REVIEW

Strategies for Optimizing Glycemic Control and Cardiovascular Prognosis in Patients With Type 2 Diabetes Mellitus

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Type 2 diabetes mellitus (DM) is a major cardiovascular (CV) risk factor and, as such, is considered a coronary artery disease risk equivalent. Although glycemic control is associated with decreased CV events epidemiologically, many prospective clinical trials have failed to conclusively demonstrate that aggressive glycemic control improves the CV prognosis of patients with type 2 DM, especially those with long-standing DM. Many therapies for type 2 DM with widely divergent mechanisms of action are available. Some of these drugs, in addition to their glucose-lowering actions, have properties that may reduce or increase CV events. Agents that lower both insulin resistance and postprandial hyperglycemia while at the same time avoiding hypoglycemia may be beneficial for CV health. This article reviews the evidence regarding the use of these agents and appropriate glycemic control targets for improving the adverse CV prognosis associated with type 2 DM. We conducted a systematic review of English articles using MEDLINE and the Cochrane Controlled Trials Register (1970-2010) using the following search terms: *cardiovascular disease, randomized trials, hypoglycemia,* and *insulin resistance*.

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ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; CAD = coronary artery disease; CI = confidence interval; CV = cardiovascular; DM = diabetes mellitus; DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide-1; HbA_{1c} = glycated hemoglobin; HF = heart failure; LDL-C = low-density lipoprotein cholesterol; LV = left ventricular; LVEF = LV ejection fraction; MI = myocardial infarction; OR = odds ratio; TZD = thiazolidinedione; UKPDS = United Kingdom Prospective Diabetes Study; VADT = Veterans Affairs Diabetes Trial

The importance of abnormally elevated blood glucose as a cardiovascular (CV) risk factor is well established epidemiologically.[1-4] Glycated hemoglobin (HbA_{1c}), a marker of long-term glycemic control, is directly associated with CV risk[2] and all-cause mortality (Figure 1).[3] The UKPDS (United Kingdom Prospective Diabetes Study), a study of recent-onset diabetes, showed a 14% reduction in the risk of myocardial infarction (MI) for each 1% decrease in the mean level of HbA_{1c}.[2] Similarly, in a study of 48,444 patients with type 2 diabetes mellitus (DM) and without known CV disease, each 1% increase in the level of HbA_{1c} during a period of 2.4 years was associated with an 8% increase in MI and a 9% increase in stroke.[4]

IS LOWER BETTER?

The UKPDS randomized 3867 patients newly diagnosed as having DM to either intensive therapy (with either a sulfonylurea or insulin) or conventional therapy (predominantly diet alone).[5] The median achieved HbA_{1c} value during the study was 7.0% for the intensive therapy group compared with 7.9% for the conventional group.[6] The intensive therapy group had a 25% lower risk of developing microvascular complications, which was primarily driven by a lower frequency of retinal photo-coagulation. A trend toward reduction of MI was noted in the intensive therapy group during 10 years of follow-up; however, it was not statistically significant.[5]

In contrast, in another arm of the UKPDS trial in which obese patients with type 2 DM were randomized to either metformin or conventional therapy (primarily diet), a lower all-cause mortality was found with metformin therapy.[7] A median HbA_{1c} value of 7.4% was achieved in the group assigned to metformin vs an HbA_{1c} value of 8.0% in the conventional therapy group.[7] Compared with conventional therapy, metformin lowered diabetes-related death and all-cause mortality during a 10-year period in these patients with newly diagnosed type 2 DM.[7] Although metformin was less effective at lowering HbA_{1c} values than intensive therapy regimens with a sulfonylurea or insulin, it was associated with a lower risk of death and stroke (although not MI) and, importantly, a much lower risk of hypoglycemia (Figure 2).[7] Yet, the UKPDS patients who received metformin as an add-on to maximum-dose sulfonylurea had an increased mortality rate, a controversial finding because this subgroup of patients was small.[7]

In the epidemiological 10-year UKPDS follow-up study, patients were monitored on an annual basis after the end of the intervention portion of the trial. Despite similar HbA_{1c} levels in the 2 groups for the remainder of the follow-up study, the original intensive therapy group (insulin/sulfonylurea) had a 15% lower risk of an MI

