary end point was the change in A1C from baseline to week 12. A total of 65 patients were randomized to receive either colesevelam, 3.75 g daily (six 625-mg tablets), or matching placebo. When compared to placebo, colesevelam resulted in a 0.5% lower A1C ($P = 0.007$) and fasting plasma glucose (FPG) at 4 weeks (–23.3 mg/dl; $P = 0.016$) and 8 weeks (–18.3 mg/dl; $P = 0.011$). Adverse events were similar between colesevelam and placebo, with gastrointestinal disorders observed most frequently. These data led to the additional indication (for colesevelam) to improve glycemic control in patients with diabetes.[34] Clinicians should keep in mind that bile acid sequestrants cause multiple drug-drug interactions by blocking intestinal absorption. They can also potentially increase triglyceride levels.

Recommendation: Lipid-lowering therapy—especially with statins—has been shown to be beneficial in patients with diabetes. The ADA recommendation and best practice is to use statin therapy, in addition to lifestyle therapy, regardless of baseline lipid levels for patients with diabetes with overt CVD and patients without CVD who are > 40 years of age and have one or more other CVD risk factors.[18]

Antiplatelet Therapy

Patients with diabetes, particularly type 2 diabetes, have a myriad of disorders that place them at high risk of CVD and cerebrovascular disease. Increased activity of platelets is just one of the major factors that contribute to this risk and is a very important area for intervention. In patients with diabetes, platelet levels of the activators adenosine triphosphate and adenosine diphosphate, as well as platelet aggregation, are 18–80% higher than in healthy individuals.[35] Table 2 contains a list of potential alterations that place patients with diabetes at a higher risk

for thrombosis, highlighting the need for intervention.

Antiplatelet agents such as aspirin and clopidogrel act by irreversibly inactivating platelet function for the 7- to 10-day lifespan of the platelet.[36] Both agents have been studied in patients with diabetes and are highly recommended in certain situations.[18] Aspirin has been evaluated as both primary prevention and secondary prevention of CVD.

In the Physician's Health Study primary prevention trial, 22,071 patients (533 with diabetes) were randomized to receive aspirin, 325 mg every other day, or placebo.[37] None of these patients had a history of cardiovascular events. The primary outcome was proportion of patients who experienced an MI by the end of the 5-year study. Among men with diabetes, 4.0% of those treated with 325 mg aspirin every other day had an MI versus 10.1% of those who received placebo (relative risk 0.39).

In the Early Treatment of Diabetic Retinopathy Study, 3,711 diabetic patients were randomized to aspirin, 650 mg daily, or placebo.[38] This study is considered a mixed primary and secondary prevention study because of the sample that was evaluated. In this study, aspirin reduced the risk of MI by 28% (9.1% had an MI on aspirin vs. 12.3% on placebo; $P = 0.038$). This benefit occurred without an excess of retinal or vitreous hemorrhage. The Hypertension Optimal Treatment study evaluated 18,790 hypertensive individuals, 1,501 of whom had diabetes.[39] Patients were randomized to either low-dose aspirin (75 mg/day) or placebo. Of the study participants, < 10% had clinical evidence of previous MI, stroke, or other coronary heart disease. Aspirin resulted in a 15% reduction in pooled cardiovascular events ($P = 0.03$) and a 36% reduction in the risk of MI ($P = 0.002$). Nonfatal bleeding was more common in patients taking aspirin; however, their rates of fatal bleeding were comparable to those taking placebo.

ADA recommends aspirin, 75–162 mg daily, as primary prevention for patients with diabetes who are > 40 years of age or who have additional risk factors, such as family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria.[18]

Several secondary prevention trials and analyses with antiplatelet agents have been conducted in patients with diabetes. The Antiplatelet Trialists' Collaboration conducted a meta-analysis of 145 prospective controlled trials of antiplatelet therapy.[40] Among the > 4,500 patients with diabetes, the incidence of vascular events was reduced from 23.5% (in subjects receiving control treatment) to 19.3% with antiplatelet therapy ($P < 0.01$). There was an overall risk reduction of 38 ± 12 vascular events per 1,000 diabetic patients treated ($P < 0.02$).

