Divergent Effects of Various Diabetes Drugs on Cardiovascular Prognosis

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This review discusses the current data on various antidiabetic medications and their effects on major adverse cardiovascular events (MACE). Diabetes mellitus is a potent independent risk factor for MACE, and this risk increases in proportion to the elevation of hemoglobin A_{1c}. Available data suggest that tight glycemic control in patients with diabetes reduces microvascular complications, but has limited effect or may even increase the risk of MACE and other macrovascular complications. For individuals with type 2 diabetes mellitus (T2DM) drugs that reduce postprandial glucose (α-glucosidase inhibitors, incretin mimetics, quick-acting bromocriptine, dipeptidyl peptidase-4 inhibitors, and colesevelam) are associated with a decrease in MACE. Drugs that directly reduce insulin resistance (pioglitazone and metformin) are also associated with lesser but still significant decreases in MACE. Insulin, rosiglitazone (but not pioglitazone), and sulfonylureas (especially with glyburide and particularly the glyburide + metformin combination) are associated with increases in MACE. In summary, drugs that reduce postprandial glucose and improve insulin resistance without predisposing patients to hypoglycemia appear to both control hyperglycemia and improve cardiovascular prognosis. However, many of the traditional agents used for treating T2DM, such as insulin and sulfonylureas, do not improve cardiovascular prognosis despite improving hyperglycemia.

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KEY WORDS

Major adverse cardiovascular events • Type 2 diabetes mellitus • Sulfonylureas • Thiazoledinediones • Metformin • Increta mimetics • DPP4 inhibitors • Quick-release bromocriptine • Insulin resistance • Postprandial hypergylcemia

In 2008, the US Food and Drug Administration (FDA) advisory committee recommended that the sponsor for newer antidiabetic medications should include more patients with diabetes who are at higher risk of major adverse cardiovascular events (MACE) in clinical trials, and that phase 2 and phase 3 clinical trials for new drugs should be pooled for systematic analysis for cardiovascular

(CV) death, myocardial infarction (MI), and stroke. As a response to this recommendation, this review discusses the existing data on the effects of antidiabetic medications on MACE.

The recent European Association for the Study of Diabetes/American Diabetes Association recommendations on management of hyperglycemia in type 2 diabetes mellitus (T2DM) have clearly stated that a major treatment goal must be comprehensive multifactorial CV risk reduction.[1] The United Kingdom Prospective Diabetes Study (UKPDS) showed that with new-onset T2DM, an elevated low-density lipoprotein (LDL) cholesterol presented the greatest risk for future MI, followed in descending order by a low high-density lipoprotein (HDL) cholesterol level, an elevated hemoglobin A_{1c}, (HbA_{1c}), systolic hypertension, and cigarette smoking.[2]

In the Steno-2 study, intensively treating CV risk factors (fasting glucose, triglyceride, total cholesterol, LDL, and hypertension) over almost 8 years resulted in significant decreases in mortality (46%), CV death (57%), and CV events (59%).[3] A 10-year follow-up of the UKPDS showed that the decrease in CV events with better glycemic control in the initial study was maintained with significant decreases in MI in the intensive therapy group.[4] The long-term decrease in CV events occurred in the group that was initially better controlled in spite of equivalent HbA_{1c} levels in the intensive and conventional groups during the 10 years that followed the completion of the original study. This "legacy effect" that occurred with glycemic control did not occur with control of systolic hypertension, which also did not differ between the intensive and conventional groups after the completion of the study.[5]

In spite of the association of glycemic control with CV events in UKPDS, in which only those with new-onset diabetes were studied, prospective trials (Action to Control Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease [ADVANCE], and Veterans' Administration Diabetes Trial [VADT]) that were performed in patients with a longer duration of diabetes have not shown significant decreases in CV events with better glycemic control.[6-8] However, a meta-analysis of these studies with the addition of the UKPDS and Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) studies did show a statistically significant 15% reduction in CV events (odds ratio [OR] 0.85; 95% confidence interval [CI], 0.77-0.93).[9] Also a closer look at the VADT showed that tight glycemic control did improve CV prognosis in those with a shorter duration of diabetes ($<$ 15 years) and a low baseline coronary artery calcium score ($<$ 100 Agatson units).[10,11] Therefore, it seems that with more advanced coronary atherosclerosis and/or a longer duration of T2DM, the frequency of CV events does not improve with better glycemic control.