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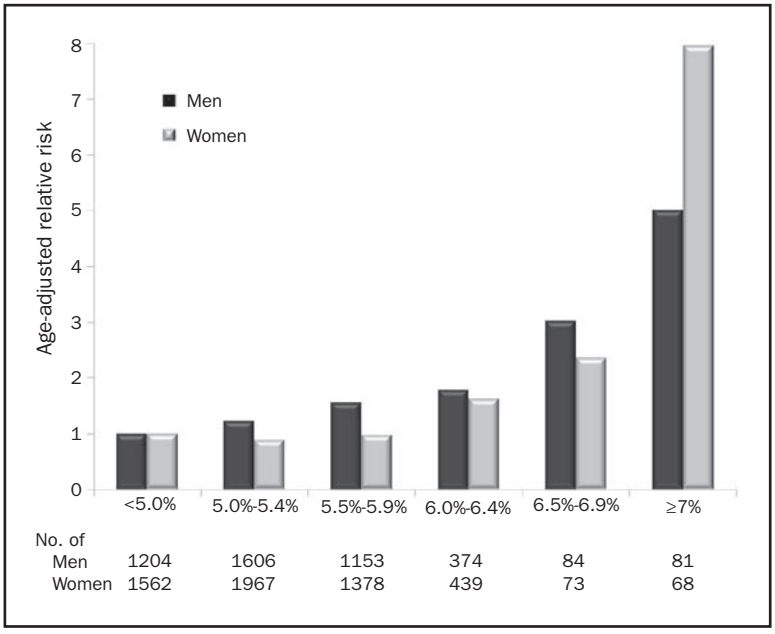

FIGURE 1. Age-adjusted relative risks for cardiovascular events by glycated hemoglobin category from the European Prospective Investigation into Cancer in Norfolk study.[3]

(*P*=.01), as well as a 13% decrease in all-cause mortality (*P*=.007), compared with the original conventional therapy group.[8] Again, despite similar HbA_{1c} levels during the poststudy follow-up, MI decreased by 33% (*P*=.005) and all-cause mortality by 27% (*P*=.002) in the metformin group when compared with those originally receiving conventional therapy.[8] Similarly, the DCCT (the Diabetes Control and Complications Trial)/EDIC (Epidemiology of Diabetes Interventions and Complications) trial, which examined intensive vs conventional control using insulin therapy for patients with type 1 DM, showed evidence for a "metabolic memory." The intensively treated patients who had a lower HbA_{1c} level during the 6.5-year study had significantly fewer events than the conventionally treated group during the 10-year posttrial period, despite similar HbA_{1c} levels in the 2 groups during the decade after the trial ended.[9]

In contrast to UKPDS, 3 recent large randomized trials have shown no reduction in CV events with aggressive vs more conservative glucose control in patients with type 2 DM, possibly because of a longer mean duration of type 2 DM and a shorter duration of follow-up than in the UKPDS trial.[6,10,11] Indeed, after 3.5 years, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial showed significantly *higher* all-cause mortality in type 2 DM patients randomized to intensive glycemic control as compared with conventional control; as a result, the glycemic control portion of ACCORD was stopped prematurely.[6] Yet, on detailed scrutiny of the data, higher HbA_{1c} values predicted increased risk of death in the intensive arm of the ACCORD trial, in which most of the deaths occurred in the subgroup of patients whose HbA_{1c} values remained high despite attempted intensive glycemic control.[12] More-

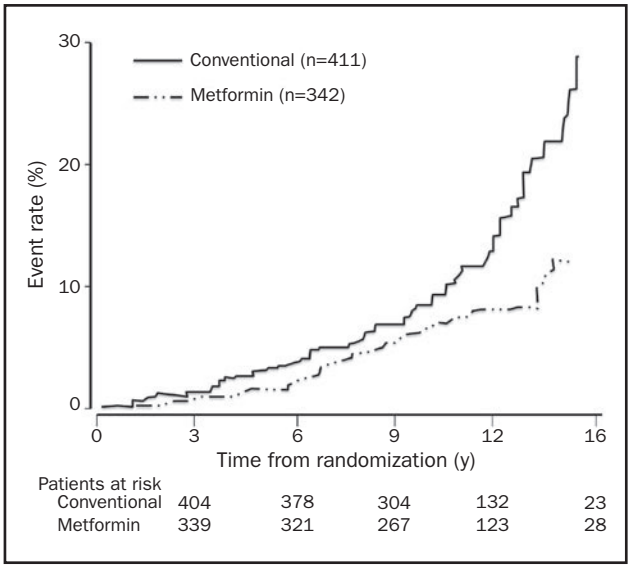

FIGURE 2. Kaplan-Meier plot for any type 2 diabetes–related death with metformin and conventional therapy in the UK Prospective Diabetes Study.
Adapted from *Lancet*,[7] with permission from Elsevier.

over, in the subgroup of patients without documented CV disease at baseline, a subanalysis suggested that intensive glycemic control was associated with a *reduced* risk of CV death and nonfatal CV events.[6]