Table 2: Reasons for Increased Platelet Aggregation and Adhesion in Patients With Diabetes

- Reduced membrane fluidity
- Altered calcium and magnesium homeostasis
- Increased arachidonic acid metabolism
- Increased thromboxane A2 synthesis
- Decreased prostacyclin production
- Decreased nitric oxide production
- Decreased antioxidant levels
- Increased expression of activation-dependent adhesion molecules (e.g., GpIIb-IIIa, P-selectin)

In the Ticlopidine in Microangiopathy of Diabetes study, patients were randomized to either ticlopidine, 250 mg twice daily, or placebo.[41] The study included 435 patients with diabetes and nonproliferative diabetic retinopathy. Patients were followed for 3 years. The investigators found that ticlopidine reduced the progression of retinopathy by 67% ($P = 0.03$) compared to placebo. However, a major side effect of ticlopidine (neutropenia) limits its utility.

ADA recommends that all patients with a history of CVD receive aspirin (75–162 mg/day) as a secondary prevention.

Combination antiplatelet therapy has also been investigated in patients with diabetes. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial investigators evaluated the use of aspirin in combination with clopidogrel in 12,562 subjects who presented to the hospital with an acute coronary syndrome within 24 hours of symptoms.[42] Patients received either aspirin, 75–325 mg every day, plus a one-time dose of clopidogrel, 300 mg, followed by clopidogrel, 75 mg daily, or aspirin alone. In 2,849 subjects who had diabetes, the combination group experienced a 14.2% event rate versus 16.8% in the aspirin-only group (P = NS). Although the relative risk favored the addition of clopidogrel, the reduction was not significant.

In the Plavix Use for Treatment Of Diabetes Trial, 70 patients with diabetes were randomized to receive clopidogrel, 75 mg daily, plus aspirin, 81 mg daily, or aspirin, 81 mg daily, alone. Approximately half of the patients in the sample had a history of coronary artery disease. The objective of this study was to compare the antiplatelet profiles of combination therapy and aspirin monotherapy. After 1 month of therapy, there appeared to be stronger platelet inhibition in the combination group. Given the short duration of the study, the investigators were unable to fully assess the safety of combination therapy in this sample.

ADA recommends the use of clopidogrel for secondary prevention in diabetic patients with an allergy to aspirin.

Recommendation: Antiplatelet therapy has been shown to be beneficial in both primary and secondary prevention. Best practice in patients with diabetes who are ≥ 40 years of age is aspirin therapy unless a contraindication exists. The dose of aspirin should be 75–325 mg. An enteric-coated product should be used to minimize gastrointestinal side effects. Clopidogrel should be used in patients with diabetes if they are allergic to aspirin. Presently, no primary prevention trials in people with diabetes have been conducted. For primary prevention in patients with multiple risk factors, the risk, benefit, and cost of clopidrogrel must be considered when deciding on antiplatelet therapy.

Glycemic Control Interventions

The evidence that improving glycemic control reduces the risk of microvascular complications is unequivocal.[43,44] The evidence for a causative relationship between macrovascular disease and blood glucose is weaker than that for microvascular disease, but ample evidence that poor glycemic control is a risk factor for macrovascular disease has been reported. Importantly, the UKPDS reported that LDL and HDL

better predict the time to first cardiovascular event than does glycemic control, firmly placing dyslipidemia, and most likely blood pressure control, ahead of hyperglycemia in the etiological factors related to macrovascular events. Three main issues are often sited when referring to glycemic control and the risk of macrovascular complications: *1*) glycemic exposure, *2*) postprandial hyperglycemia, and *3*) the antihyperglycemic agent used.

Glycemic exposure

Glycemic exposure is measured by serial A1C measurements, and limiting glycemic exposure in people with diabetes lowers the risk of complications. The ADA Expert Committee on the Diagnosis and Classification of Diabetes Mellitus reported that an A1C of ≤ 6% mitigates almost all of the risk of microvascular disease from glucose, as measured by retinopathy occurrence.[45] In contrast, macrovascular risk is still present even in the normal, nondiabetic A1C range. Khaw et al. reported that the majority of excess cardiovascular risk from A1C (82%) could be attributed to A1C levels of 5.0–6.9%.[46] Thus, macrovascular risk is present even before the diagnosis of diabetes, and A1C may act as a marker of the underlying pathology.