However, of more concern than the lack of decrease in CV events that occurred in the ACCORD, ADVANCE, and VADT trials was the increased mortality that was reported with more intensive diabetes therapy in the ACCORD study, in which the glycemic goal in the intensive treatment group was an $HbA_{1c} < 6.0\%$.[6,12] To reach this level, especially when sulfonylureas and insulin (the only therapies for T2DM that cause hypoglycemia) were being used, the occurrence of frequent and severe hypoglycemia would be expected. Indeed, in a recent report, Seaquist and colleagues,[13] using data from the ACCORD study, showed that there was a small but statistically significant inverse relationship between the number of hypoglycemic episodes and the risk of death.

The Importance of Hypoglycemia as a Cause of CV Events in Patients With T2DM

The UK General Practice Database studied more than 38,000 patients who were aged $>$ 50 years and whose diabetic therapy had recently been intensified. This group included $>$ 20,000 subjects who had advanced from oral therapy alone to oral therapy with insulin. Mortality as a function of glycemic control showed a U-shaped distribution with the nadir of the curve being at an HbA_{1c} of 7.5%; that is, the level at which there was the lowest mortality (hazard ratio [HR] 1.0). The decile in which HbA_{1c} levels were 10.1% to 11.2% had the greatest HR at 1.49; the HR was also 1.49 for those in whom insulin had been initiated versus those in whom oral antidiabetic therapy had been intensified.[14] Compared with those with an average HbA_{1c} between 8.0% and 8.9%, those with an HbA_{1c} between 9.0% and 9.9% and those with an HbA_{1c} of $>$ 10% had statistically significant increases in mortality of 11%, 36%, and 59%, respectively, compared with those with an HbA_{1c} level between 7.0% and 7.9%. Compared with those with an HbA_{1c} level between 7% and 9%, those with HbA_{1c} between 5.0% and 5.9% or $HbA_{1c} < 5\%$ had statistically significant increases in mortality of 8% and 39%, respectively.[15] In hemodialysis patients, a similar U-shaped curve has been described, with increased mortality occurring at both high and low HbA_{1c} levels.[16]