The Veterans Affairs Diabetes Trial (VADT), which compared intensive and standard treatment strategies in patients with type 2 DM, did not show a statistically significant difference in the incidence of major CV events after a median follow-up of 5.6 years.[10] In this study, the intensive control group achieved an HbA_{1c} of 6.9% compared with 8.4% in the standard control group.[10] Not surprisingly, 8.5% of the patients in the intensive therapy group were reported to have had at least 1 episode of hypoglycemia vs 3.1% in the standard therapy group.[10] In a substudy of VADT, patients without significant coronary atherosclerosis (as documented by a coronary artery calcium score of <100) experienced a decrease in CV events with intensive vs conservative therapy.[13] Although certainly not definitive, these findings from VADT and ACCORD suggest that intensive glucose control may reduce CV events in patients with a shorter duration of DM and in those who do not have significant preexisting CAD.[7,14]

After a median follow-up of 5 years, the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial showed no difference between intensive control and standard control groups in macrovascular outcomes.[13-15] Mean HbA_{1c} values achieved in the ADVANCE study were 6.5% in the intensive control group and 7.3% in the standard control group.[11] Similar to ACCORD and VADT, the rate of combined primary end point (composite of microvascular and macrovascular events) was significantly lower with intensive vs conservative glucose control among patients who did not have established CV disease at baseline.

Compared with the UKPDS, the ACCORD, ADVANCE, and VADT trials were of shorter duration, and the patients were older, had a longer duration of type 2 DM (8-10 years), and had more established CV disease at baseline. The benefits of early and intensive glycemic control may accrue only after several years, which may be why trials of longer duration, such as UKPDS, EDIC,[12] and STENO-2,[16] show stronger benefits with aggressive management of hyperglycemia than do trials of shorter duration. Likely because of a lesser availability of therapies for type 2 DM at that time, the HbA_{1c} levels achieved in the intensive treatment arm at the end of the UKPDS were higher than those achieved in the intensive therapy arms of the other 3 trials.[5,6,10,11]

A recent meta-analysis by Mannucci et al[17] examined the effects of intensive glycemic control on CV outcomes in pooled data from UKPDS, ACCORD, ADVANCE, and VADT, in addition to the PROACTIVE (Prospective Pioglitazone Clinical Trial in Macrovascular Events) study. This meta-analysis showed that an overall decrease in HbA_{1c} values of 0.9% resulted in modest reduction in the risk of CV events and MI in the intensive therapy groups (for CV events: odds ratio [OR], 0.89; 95% confidence interval [CI], 0.83-0.95; for MI: OR, 0.86; 95% CI, 0.78-0.93) but no significant reductions in all-cause or CV mortality or stroke. In a similar meta-analysis, Ray et al[18] showed a 17% reduction in nonfatal MI in the intensive vs conservative control groups that was not accompanied by a significant difference in mortality. A recent retrospective cohort study from the UK General Practice Research Database examined survival in 47,970 patients with type 2 DM who were advanced from oral monotherapy to combination oral therapy with a sulfonylurea and metformin or to an insulin-based regimen. This study showed that an HbA_{1c} value of 7.5% was associated with the lowest mortality.[19]

The cumulative data from these studies suggest that the potential for benefit or harm from intensive therapy may be determined by the presence or absence of significant atherosclerosis at the time of therapy initiation[5,6,10,11] and that a less aggressive approach, with an HbA_{1c} target of 7.0% to 7.5%, appears to be the preferred strategy for patients with limited life expectancy and/or those with established CV disease or long-standing type 2 DM (who generally also have significant coronary atherosclerosis). In contrast, patients who are younger with a shorter duration of type 2 DM and no established CV disease may be better candidates for more intensive glycemic control.

THE CV TOXICITY OF HYPOGLYCEMIA

Hypoglycemia is a common problem in patients with type 2 DM who need to be treated with insulin or sulfonylureas, and hypoglycemia occurred more frequently in the intensive therapy arms of the ACCORD, ADVANCE, VADT, and UKPDS trials.[5,6,10,11] Hypoglycemia, especially when severe, is a powerful stimulant of the sympathetic nervous system, which in turn may trigger adverse CV events, such as cardiac arrhythmias, sudden cardiac arrest, and acute MI.[20,21] Prolongation of the QT interval, ventricular arrhythmias, and impaired autonomic function are also associated with hypoglycemic episodes.[20-23] Hypoglycemia is also proinflammatory and can increase the risk of plaque inflammation, rupture, and CV events.[24,25]

In their meta-analysis of glycemic control and CV events, Mannucci et al[17] suggested an association between CV death in the intensive therapy arms and severe hypoglycemia. Moreover, a recent case control study showed