The UKPDS and Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) have given much insight into the risk of CVD and its relationship to glycemic control. The DCCT reported a lower, but non-significant reduction in CVD in type 1 diabetes with intensive glycemic control compared to conventional control (A1C 7.4 vs. 9.1%, respectively), but after its conclusion, the majority of subjects continued to be observed in the EDIC trial.[44] Despite A1C levels in each arm converging to about 7.8% over the 11-year EDIC follow-up, the risk of CVD was reduced 42% ($P = 0.02$) in the DCCT intensive control group versus those who received conventional treatment during the DCCT.[47] Thus, in type 1 diabetes, intensive glycemic control does reduce the risk of CVD, but this "metabolic memory" effect takes a substantial amount of time to be revealed.

In the UKPDS, intensive (average A1C = 7.0%) versus conventional (average A1C = 7.9%) glycemic control was achieved and maintained over 10 years in newly diagnosed type 2 diabetic subjects. The risk of MI was reduced by 16% ($P = 0.052$) with sulfonylurea or insulin therapy.[43] It should be remembered, however, that when the UKPDS was designed, sulfonylureas and insulin were suspected of increasing the risk of CVD. Stratton et al.[48] explored the risk of glycemic exposure on micro- and macrovascular disease, based on observational data from the UKPDS. Overall, as glycemic control worsened, the risk of microvascular and myocardial infarction increased (Figure 1). It should also be noted that the risk was not completely abated by normalizing A1C, highlighting that macrovascular and even microvascular risk is multifactorial. In addition, the investigators found the following outcomes associated with each 1% reduction in A1C: a 14% reduction in all cause-mortality, a 21% reduction in diabetes-related death, a 14% reduction in fatal and nonfatal MI, and a 16% reduction in the risk of heart failure.

Postprandial hyperglycemia

High glucose and A1C levels are consistently associated with a higher risk of cardiovascular events.[49] The most compelling data on postprandial glucose and macrovascular risk come from very large observational epidemiological studies.[50–53] As the 2-hour postprandial glucose or "post-challenge" glucose (such as with an oral glucose tolerance test) increases, the risk of CVD and mortality increases. It should be noted, though, that the majority of these subjects did not have diabetes at baseline. Also, significant increases in macrovascular disease risk are first evident at 2-hour values ≥ 140 mg/dl, which equates to impaired glucose tolerance values, not diabetes. This again points to the fact that significant macrovascular risk is present before the diagnosis of diabetes.

Unfortunately, there have been no large-scale cardiovascular outcome trials specifically targeting postprandial glucose in people with diabetes, although observational diabetes trials have mostly documented that postprandial glucose control is a risk factor for macrovascular risk.[54]

In one surrogate outcome trial, repaglinide was compared to glyburide therapy in 175 drug-naïve patients with type 2 diabetes. Carotid intima media thickness (CIMT), a surrogate marker of atherosclerosis, was measured after 12 months of therapy. A1C control was similar between the two groups, but glyburide significantly lowered the fasting plasma glucose versus repaglinide, and repaglinide significantly lowered postprandial glucose more than glyburide. CIMT regression (less atherosclerosis), defined as a decrease of > 0.020 mm, was significantly higher in the repaglinide (52%) versus glyburide (18%) group.[55]

These facts have been incorporated into ADA and American College of Endocrinology (ACE) guidelines, with each choosing a different cut-off based on the data. ADA, which tends to be more conservative on interpretation of postprandial data,[54] currently recommends a postprandial blood glucose goal of < 180 mg/dl, whereas ACE recommends a target of < 140 mg/dl mostly based on the large epidemiological studies previously mentioned. Both goals are supported by evidence, depending on what data are included and how the data are interpreted.[18,54,56,57]

Antihyperglycemic agents

It is reasonable to expect, at a minimum, that any antihyperglycemic agents used be neutral on CVD. If they potentially increase or decrease CVD, this should be considered, because the majority of people with diabetes die from CVD. As discussed before, the UKPDS and DCCT have clearly shown that sulfonylureas and insulin can be used without increasing the risk of CVD. The UKPDS also reported on overweight subjects assigned to intensive control with metformin. Metformin reduced all-cause mortality (the only antihyperglycemic ever to report this outcome) and stroke versus intensive therapy with sulfonylurea/insulin.[58] It should be remembered that virtually none of the subjects were on lipid-lowering therapy at baseline. Whether metformin would lower the risk of CVD in type 2 diabetic subjects with well-treated hypertension, dyslipidemia, and aspirin use is unknown. Nevertheless, metformin is generic, lipid neutral, and weight neutral (or subjects may lose several pounds) and based on the UKPDS is considered first-line therapy in overweight type 2 diabetes patients.