Confirmation of the danger of hypoglycemia in patients with

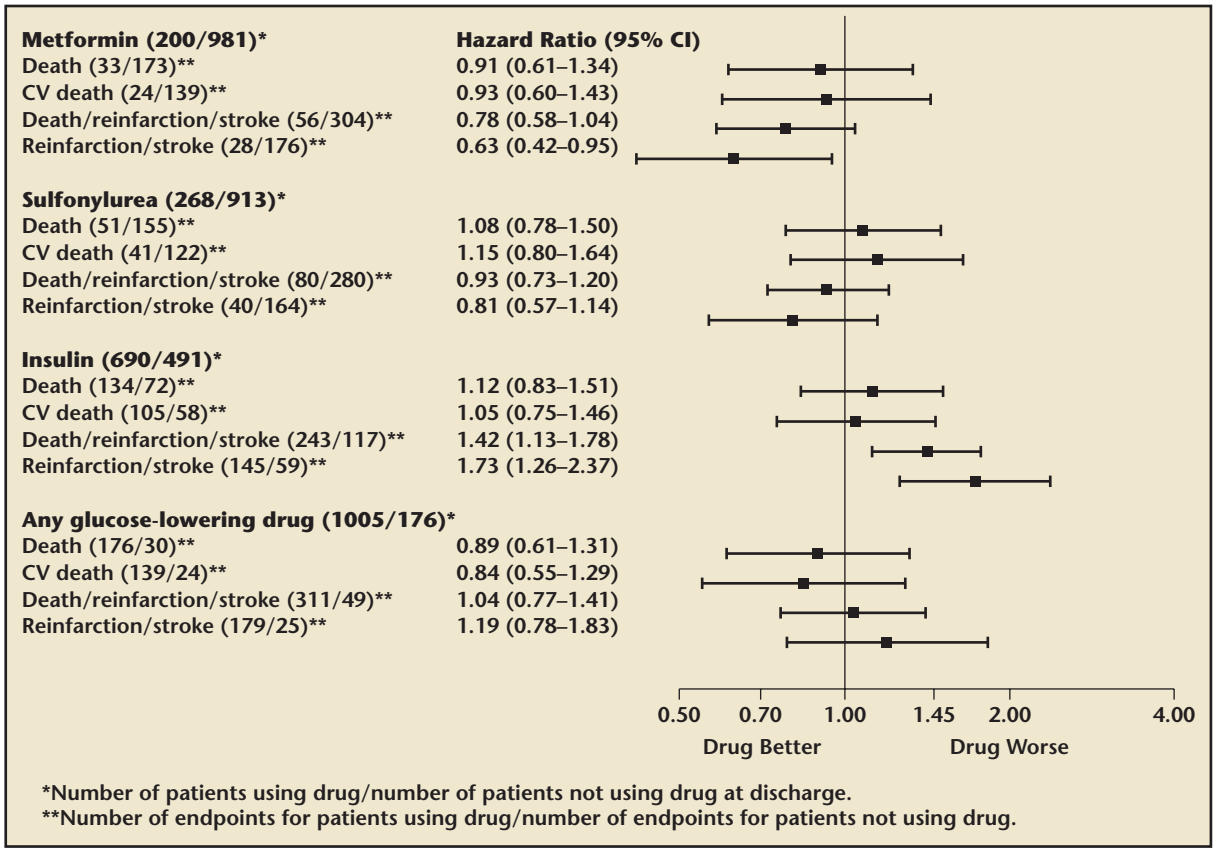

Figure 1. Effect of different updated glucose-lowering treatments on mortality and morbidity. CI, confidence interval, CV, cardiovascular. Reprinted with permission from Mellbin LG et al, *Eur Heart J.* 2008;29:166-176.

T2DM was also shown in a nested case-control study that used a major pharmaceutical database and showed that those subjects who had an $HbA_{1c} < 6\%$, when compared with those who had an HbA_{1c} between 6.0% and 8.0%, had a 16% increase in mortality.[16] In the Treating to Target in Type 2 diabetes (4-T) study, patients with insulin-requiring T2DM were randomized to either biphasic insulin twice daily, basal insulin once daily, or preprandial short-acting insulin three times daily. The highest incidence of hypoglycemia occurred in the prandial short-acting insulin group (5.5 events/year vs 3.0 events/year with biphasic twice-daily insulin and 1.7 events/year with basal insulin) and the highest number of CV deaths occurred in the prandial insulin group (9 vs 4 in both the biphasic group and basal insulin groups; $P = .002$) suggesting an association of hypoglycemia and cardiac death.[17] In the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction 2 (DIGAMI-2) study, those patients who used metformin, which is not associated with major hypoglycemia, had a decreased incidence of both nonfatal MI and stroke (HR 0.63; 95% CI, 0.63-1.42; $P = .23$) compared with those on insulin who had a significant increase in CV events (HR 1.73; 95%, CI, 1.26-1.73; $P = .0007$) (Figures 1 and 2).[18]

Interestingly, the increase in CV events was similar in those who were already using insulin when the study began and those who were initiated on insulin after randomization.[18] At the 2011 European Society of Cardiology Congress, Bernard[19] reported that after controlling for the duration of diabetes, demographics, diabetic complications, comorbidities, alcohol use, smoking, and hypertension, the use of insulin was associated with a > fivefold increase in mortality compared with subjects without diabetes, probably due to insulin-induced hypoglycemia.[19] In a study that used the Saskatchewan Prescription Database, over 12,000 new users of oral antidiabetic therapy in the years between 1991 and 1996 were identified and were categorized based on the total number of insulin prescriptions that were dispensed in 2009. The mortality rate and the number of CV-related deaths were proportional to insulin exposure, and the association of insulin exposure with total and CV mortality persisted after multivariable adjustments.[20] A retrospective cohort study of 3944 patients on insulin monotherapy compared with 58,532 patients on metformin monotherapy in the UK General Practice Research Database showed