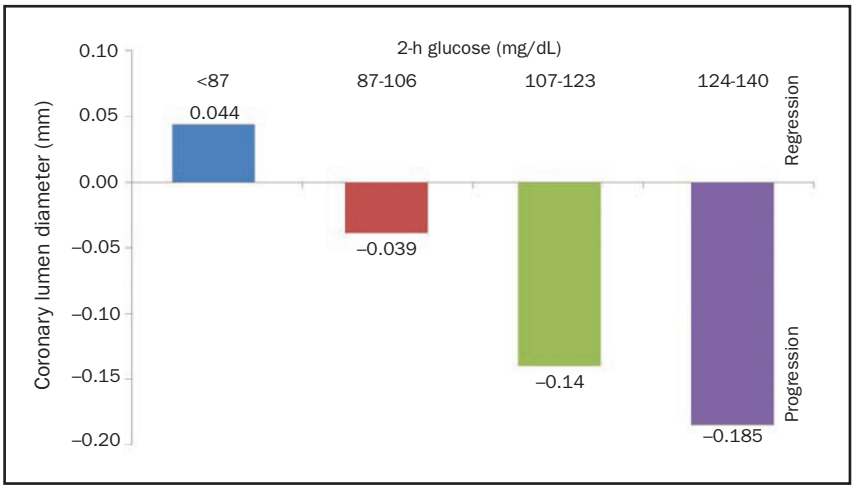

FIGURE 3. Postchallenge glucose and coronary atherosclerosis progression. Only women with postchallenge glucose values of less than 87 mg/dL (to convert to mmol/L, multiply by 0.0555) had regression in coronary atherosclerosis.
From *J Am Coll Cardiol*,[28] with permission from Elsevier.

that, when compared with a control group, patients with type 2 DM with a first MI were more likely to have had a major hypoglycemic episode within the previous year, especially within the 2-week period before the MI.[26]

Although speculative, the CV toxicity caused by recurrent or severe hypoglycemia induced by an aggressive glycemic control strategy (particularly with insulin or sulfonylureas) may supersede the CV benefits of improved glycemic control. This may be particularly true for those who have a predisposition to adverse CV events, such as persons with significant atherosclerosis and/or structural heart disease, such as left ventricular (LV) hypertrophy or systolic and/or diastolic dysfunction. Thus, it is not surprising that patients with long-standing type 2 DM (with its associations with atherosclerosis and myocardial structural and functional abnormalities) and/or existing CV disease may be more susceptible to the cardiotoxicity induced by hypoglycemia.

THE CARDIOTOXICITY OF POSTPRANDIAL HYPERGLYCEMIA

Another possible reason for the failure of glucose-lowering strategies to improve CV prognosis is the use of glucose-lowering therapies that are directed more to the lowering of fasting and preprandial glucose levels than to the lowering of postprandial glucose levels. Postprandial hyperglycemia has been shown to be associated with an increased risk of CV events in patients with and without type 2 DM.[27-30] Postprandial glucose excursions, especially when accompanied by increased postprandial triglyceride levels, are pathophysiologically linked to increased oxidative stress, systemic inflammation, and endothelial dysfunction, all of which are related to increases in atherosclerosis and CV events.[31,32] Importantly, even in the setting of controlled fasting glucose levels, postprandial spikes in glucose powerfully increase both atherogenesis and CV events.[27-30]

A study of postmenopausal women without DM but with coronary artery disease (CAD) showed that the change in the minimal vessel diameter on quantitative coronary angiography during 3 years of follow-up was inversely proportional to the 2-hour postchallenge, but not fasting, glucose levels (Figure 3).[33] In fact, a 2-hour postprandial glucose level of less than 87 mg/dL (to convert to mmol/L, multiply by 0.0555) was associated with regression of atheroma.[33]

Pharmacological lowering of postprandial glucose generally has been shown to decrease CV events.[34] The STOP-NIDDM (STOP Noninsulin-Dependent Diabetes Mellitus) trial was a large randomized placebo-controlled trial assessing the effects of acarbose in the prevention of type 2 DM in patients with impaired glucose tolerance.[34] Acarbose, an α-glucosidase inhibitor that slows the digestive breakdown of starch and sucrose to glucose and therefore almost exclusively affects postprandial glucose, was associated with not only a 25% reduction in progression to type 2 DM but also a 49% reduction in CV events during the 3.3 years of this randomized trial (Figure 4).[34] Although the rate of discontinuation of the study medication was higher in the active treatment arm, mainly due to gastrointestinal adverse effects (eg, flatulence), these results were statistically significant.[34] To further investigate the