Thiazolidinediones (TZDs) have caused much controversy in the CVD arena. Both pioglitazone and rosiglitazone increase the risk of pulmonary edema or heart failure, and using these agents with insulin or in people

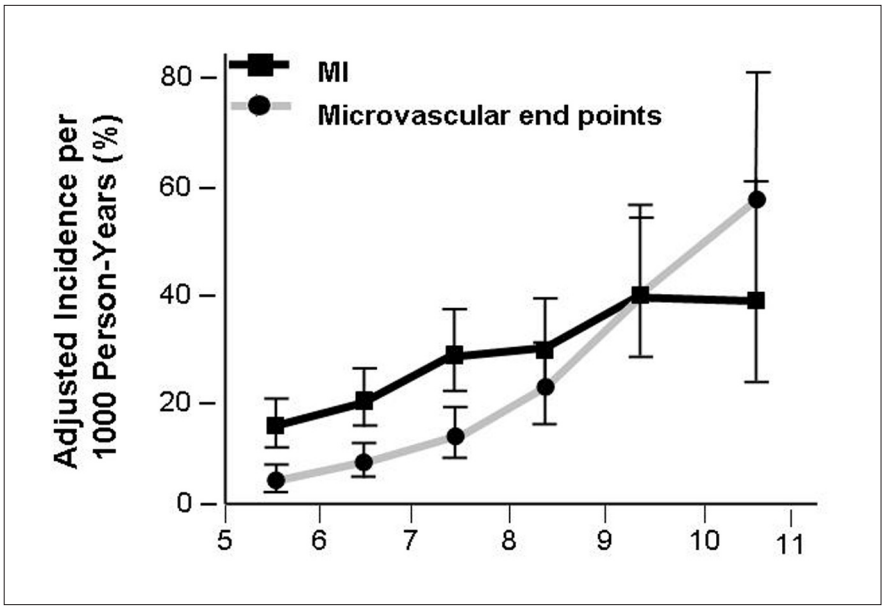

Figure 1: Risk of microvascular and myocardial infarction outcomes based on A1C in the UKPDS. Adapted from ref. 48.

with pre-existing heart failure may further increase these complications. Importantly, TZDs do not appear to increase the risk of death due to heart failure. With this noted, most of the remainder of the discussion on TZDs and CVD will be limited to ischemic events, such as MI and stroke.

Several meta-analyses have reported an increased risk of MI with the use of rosiglitazone.[59,60] Singh et al. reported a meta-analysis on rosiglitazone trials of at least 12 months duration that reported cardiovascular outcomes when compared to placebo, metformin, or glyburide. The risk of MI (1.42; 95% CI 1.06–1.91) or heart failure (2.09; 95% CI 1.52–2.88) was increased with rosiglitazone, but no increase in cardiovascular mortality has been noted.[59] In contrast, pioglitazone has not been associated with an increase in MI. Lincoff et al. reported a meta-analysis of pioglitazone studies encompassing 19 trials with a total of 16,390 patients compared to insulin, sulfonylureas, metformin, or rosiglitazone for macrovascular outcomes. Pioglitazone versus comparators reduced the hazard ratio for the combined end point of death, non-fatal MI, or non-fatal stroke (0.82; 95% HR 0.72–0.94; $P = 0.005$), but also increased the risk for serious heart failure (1.41; 95% HR 1.14–1.76).