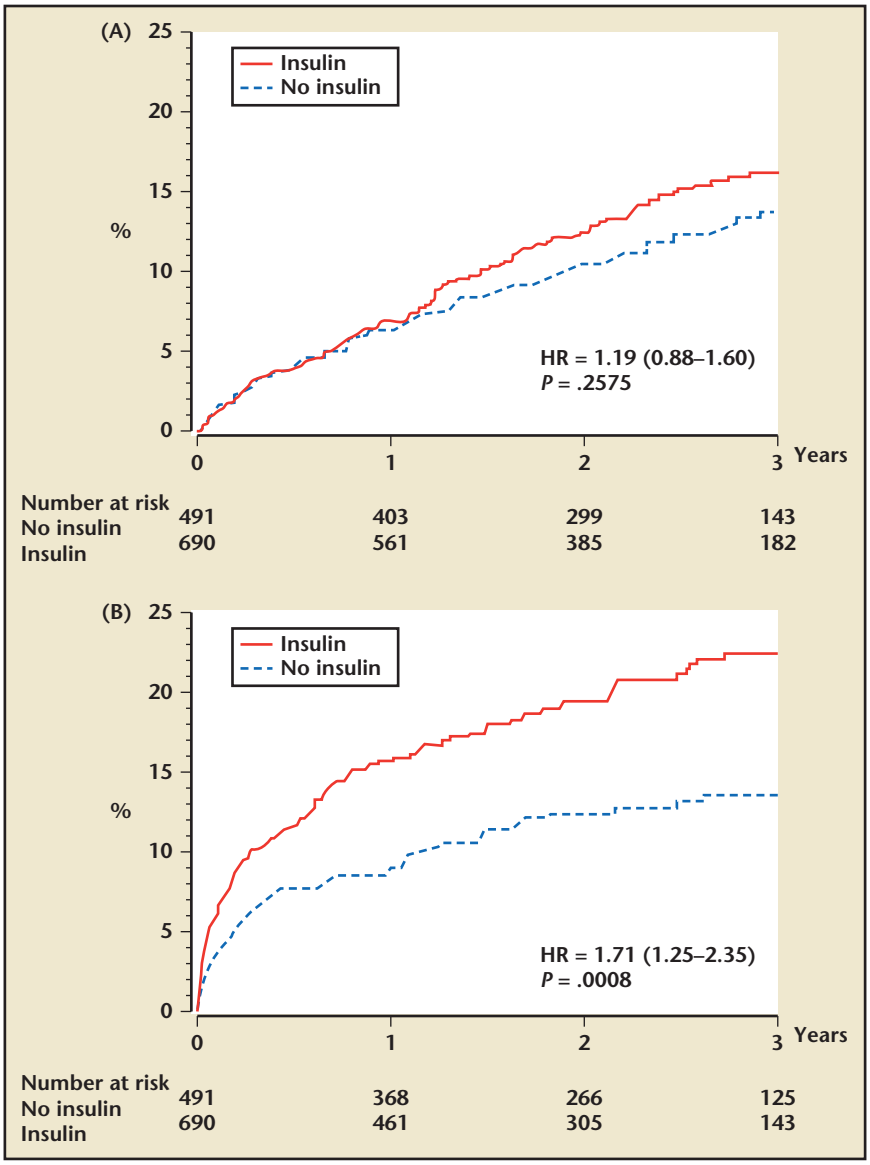

Figure 2. Kaplan-Meier estimates of all-cause mortality (A) and nonfatal reinfarction or stroke (B) in patients with and without insulin treatment at hospital discharge. HR, hazard ratio. Reprinted with permission from Mellbin LG et al, *Eur Heart J.* 2008;29:166-176.

a 95% increase in MI and a 74% increase in MACE within the insulin monotherapy group.[21] The implication from these data is that, if improved glycemic control can be obtained with medications that do not increase the frequency and/or severity of hypoglycemia (metformin, incretin mimetics, dipeptidyl peptidase-4 [DPP4] inhibitors, thiazolidinediones, α-glucosidase inhibitors, and quick-acting bromocriptine and colesevelam), then the lower the HbA_{1c}, the lower the risk of a CV event. However, when agents that have the potential to cause hypoglycemia (insulins and sulfonylureas) are used, a target HbA_{1c} between 7% and 8% and avoidance of severe hypoglycemia will likely lower the long-term rate of CV events.

Why does hypoglycemia play such a powerful role in the induction of CV events? Hypoglycemia impairs the ability of the myocardium to adapt from the utilization of free fatty acids toward the use of glucose as a substrate for the energy required to lower cardiac work load and preserve myocardial function.[22] More importantly, hypoglycemia increases catecholamine levels, which prolongs the QTc interval and increases the risk of cardiac arrhythmia.[23] In addition, antecedent hypoglycemia has been shown to reduce the catecholamine response to a subsequent hypoglycemic event leading to a temporary baroreceptor paralysis, which results in hypotension and further increases the risk for cardiac arrhythmias. When measured 24 hours after a hypoglycemic clamp (serum glucose maintained at 50 mg/dL) in nondiabetic individuals, testing revealed a decreased baroreceptor sensitivity, decreased sympathetic response to hypotension, and a decreased norepinephrine response to negative lower body pressure.[24] A further increase in the baroreceptor paralysis is even more likely to result in a cardiac arrhythmia when preexisting cardiac autonomic neuropathy is present in the patient with diabetes.[25] Thus, hypoglycemia-induced catecholamine release results in QT prolongation, an increased frequency of cardiac arrhythmias, and baroreceptor paralysis. Furthermore, overzealous use of antidiabetic therapies that can cause severe and/or frequent hypoglycemia (insulin and sulfonylureas) could explain the increases in CV events and mortality that have been associated with the intensification of glycemic control in patients with T2DM.[6]