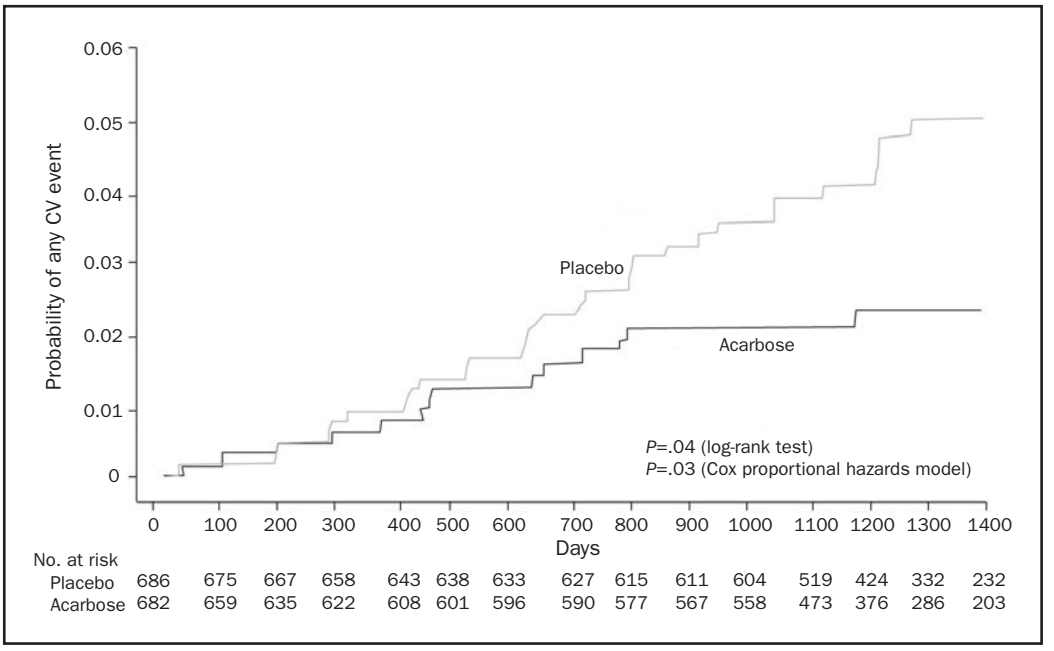

FIGURE 4. Cardiovascular (CV) events in STOP-NIDDM (STOP Noninsulin-Dependent Diabetes Mellitus). Probability of remaining free of CV disease (chronic heart disease, CV death, heart failure, cerebrovascular event, and peripheral vascular disease) from STOP- NIDDM.
From *JAMA*,[34] with permission. Copyright © 2003 American Medical Association. All rights reserved.

favorable effects of acarbose on CV events, a meta-analysis of 7 studies of acarbose in patients with type 2 DM was preformed. Compared with other medications used in the treatment of patients with type 2 DM, acarbose was associated with a 35% relative risk reduction for any CV event. This statistically significant finding was driven primarily by a markedly decreased risk of MI (OR, 0.36; 95% CI, 0.16-0.80).[35] Moreover, a prospective subgroup analysis of STOP-NIDDM showed that acarbose, as compared with placebo, slowed carotid intima-media thickening by 50%, a benefit that abated after discontinuation of acarbose.[36]

However, not all agents that lower postprandial glucose levels are effective for reducing CV events. The NAVIGATOR (Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research) trial showed that nateglinide, a sulfonylurea-like agent that lowers postprandial glucose, was ineffective at halting progression from impaired glucose tolerance to overt type 2 DM and had no significant impact on reducing CV events.[37] However, for uncertain reasons, nateglinide did not lower the post–glucose challenge glucose levels for the patients in the NAVIGATOR trial.

CARDIOTOXICITY OF INSULIN RESISTANCE

Insulin resistance is associated with increases in a plethora of CAD risk factors, including hypertension,[38] low levels of high-density lipoprotein cholesterol,[38,39] high triglyceride levels,[38,39] an increased number and decreased size of low-density lipoprotein cholesterol (LDL-C) particles,[39] higher C-reactive protein levels,[40] decreased fibrinolysis,[39] and endothelial dysfunction.[41] Epidemiologically, insulin resistance has also been shown to be associated with increased atherosclerosis and increased CV events.[42] Lowering insulin resistance may also result in less atherosclerosis and decreased CV events.

PROMISING APPROACHES TO IMPROVING CV PROGNOSIS IN TYPE 2 DM

Taken together, these data suggest that a logical and promising approach to improving the CV prognosis for the patient with type 2 DM would be to use therapies that (1) improve glycemic control without leading to hypoglycemia, (2) effectively lower postprandial glucose excursions (or lower both fasting and postprandial glucose), and (3) lower insulin resistance. In fact, therapeutic strategies using agents that have these 3 features have shown promise for reducing CV events in prospective trials. These therapies include metformin, acarbose, bile acid sequestrants, incretin mimetics, and dipeptidyl peptidase 4 (DPP-4) inhibitors. Although pioglitazone, which improves CV risk markers, offers another option, its tendency to cause fluid retention and weight gain and adversely affect bone

health is problematic.[43] Bariatric surgery in the treatment of patients with morbid obesity has been shown to confer glucose-lowering and insulin-sensitizing effects. The relative effects of glucose-lowering drugs on the triad of postprandial glucose, insulin resistance, and hypoglycemia are shown in the Table. Although insulin use requires injections and can cause hypoglycemia, many patients with type 2 DM, especially those who have had the disease for a decade or more, will require insulin therapy to maintain reasonable glycemic control. In such patients, as in patients with type 1 DM, modern insulin agents, when used in conjunction with frequent glucose monitoring and close follow-up with a health care professional, have been shown to improve prognosis.[12,16]