Three clinical trials of pioglitazone treatment have shown potential benefit. The Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) study measured CIMT as a surrogate marker for atherosclerosis. Over 72 weeks, pioglitazone versus glimepiride reduced CIMT –0.024 mm (95% CI –0.042 to –0.006; $P = 0.008$) and was neutral on CIMT versus baseline values. The Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation study (PERISCOPE), using intravascular ultrasound to view atheroma volume in coronary arteries, was a prospective, randomized, double-blind clinical trial compared pioglitazone versus glimepiride. After 18 months on treatment, these surrogate markers of atherosclerosis were re-examined.[62,63] Pioglitazone was neutral on atheroma volume, whereas glimepiride significantly increased atheroma volume, and pioglitazone significantly reduced the percentage of atheroma volume and maximum atheroma thickness versus glimepiride.[63] In addition, the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) placed high-risk type 2 diabetes subjects on pioglitazone, 45 mg, and followed them for > 3 years. The primary outcome of death or time to MI, stroke, leg amputation, acute coronary syndrome, cardiac bypass or balloon, or leg revascularization was reduced 10%, $P = 0.095$. The main secondary end point of death, nonfatal MI, or stroke was reduced 16%, $P = 0.027$.[64]

In conclusion, it is unclear at present whether rosiglitazone may increase the risk of MI in type 2 diabetic patients. Thus, there is a black box warning on the rosiglitazone prescribing information regarding ischemic events, whereas there is no such warning for pioglitazone. Trials with pioglitazone have shown neutrality versus baseline or cardiovascular benefit versus comparators. Both equally increase the chance of heart failure. This warrants a best practice recommendation of pioglitazone as the TZD of choice until further compelling cardiovascular evidence of neutrality with rosiglitazone is published.

Recent trials and controversies

Several recent trials have led to conflicting outcomes in relation to the issue of glycemic control and cardiovascular complications in people with type 2 diabetes. First, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, a National Heart, Lung, and Blood Institute study of 10,251 type 2 diabetes subjects, the intensive glycemic control arm was stopped prematurely after 3.5 years of follow-up due to excess death. All subjects were randomized to either intensive glycemic control (goal A1C < 6%; achieved A1C 6.4%) or standard strategy (goal A1C 7–7.9%; achieved 7.5%). In addition, subjects could be randomized to additional blood pressure and lipid treatment if they qualified, and these arms of the study are ongoing. Intensive glycemic control versus standard control resulted in significantly higher death from any cause (1.22; 95% CI 1.01–1.46; $P = 0.04$) and cardiovascular causes (1.35; 95% CI 1.04–1.76; $P = 0.02$). Intensive therapy reduced the risk of nonfatal MI by 24% ($P = 0.004$), but if a cardiovascular event occurred, it was more likely to be fatal. Preliminarily, the increase in cardiovascular events was not the result of a particular diabetes medication or hypoglycemia, but hypoglycemia needing assistance was threefold higher in the intensively managed group. Other factors mentioned as potential contributors included: rapid drop to A1C goal in first 4 months (though mortality differences started around 1 year into the study), excess weight gain in the intensive group, hypoglycemia, or other factors as yet determined.[65] Further analysis may help explain these findings.

In contrast, the Action in Diabetes and Vascular Disease (ADVANCE) trial investigated intensive blood pressure and glycemic control in 11,140 high-risk subjects with type 2 dia-

betes. Subjects were followed for 5 years, and the intensive control group achieved a median A1C of 6.4% versus 7.0% in the standard control group. Other factors such as weight, aspirin use, blood pressure, statins, and lipids were similar between groups. No significant difference in major macrovascular events or death from any cause was noted between groups.[66] Subgroup analysis revealed that subjects without a history of macro- or microvacular disease benefited the most from intensive glycemic control. Counterintuitively, this means intensive glycemic control may reduce macrovascular events for newly diagnosed patients without macrovascular disease, but once significant macrovascular disease is present, it may not be beneficial and may be harmful.[65,66] Because of the conflicting information recently released, it is best to wait for all data to be published before drastic changes to practice models are implemented.

Recommendation: The best practice model for glycemic goals is the ADA clinical practice recommendation. ADA currently recommends a general A1C goal of < 7% and, in selected individuals, a goal A1C as close to normal (< 6%) as possible without significant hypoglycemia. In addition, less stringent A1C goals may be appropriate for patients with a history of severe hypoglycemia, limited life expectancies, co-morbid conditions, and for children and individuals with longstanding diabetes and minimal microvascular complications.[67] ACCORD had older diabetes subjects with multiple co-morbidities, and this patient set would potentially fit into the category for less stringent glycemic control. Future studies may reveal necessary alterations to these guidelines.