In addition to cardiac arrhythmias and hypotension, severe hypoglycemia and recurrent severe hypoglycemia have been associated with increased platelet aggregation, decreased fibrinolysis, increased coagulation, vasoconstriction, increased inflammation due to increased cytokine production, increased oxidative stress, decreased intracellular potassium, increased intracellular calcium, and increased myocardial oxygen consumption—all of which have

TABLE 1

Risk of Developing CAD With Initial Oral Hypoglycemic Treatments in Patients With Type 2 Diabetes

	Cases with CAD (N = 76)[a]	Controls[b] without CAD (N = 152)[a]	OR (95% CI)	*P* value
Glibenclamide				
Yes	31	34		
No	45	118	2.4 (1.3-4.3)	0.004
Glipizide				
Yes	12	13		
No	64	139	2.0 (0.9-4.6)	0.099
Glimepiride				
Yes	7	20		
No	69	132	0.7 (0.3-1.7)	0.385
Gliclazide				
Yes	11	33		
No	65	119	0.6 (0.3-1.3)	0.192
Older agents, glibenclamide or glipizide				
Yes	43	47		
No	33	105	2.9 (1.6-5.1)	0.000
Newer agents, glimepiride, or gliclazide				
Yes	18	53		
No	58	99	0.6 (0.3-1.1)	0.090
Metformin				
Yes	19	37		
No	57	115	1.0 (0.5-2.0)	0.913

[a]Patients received more than one drug, and column totals may exceed N.
[b]Controls are matched with cases for 20-year CAD risk at diagnosis of diabetes.
CAD, coronary artery disease; CI, confidence interval; OR, odds ratio.
Reprinted with permission from Sadikot and Mogensen.[28]

the potential to increase the risk of a CV event.[25]

Sulfonylureas

Since the early 1970s there has been evidence, albeit controversial, that sulfonylureas increase CV events. In the University Group Diabetes Program, tolbutamide therapy was shown to increase both cardiac and total mortality when compared with diet alone and insulin therapy.[26] However, in the UKPDS, sulfonylureas were shown only to increase CV events when combined with metformin in thinner individuals. Because subjects in the UKPDS were newly diagnosed and therefore less likely to have CV disease, a sulfonylurea would not have been expected to increase CV events.[27] When sulfonylureas were used as initial therapy in a case-controlled study, the relative risk of CV events was two- to threefold higher in subjects taking glipizide or glyburide compared with those taking gliclazide or glimepiride (Table 1).[28] A retrospective cohort study of 16,218 patients using sulfonylurea monotherapy compared with 58,532 patients on metformin monotherapy showed a significant 39% increase in CV events and 75% increase in mortality.[21] Although hypoglycemia could account for the increase in CV events shown with the use of these older sulfonylureas, a more likely explanation is that impaired myocardial ischemic preconditioning, which has been shown to occur with glipizide and glyburide (but not with glimepiride or gliclazide) is the likely reason for this difference.

In animal models, ischemic preconditioning occurs when repeated and brief occlusions of a coronary artery preceding complete coronary artery ligation result in a smaller infarct than that which occurs when the coronary artery is ligated without the preceding brief occlusions. This is because

multiple brief arterial occlusions cause intermittent ischemia, which opens the K^+ATPase channels in the cardiomyocyte cell membrane; this results in increases in intramyocardial ATP levels, which limits myocardial damage.[29,30] By blocking K^+ATPase channels in the pancreatic β-cell membrane, sulfonylureas depolarize the β cell, resulting in an influx of calcium and an increase in the release of insulin. Unfortunately, with traditional sulfonylureas the K^+ATPase channels are blocked not only in the pancreatic β cells but also in the myocardium, where the resulting decreased intramyocardial energy can lead to larger MIs, decreased cardiac output, heart failure (HF), and death.[28,31]