TABLE. **Effects of Antidiabetic Drugs on the Triad of Postprandial Glucose, Insulin Resistance, and Hypoglycemia**

Drug class	Lower(s) postprandial glucose	Lower(s) insulin resistance	Avoid(s) hypoglycemia
Sulfonylureas	+	–	–
Metformin	–	+	+
Thiazolidinediones	+	+	+
Incretin-based therapies	+	–	+
Bile acid sequestrants	+	–	+
α-Glucosidase inhibitors	+	–	+

Metformin

The hypoglycemic effect of metformin is due to decreased resistance to the action of insulin on the liver and kidneys, which reduces the hepatic and renal production of glucose.[44] In addition, probably as a result of its anorectic effect and/or the weight loss it induces, metformin lowers peripheral insulin resistance and is associated with a low risk of hypoglycemia. However, only modest reductions in postprandial glucose excursions are achieved with metformin.[45]

Using the UK General Practice Research Database, a recent retrospective study by Tzoulaki et al[46] showed that, compared with sulfonylureas, metformin was associated with a lower risk of all-cause mortality and was nonsignificantly associated with a lower risk of a first MI.[46] The differences between metformin and sulfonylureas could simply be due to the low risk of hypoglycemia that occurs with metformin.[7] However, another contributing factor may be that sulfonylureas inhibit myocardial ischemic preconditioning by blocking the adenosine triphosphate–sensitive potassium channels, thereby worsening myocardial ischemia and potentially resulting in larger infarcts, more arrhythmias, and heart failure (HF).[47] Nevertheless, sulfonylureas are very inexpensive and thus are commonly used, especially for patients who have a difficult time affording their DM medications.

Thiazolidinediones

Thiazolidinediones (TZDs) lower insulin resistance[45] and increase adiponectin levels,[48] thereby improving CV risk factors (inflammation,[49] endothelial dysfunction,[50] albuminuria,[51] high-density lipoprotein cholesterol levels,[49] triglyceride levels,[49] plasminogen activator inhibitor levels,[52] and platelet aggregation[53]). Both rosiglitazone and pioglitazone have been shown to decrease carotid intima-media thickening; however, pioglitazone, but not rosiglitazone, has been shown to decelerate the formation of coronary artery atheroma as assessed by intravascular ultrasonography.[54-57]

Of more importance is whether the favorable effects of pioglitazone on CV risk factors and formation of atheroma translate into a decrease in CV events. The PROACTIVE study randomized 5238 patients with CV disease and suboptimally controlled type 2 DM to the addition of pioglitazone or placebo to their existing type 2 DM therapy.[58] After 3 years, a nonsignificant favorable trend in the primary composite end point of adverse CV and peripheral artery disease events was found in the pioglitazone arm.[58] A statistically significant 16% improvement in the secondary end point of the composite of all-cause mortality, nonfatal MI, and stroke occurred in the pioglitazone arm (Figure 5).[58] Pioglitazone also reduced the recurrence of both MI and stroke.[59,60] As expected, the frequency of reported HF and hospital admissions for HF in the pioglitazone arm was increased compared with placebo.[61]

Although rosiglitazone has been shown to lower some CV risk factors and limit formation of carotid but not coronary atheroma, it has not been shown to decrease CV events.[62] Rosiglitazone was the TZD used in the RECORD (Rosiglitazone Evaluated for Outcomes and Regulation of Glycaemia in Diabetes), ACCORD, VADT, and BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes)[63] randomized controlled trials without any significant adverse effect on CV events.[64] However, a possible association between rosiglitazone and an increased risk of MI was reported in a widely publicized meta-analysis by Nissen and Wolski[65] and in some large retrospective database studies.[66-68] Recently, the European Medicines Agency ruled that rosiglitazone could no longer be marketed or available in Europe, and the US Food and Drug Administration mandated that rosiglitazone remain available only under very restricted access conditions (inability to achieve glycemic control using other agents, including pioglitazone).