Hypertension Medications

Many different disease states in diabetes use antihypertensive medications to lower risk. MI, stroke, heart failure, renal disease, retinopathy, and potentially even the risk of neuropathy may be lowered by antihypertensive medications.

Hypertension therapy

Sixty to eighty percent of people with type 2 diabetes also have hypertension, and this can increase the risk of MI, stroke, heart failure, nephropathy, and retinopathy. In type 1 diabetes, the risk of hypertension increases only with the onset of renal disease. On the positive side, treating high blood pressure in people with diabetes reduces the risk of both macrovascular and microvascular disease. Also, people with diabetes get equal or often more reduction in cardiovascular events when compared to hypertension treatment in non-diabetes patients.

First and most important, hypertension in people with diabetes should be adequately treated to currently established goals. Almost all professional groups agree that the blood pressure goal is < 130/80 mmHg.[18] Several clinical trials have established that < 80 mmHg for diastolic blood pressure will lower the risk of CVD, but a systolic blood pressure of < 130 mmHg has been found extremely difficult to achieve in clinical trials.[39,68] This is also true in clinical practice, with diastolic goals often being easily met but systolic goals being much harder to achieve. Despite current goals, the UKPDS reported no threshold effect for systolic blood pressure (as with glycemia for microvascular events), and lowering the mean systolic blood pressure to 110 mmHg further lowered the risk of MI. For each 10-mmHg reduction in systolic blood pressure, there was an 11% reduction in the risk of MI and a 13% reduction in the risk of microvascular complications.[69]

Choice of antihypertensive agents

The choice of first antihypertensive agent in people with type 2 diabetes is probably pointless because most people with diabetes require two or three medications to adequately control their blood pressure. Nevertheless, how to combine antihypertensive medications continues to be debated.

To date, one of the largest hypertension studies in diabetic patients was a subset of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[70] At baseline, > 15,000 people had diabetes, and approximately one-third had CVD. Subjects were randomized to chlorthalidone, a thiazide diuretic; amlodipine, a calcium channel blocker (CCB); lisinopril, an angiotensin-converting enzyme (ACE) inhibitor; or doxazosin, an α-blocker. The doxazosin arm was stopped prematurely because of an increased incidence of CVD and heart failure versus the thiazide diuretic. As a result, α-blocker therapy has been relegated to fourth- or fifth-line therapy for the treatment of hypertension. In diabetic subjects, all three (thiazide diuretic, CCB, and ACE inhibitor) were equally effective in reducing CVD outcomes. Heart failure outcomes were better with the thiazide diuretic, but these outcomes have been widely disputed and criticized. Thus, all three classes may be used for cardiovascular protection in people with diabetes, and none has proven to be superior compared to the others.[71]

The Microalbuminuria, Cardiovascular, and Renal Outcomes-Heart Outcomes Prevention Evaluation (MICRO-HOPE) study, the diabetic subset of the Heart Outcomes Prevention Evaluation (HOPE) trial, has led some to believe that ACE inhibitors have superior CVD protection compared to other agents. Total mortality, MI, stroke, and overt nephropathy were all significantly reduced in patients who took ramipril, 10 mg daily, versus placebo.[72] Because this was a placebo-controlled trial in diabetes patients at high risk of CVD and blood pressure was only modestly reduced, many came to the conclusion that an ACE inhibitor or ramipril must have additional CVD protection in diabetic patients above and beyond simple blood pressure control. Unfortunately, the ALLHAT did not report additional benefit with lisinopril over other agents in people with diabetes.[71] Recently, the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial reported noninferiority of telmisartan 80 mg daily, to ramipril 10 mg daily, in a population of patients very similar to the MICRO-HOPE.[73] Thus, many feel that ACE inhibitors and angiotensin receptor blockers (ARBs) are equivalent in the their ability to prevent CVD.