Ischemic preconditioning reduces the amount of exercise-induced myocardial ischemia for subsequent episodes of physical activity, and increases exercise tolerance when a second stress test is performed shortly after the original ischemia-inducing test. These improvements are blocked when glyburide is administered before the test.[32,33] With coronary angioplasty, balloon inflation causes transient coronary occlusion with resultant ischemia; with subsequent inflations the amount of ischemic myocardium is reduced due to opening of the K^+ATPase channels and ischemic preconditioning. Clinically, this manifests as less chest pain and less impressive ischemia by electrocardiographic appearances (milder ST and T-wave changes). These favorable effects from ischemic preconditioning are abolished with glyburide pretreatment but not with glimepiride.[33-35] Reperfusion injury to the myocardium is also minimized by opening of K^+ATPase channels and due to ischemic preconditioning, patients who have preinfarction angina have less myocardial necrosis than those without preinfarction angina. Both of these favorable effects of ischemic preconditioning, reduction in reperfusion injury and decreased myocardial infarct volume, are blocked with the use of traditional sulfonylureas.[36,37] Following a transmural MI, opening of K^+ATPase channels are needed for ST-segment elevation on the electrocardiogram to occur. Should the K^+ATPase channels be blocked with a traditional sulfonylurea, ST-segment elevation will not occur, thus masking the infarct on the electrocardiogram and possibly depriving the patient of potentially life-saving reperfusion therapy.[38] Therefore, closure of K^+ATPase channels in the myocardium with sulfonylureas robs the myocardium of the protective effects of the preceding myocardial ischemia, resulting in larger myocardial infarcts that, with the omission of reperfusion therapy, could result in even more myocardial damage. Fortunately, the sulfonylureas glimepiride and gliclazide do not close myocardial K^+ATPase channels and are not associated with increases in the frequency and severity of CV events.[28,29] Further evidence of this was shown in a retrospective cohort study of almost 24,000 patients wherein all sulfonylureas were associated with an increased mortality when compared with metformin. However, in those participants who had documented coronary artery disease (CAD), an increased risk of mortality was found with the traditional sulfonylureas glipizide (HR 1.41; 95% CI, 1.07-1.87) and glyburide (HR 1.38; 95% CI, 1.04-1.83), but not with glimepiride.[39]

Should the K^+ATPase channels be blocked with a traditional sulfonylurea, ST-segment elevation will not occur, thus masking the infarct on the electrocardiogram and possibly depriving the patient of potentially life-saving reperfusion therapy.

When sulfonylureas are combined with metformin, even in the presence of recent-onset diabetes, CV events may be increased. This was first observed in the UKPDS in which, in nonobese subjects, a 96% statistically significant increase in mortality with the addition of metformin to failing sulfonylurea therapy compared with continuing sulfonylurea monotherapy and inferior glycemic control was dismissed by the authors as being "an artifact" due to the small number of subjects who were using this combination.[27] However, other studies have confirmed the suspicion of an increased risk of a CV event with the combination of a sulfonylurea and metformin. A 7.7-year Israeli study of subjects with diabetes and CAD showed that, when compared with nondiabetic control subjects with CAD, mortality was significantly increased with glyburide monotherapy by 22%, metformin monotherapy by 26%, and with the combination of glyburide and metformin by 53%.[40] In a Scottish prospective study in which patients were treated with either sulfonylurea monotherapy or a combination of sulfonylurea and metformin, after adjustments for cardiac risk factors, those on the sulfonylurea-metformin combination had a 43% increase in total mortality and a 70% increase in CV mortality compared with those who were treated with metformin monotherapy.[41] In a meta-analysis of observational studies of subjects on a combination of metformin and a sulfonylurea, when compared with control subjects, hospitalizations for CV disease and deaths were significantly increased

by 43%; all-cause mortality was nonsignificantly increased by 19% and CV mortality was nonsignificantly increased by 29%.[42] A meta-regression analysis of the effect of metformin on CV events showed that metformin monotherapy was associated with a trend toward lower mortality, whereas with the combination of metformin and a sulfonylurea there was a 43% significantly increased mortality.[43]

A retrospective review of an observational cohort study from Florence, Italy, showed that the combination of metformin and a sulfonylurea resulted in a significantly higher annual mortality compared with other therapies (6.2% vs 3.6%, respectively) used in T2DM patients with known CV disease.[44] Another epidemiologic study showed that, when compared with other oral antidiabetic agents, the combination of metformin and a sulfonylurea was associated with a > twofold increase in mortality, especially in patients with diabetes and known CV disease.[45]

That glyburide is the sulfonylurea that, when combined with metformin, most commonly leads to increased mortality was suggested in another epidemiologic study in which the outcomes of glyburide therapy were compared with those of other secretagogues and insulin.[46] Furthermore, using the UK General Practice Database it was shown that, compared with metformin monotherapy, the combination of metformin and a sulfonylurea significantly increased mortality by 24% to 61% and HF by 18% to 30%.[47]

Conversely, another British general practice study showed no evidence of increased mortality with the combination of a sulfonylurea and metformin, which matched the results of the Australian Freemantle study, which showed after correction for variables, a metformin/sulfonylurea combination was as safe as other therapies.[48,49]

Taken together, these results suggest that there may be an increased risk of CV events when the metformin/sulfonylurea combination is used, especially in the presence of known ischemic heart disease, and when the sulfonylurea used is neither gliclazide nor glimepiride. A possible explanation for this phenomenon is that the increased energy level within the cardiomyocyte, which occurs with metformin monotherapy, is actually lowered due to blockade of the K^+ATPase channels by a traditional sulfonylurea.