Treatment with TZDs increases the plasma volume by as much as 5%, which is usually manifest as dependent edema and weight gain. However, in the type 2 DM

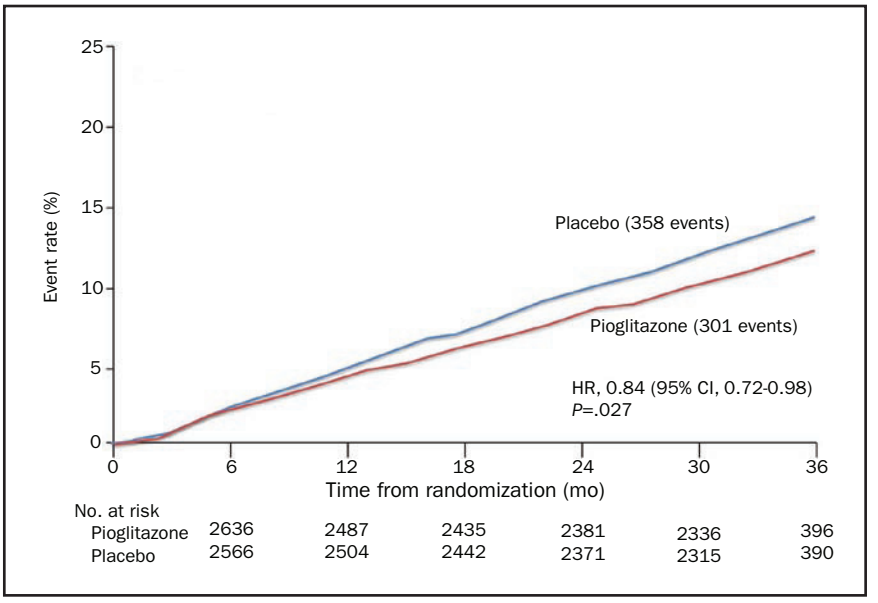

FIGURE 5. Main secondary end point of Prospective Pioglitazone Clinical Trial In Macrovascular Events. Kaplan-Meier plot of time to death from any cause, nonfatal myocardial infarction, or stroke. CI = confidence interval; HR = hazard ratio.
From *Lancet*,[58] with permission from Elsevier.

patient population, 70% of whom have LV hypertrophy and 50% to 60% of whom have diastolic dysfunction, this TZD-induced volume expansion can precipitate HF. The diuretics that are most effective for improving the fluid retention associated with TZDs are the aldosterone receptor blockers spironolactone and eplerenone.[69] Although the effects of TZDs on LV function are neutral, their tendency to increase plasma volume could precipitate HF.[67,68,70]

In summary, pioglitazone, but not rosiglitazone, appears to be helpful in slowing the progression of atherosclerosis in the carotid and coronary arteries and may decrease CV events. However, the TZDs definitely increase the risk of HF and may also increase the risk of bone fractures.[43] Pioglitazone, which is slated to be available generically in 2012, may be beneficial in selected patients with type 2 DM, especially when used in combination with metformin. Patients with HF should not be treated with a TZD. Rosiglitazone should not be used because of concerns about CV safety.

α-Glucosidase Inhibitors

By blocking the activity of α-glucosidase, α-glucosidase inhibitors slow the digestion of starches and disaccharides into glucose, decreasing both postprandial hyperglycemia and hypertriglyceridemia.[71] As already described herein, acarbose therapy decreases the progression of thickening of the intima and media of carotid arteries and decreases the incidence of MI and other CV events.[34-36] The improvement in CV events that has been shown with α-glucosidase inhibitors likely results from the lowering of postprandial glucose and triglyceride levels. In addition, α-glucosidase inhibitors do not cause hypoglycemia.[35]

Bile Acid Sequestrants

Bile acid sequestrants are nonsystemic medications that lower both LDL-C and glucose levels and therefore offer a dual benefit on 2 major CV risk factors.[72,73] One bile acid sequestrant (cholestyramine) has been proven to reduce adverse CV events. In a 7-year randomized placebo-controlled primary prevention trial of 3800 patients, cholestyramine lowered the risk of CV death by 24% and MI by 18%, despite lowering LDL-C by only 12.6%.[72] Colesevelam is a newer and better-tolerated bile acid sequestrant that has been shown to have glucose-lowering effects in addition to lipid-lowering and anti-inflammatory effects, especially when combined with a statin.[73,74] Colesevelam has therefore been approved by the US Food and Drug Administration for the treatment of type 2 DM and has been shown to lower postprandial glucose levels and not to cause hypoglycemia.[75] However, long-term, randomized outcome studies of CV events using colesevelam in patients with type 2 DM have not been performed.