Why then, if not superior CVD protection, do we recommend ACE inhibitors or ARBs as first-line therapy in people with diabetes? Both classes are clearly cardioprotective but have the added advantage of superior renal protection when compared to most other classes of antihypertensives. In addition, people at risk of developing diabetes, such as people with metabolic syndrome, may reduce the development of diabetes by using ACE inhibitors or ARBs rather than other antihypertensives.[74] Overall, it is thought that both ACE inhibitors and ARBs reduce the progression of diabetic nephropathy to end-stage renal disease, reduce the progression of microalbuminuria to

nephropathy, and reduce the appearance of microalbuminuria.[75–78]

There are several important points about the use of these two classes for the prevention of nephropathy. First, in the presence of microalbuminuria/nephropathy, consideration should be made for increasing these medications to the maximum dose.[77] Increasing the dose of these medications from half the maximum dose to the maximum dose may only lower blood pressure by 1–2 mmHg, but studies have shown that additional reduction in urine microalbumin excretion is often seen.[77] If additional blood pressure lowering is needed, an additional blood pressure medication should be added to the maximized ACE inhibitor or ARB. Second, combination of these two classes in diabetic renal disease has garnered much attention, but very few well-designed trials have been completed. Just as the maximum dose of either an ACE inhibitor or an ARB results in maximum reductions in microalbuminuria, it is obvious that in a well-designed trial, the maximum dose of one agent should be implemented before the addition of the other class of medication to ascertain the true effect on microalbuminuria. Of the limited studies that have combined adequate dosing of both agents, most have found no additional cardiovascular benefit, though the renal effects are still of interest.[73,79]

Aldosterone receptor blockers, such as spironolactone or eplerenone, may have renal advantages in combination with an ACE inhibitor or ARB, but larger trials are needed to confirm preliminary results.[80] In addition, data with aliskiren, a direct renin inhibitor, shows promise. Aliskiren, when added to the maximum dose of losartan, further reduced microalbuminuria in type 2 diabetes, although more evidence will be needed before this can be considered a best practice.[81]

ALLHAT reported that one in every 29 people treated with a thiazide diuretic and one in 59 people treated with a CCB instead of an ACE inhibitor developed diabetes diagnosed by a fasting plasma glucose level.[70] Although definitive diabetes diagnosis from ALLHAT can not be confirmed, it still seems counterintuitive for the National Heart, Lung, and Blood Institute to recommend diuretics as first-line therapy when they likely increase the development of the very disease trying to be optimally managed.[74]

African Americans with diabetes and hypertension require special consideration for treatment. ALLHAT reported no significant difference in cardiovacular outcomes using a thiazide diuretic or a CCB in African Americans. In contrast, the ACE inhibitor was inferior to the thiazide diuretic and resulted in significantly higher rates of combined CVD and stroke. Much of this difference can be explained by the fact that blood pressure reduction with the ACE inhibitor was slightly less than with the thiazide diuretic.[74,82] Based on this fact, clinically, should we use ACE inhibitors or ARBs as first-line treatment for hypertension in African Americans? ACE inhibitors, compared to a CCB or metoprolol, have proven in African Americans to provide at least equal, if not superior, renal protection.[83] Thus, ACE inhibitors or ARBs can still be used as first-line therapy for hypertension in African Americans with diabetes, but additional blood pressure lowering will often be needed. To overcome this problem, an ACE inhibitor or ARB may be started in combination with either a thiazide diuretic or a CCB as initial therapy in these patients.

Post-MI and Heart Failure

People with diabetes who have experienced an MI have worse cardiovascular outcomes compared to patients without diabetes. Data on acute coronary syndrome outcomes over 1 year have shown that mortality in people with diabetes was two to three times that of people without diabetes.[84] In the Survival and Ventricular Enlargement trial in patients post-MI with heart failure, diabetic patients had higher mortality rates than nondiabetic patients (31.3 vs. 21.1%; $P < 0.001$), respectively.[85] No evidence has clearly shown that interventions to decrease recurrent MI or heart failure have inferior outcomes in people with diabetes, but people with diabetes tend to have more comorbidities, which may explain why they have worse outcomes after an MI. Aggressive treatment with agents that have proven to reduce morbidity and mortality should be used. These include ACE inhibitors or ARBs and β-blockers, as well as previously discussed medications, such as antiplatelet and lipid-lowering therapies.