Metformin

In the UKPDS, metformin significantly decreased all-cause mortality, diabetes-related mortality, and MI by 39% in overweight recently diagnosed individuals with diabetes.[27] A meta-regression analysis has confirmed that metformin significantly reduced CV events by 21% and trended toward a lower mortality when used as monotherapy and not used with sulfonylureas when compared with placebo, but not when compared with other antidiabetic medications.[43] To the contrary, a 2012 meta-analysis of 13 trials involving over 13,000 subjects, of whom 75% were taking metformin, showed no significant decreases in total or CV events. In this meta-analysis, there was considerable heterogeneity which corrected after removal of UKPDS data.[50] Metformin also appeared to be more cardioprotective in trials that were of longer duration and trials that were performed in younger subjects.[43] If metformin does lower the risk of a CV event, it may be due to decreased cardiac risk factors such as body weight, total cholesterol, and diastolic blood pressure.[51] In addition, metformin lowers insulin resistance and plasminogen activator inhibitor-1 and improves endothelial function, as evidenced by its ability to decrease urine albumin.[52] Other cardiac risk factors, such as inflammation (elevated high-sensitivity C-reactive protein), elevated factor VIII, increased platelet aggregation, and insulin resistance–induced alteration of the structure of the fibrin molecule are also improved with metformin use.[53]

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Metformin has been shown to reduce mortality and hospital readmission in patients with diabetes and HF. According to a study of the Medicare billing records of 16,417 patients with diabetes and HF discharged from the hospital on metformin, when compared with those patients with diabetes and HF who were discharged on either a sulfonylurea or insulin, metformin significantly reduced mortality by 13% and hospital readmission with HF by 8%.[54] A nested case-control study that used the UK General Practice Database showed that, in patients with diabetes and HF, the use of metformin significantly reduced mortality by 35%, which compared very favorably with blockers of the renin-angiotensin system (RAS) and β-blockers, where mortality was decreased by 45% and 24%, respectively.[55] In addition, a retrospective study of patients with diabetes and advanced systolic HF showed

that being treated with metformin significantly improved 1-year survival (91% vs 76%; relative risk 0.37; $P = .007$).[56] Therefore, although the protective effect of metformin on reducing the incidence of MI is disputable, its effect on HF is much more robust and treated HF should never be a contraindication to the use of metformin.

The positive myocardial effects of metformin, especially in HF, are probably due to metformin's effect on 5'-AMP-activated protein kinase 5 (5'-AMPK).[57] 5'-AMPK is activated in myocytes and cardiomyocytes when there is a limited supply of nutrients, the generation of ATP is impaired, or the energy demands of the cell increase. 5'-AMPK, therefore, acts as a "fuel gauge" that is activated when cellular ATP levels fall; it increases cellular ATP levels by increasing the generation of ATP and by decreasing any unnecessary ATP utilization.[58] Following ischemia and reperfusion, 5'-AMPK has been shown to increase glucose uptake, accelerate glycolysis, and limit cellular apoptosis in the cardiomyocyte.[59] Therefore, by activating 5'-AMPK in the myocardium, metformin preserves both myocardial mass and function, leading to improved cardiac outcomes in diabetic patients, particularly those with HF.

Thiazolidinediones

Thiazolidinediones (TZDs), by reducing insulin resistance, clearly lower both cardiac risk factors and surrogate markers of atherosclerosis in patients with diabetes. In addition, the only currently available TZD, pioglitazone, has been shown to decrease CV events in a randomized prospective study. On the other hand, rosiglitazone, which is no longer available at retail pharmacies, was shown in several meta-analyses to be associated with increased CV events.