Incretin Mimetics and DPP-4 Inhibitors

Agents that modulate the incretin system, such as incretin mimetics (exenatide and liraglutide), slow gastric empty-

ing, suppress glucagon production, and increase glucose-stimulated insulin release, thereby effectively reducing postprandial glucose levels and posing a low risk of hypoglycemia.[76] Dipeptidyl peptidase 4 inhibitors (sitagliptin and saxagliptin) also increase glucose-stimulated insulin release and suppress glucagon production but do not decrease gastric emptying[76] and are therefore effective in reducing postprandial glucose levels without inducing hypoglycemia.[76] Drugs modulating the incretin system are promising agents for improving the adverse CV prognosis associated with type 2 DM. By either increasing the levels of glucagon-like peptide 1 (GLP-1) or mimicking its effects, these drugs appear to improve LV function and some CV risk factors.[76] Continuous intravenous infusion of GLP-1 for 5 weeks was shown to improve LV ejection fraction (LVEF) and functional status in patients with class III/IV HF.[77] Additionally, a 72-hour intravenous infusion of GLP-1 after successful primary angioplasty resulted in improved LVEF in patients who had had an acute MI and severe LV dysfunction (LVEF <40%).[78] A recent meta-analysis of 41 randomized controlled trials examining CV events with the use of DPP-4 inhibitors suggested that these agents did not increase CV risk or all-cause mortality and were associated with a favorable trend toward lower CV events.[79] A study evaluating CV outcomes with use of sitagliptin is currently under way (ClinicalTrials.gov identifier: NCT00790205) and is expected to finish in 2015.[80]

By improving postprandial hyperglycemia, CV risk factors, and LV function without causing hypoglycemia, incretin mimetics and DDP-4 inhibitors may prove to be effective in reducing CV events; however, this potential benefit remains purely speculative at this point. The major adverse effect of incretin mimetics is nausea; pancreatitis has been seen rarely in association with both incretin mimetics and DPP-4 inhibitors.[79]

Bariatric Surgery

Excess abdominal adipose tissue increases insulin resistance and inflammation and markedly increases the likelihood of type 2 DM and adverse CV events.[81-83] Bariatric surgery, which increases GLP-1 levels likely as a result of rapid dumping of chyme into the small intestine, is an option for morbidly obese patients with type 2 DM.[84] The "cure" of type 2 DM after a Roux-en-Y gastric bypass procedure usually happens early, often before significant weight loss has occurred.[85] This suggests that a role in the resolution of type 2 DM is played by an alternative mechanism, such as increased GLP-1 levels that in turn improve β-cell function and insulin production.[85] In a large, prospective, controlled, nonrandomized trial, bariatric surgery was associated with resolution of type 2 DM in 72% of patients after 2 years and 36% after 10 years.[86] During 7.1 years of follow-up, a large retrospective cohort study showed a 40% reduction in all-cause mortality in morbidly obese patients who underwent gastric bypass surgery compared with age-, sex-, and body mass index–matched controls.[87] Because of the increased insulin production associated with Roux-en-Y gastric bypass, hypoglycemia can be a problem.[85] Other complications of bariatric surgery include dumping syndrome and malabsorption of essential nutrients, such as vitamin B_{12}, iron, and fat-soluble vitamins.[85]

CONCLUSION

Type 2 DM is a major risk factor for CAD. The main target for prevention of CAD remains the strict control of the major associated CV risk factors that tend to cluster with type 2 DM—primarily hypertension and dyslipidemia.[16] Glycemic control is important for preventing microvascular complications, such as retinopathy, nephropathy, and neuropathy. Improved glycemic control may also confer macrovascular CV benefits, especially in those with a more recent onset of type 2 DM and without established CAD, and when therapies that lower postprandial hyperglycemia and do not cause hypoglycemia are used. Therapies that lower insulin resistance may also independently reduce CV events.

According to the American Diabetes Association, the American College of Cardiology, and the American Heart Association, the current HbA_{1c} target for patients with type 2 DM is less than 7%.[88] Available data suggest that aggressive control below this goal does not provide benefit and may be harmful, particularly in patients of advanced age, those with a longer duration of type 2 DM, and those with established CAD. In contrast, younger patients with relatively recently diagnosed type 2 DM and no known CAD are more likely to benefit from a more aggressive approach to glycemic control.

The major factor in improving CV events with glycemic control may well be the therapies that are used to achieve this control. Preferred treatments rely on drugs that do not cause hypoglycemia (metformin, pioglitazone, α-glucosidase inhibitors, incretin mimetics, and bile acid sequestrants) rather than on insulin or sulfonylureas, which are associated with a higher risk of hypoglycemia. If possible, sulfonylureas should be the last oral agents to be used in patients with type 2 DM and may be bypassed by using insulin. When insulin therapy is required, insulin analogues, which may be associated with a lower risk of hypoglycemia, are preferred. Furthermore, drugs that have shown favorable effects on insulin resistance, postprandial glucose levels, atherosclerosis, and CV events should be

favored. The CV benefits of pioglitazone may outweigh the risks of this medication for some patients, but it should not be used in patients with HF. Because of concerns about its CV safety, rosiglitazone should not be used. The CV prognosis for patients with type 2 DM may depend less on the HbA_{1c} level achieved than on the way in which it was attained.

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