Diabetes increases the risk of heart failure. Importantly, it should be remembered that metformin and TZD therapy should be stopped in heart failure, especially if New York Heart Association function class III or IV is present. The risk of lactic acidosis may be increased with metformin, and the risk of peripheral or pulmonary edema and heart failure can increase with the use of TZDs. In patients with pre-existing heart failure, pioglitazone and rosiglitazone may worsen the heart failure. Patients given TZDs were more likely to have worsening edema, dyspnea, and increases in heart failure–related medications, but this did not increase death from heart failure. Extreme caution and frequent monitoring should be implemented if a TZD is considered in this population.

β-blocker therapy

β-blockers reduce mortality in people with diabetes who have experienced an MI. β-blockers are antiarrhythmic and reduce sudden cardiac death, myocardial oxygen demand, and infarct size. Originally, there was a concern about hypoglycemia unawareness induced by β-blockers in this population, but multiple studies have documented mortality reductions with the implementation of β-blockers. Because reducing the risk of death is more important than the potential risk of hypoglycemia, which is rarely fatal, β-blockers should be used in all diabetic patients who do not have absolute contraindications.[86–88] In the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, use of a β-blocker post-MI significantly reduced 1-year mortality by 50%.[89]

ACE inhibition

As mentioned previously, ACE inhibitors are used for hypertension and renal protection in people with diabetes. In addition, they have been proven to help post-MI patients and are the cornerstone of therapy in heart failure. In both, the renin-angiotensin aldosterone system (RAAS) is activated. Post-MI, ACE inhibition appears to limit remodeling and infarct expansion, which can be involved in the development of heart failure post-MI and indirectly, arrhythmias. ARBs appear be an excellent alternative to

ACE inhibitors in heart failure and post-MI patients.[90]

Aldosterone receptor blockers

Aldosterone receptor blockers have also been shown to help heart failure in post-MI patients. In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study, eplerenone was added to standard therapy in post-MI patients with heart failure (approximately one-third of whom had diabetes). Eplerenone decreased the risk of death in nondiabetic patients when added to standard therapy. The study was not powered to examine diabetes, but the risk of death was reduced, although the reduction did not reach statistical significance.[91] Other than aldosterone receptor blockers combined with an ACE inhibitor or ARB, most data for combined RAAS blockade are not positive for cardiovascular outcomes. The combination of ACE inhibitors and ARBs has not proven to further help post-MI, heart failure mortality, or high-risk CVD patients. The combination may, however, further reduce hospitalizations for heart failure.[92]

Glycemic control

It should also be remembered that glycemic control can have a profound effect on the morbidity and mortality post-MI or in heart failure. Inpatient glycemic control continues to be a hotly discussed topic for reduction of macrovascular events, and an in-depth discussion is beyond the scope of this paper. In the DIGAMI trial, intensive insulin therapy post-MI reduced the risk of mortality by 28% ($P = 0.011$), and the DIGAMI-2 trial, where no differences in glycemic control were noted, reported no differences, although it was underpowered as a study.[93,94] In addition, the UKPDS reported a 16% reduction in the risk of heart failure for each 1% reduction in A1C.[48]

Conclusion

Risk factors for CVD must be treated aggressively in people with diabetes because cardiovascular outcomes are often worse compared to people without diabetes. To reduce the CVD burden common among individuals with diabetes, it is imperative to implement multifactorial interventions that include diet, exercise, smoking cessation, and obesity management.

Pharmacological therapy is another crucial intervention that should be initiated in most people with diabetes. Statin therapy, antiplatelet therapy, hypertension management, proper post-MI and heart failure treatment, and the use of ACE inhibitors or ARBs for renal protection can all reduce the burden of CVD in people with diabetes.

In an urban setting, it has been reported that < 5% of people had their glucose, blood pressure, and LDL cholesterol at current recommended goals.[95] Control rates are improving, but it is disturbing that this is still such a frequent occurrence. The reasons are multifactorial, but require action when an abnormal parameter is identified; adequate follow-up and education of the practitioner, patient, and health system; and an active partnership with people with diabetes. In this high-risk population, intensive, multifactorial intervention gives the patient the best chance of avoiding CVD.

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