Insulin resistance is an inflammatory state associated with increased levels of high-sensitivity C-reactive protein and adipocytokines, and leads to oxidative stress and endothelial dysfunction. When endothelial dysfunction is present in the glomerulus, which is effectively an arteriole, albuminuria occurs. Therefore, albuminuria (in addition to being a marker for the development of diabetic nephropathy) is also an indicator of the extent of atherosclerosis and the risk of CV events. High insulin levels associated with insulin resistance cause renal salt and water retention and stimulate the sympathetic nervous system. As a result of the increase in sodium levels and sympathetic activity, 75% of T2DM subjects are hypertensive and 50% of all hypertensive subjects are insulin resistant. Insulin resistance is also associated with the characteristic lipid profile of elevated triglycerides and decreased HDL levels, so that a triglyceride to HDL ratio of more than 3.6 is diagnostic of insulin resistance even in subjects without diabetes. This simple calculation correlates well with the level of insulin resistance demonstrated on the hyperinsulinemic insulin clamp studies, which are the gold standard for measuring insulin resistance.[60] Although total cholesterol and LDL levels are not increased with insulin resistance, the LDL particle number is increased because, with insulin resistance, the LDL particles are smaller and more dense. These small, dense LDL particles are more easily picked up by the scavenger receptor on the macrophage, which allows for an increased penetration of the vessel wall by LDL particles, which initiates and accelerates the formation of atheromatous plaques.[61] In addition, levels of plasminogen activator inhibitor-1, which opposes the effect of tissue plasminogen activator, are elevated with insulin resistance, leading to decreased fibrinolysis. Decreased fibrinolysis in conjunction with increased platelet aggregation, which is also increased with insulin resistance, leads to an increase in thromboembolic phenomena. All of the aforementioned risk factors, which are associated with insulin resistance, are decreased with TZDs, which lower insulin resistance three times more effectively than with metformin.[62,63]

Thiazolidinediones, by reducing insulin resistance, clearly lower both cardiac risk factors and surrogate markers of atherosclerosis in diabetic patients.

The improvement in cardiac risk factors associated with TZD use results in decreased formation and expansion of atheromatous plaques, as has been shown in subjects with diabetes by decreases in carotid intima-media thickening (CIMT).[64] Stabilization of the coronary atheroma volume with pioglitazone as compared with glimepiride over 6 months was also shown in the Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) study, which used intravascular ultrasound.[65] Conversely, although rosiglitazone decreases CIMT, it was not shown by intravascular ultrasound to stabilize the volume of coronary atheroma.[66,67]

Whether the effects of pioglitazone on cardiac risk factors and accumulation of coronary and carotid artery atheroma translate into decreased CV events is controversial. The PROactive study, in which pioglitazone or placebo were randomly added to existing failing diabetes therapy for just over

3 years after the termination of the study, was event-driven; the primary composite endpoint, which included the manifestations of peripheral vascular disease, showed a statistically nonsignificant reduction in events.[68] However, if only the combination of death, nonfatal MI, or stroke (a predetermined secondary endpoint) was addressed, there was a statistically significant 16% decrease in events.[68] Of greater importance was that there were significant reductions in the recurrence of MI (28%), acute coronary syndromes (37%), and stroke (47%).[69,70] Unlike the negative cardiac outcomes associated with rosiglitazone use that were found in several meta-analyses, a meta-analysis of pioglitazone studies showed a statistically significant 23% reduction in the composite of death, MI, and stroke.[71,72] However, in the PROactive study, the protective effects of pioglitazone were negated by the use of statins, angiotensin-converting enzyme inhibitors, and β-blockers.[73]

TZDs, by stimulating the peroxisome proliferator-activated receptor-γ in the very distal renal tubule, increase sodium retention, which can result not only in dependent edema but also an increase in plasma volume of as much as 5%. This increase in plasma volume results in a "myocardial stress test." More than 40% of patients admitted to the hospital in the United States with HF have diabetes because, in addition to an increased prevalence of CAD in the diabetic population, there is also an increase in the prevalence of left ventricular hypertrophy and diastolic dysfunction due to diabetic cardiomyopathy.[74] Therefore, HF is more common in the patient with diabetes and the increase in plasma volume caused by TZDs may result in an earlier onset of HF than would have occurred if TZDs had not been used. If HF occurs with TZDs, cardioprotective therapy that will prolong survival (RAS blockers, spironolactone, and β-blockers) will be initiated at a much earlier time and myocardial remodeling prevented and/or maximally reversed. In the PROactive study, in which patients were quickly titrated to a maximum dose of pioglitazone in spite of being on insulin or sulfonylureas (both of which are associated with sodium retention), there was a significant increase in edema and admissions to the hospital with HF in those randomized to pioglitazone when compared with those on placebo. However, the mortality rate from HF was not increased and the death rate from HF was higher in those who developed HF while on placebo.[75] In a study of Medicare billing data, HF patients with diabetes discharged from the hospital on a TZD had a 13% decrease in mortality but also had a 6% increased risk of readmission because of recurrent HF.[54]

The likely reason for the effects of TZDs on survival in patients with diabetes and HF is that the failing heart needs to shift its substrate for generation of energy from free fatty acids to glucose so that the cardiac workload can be reduced. This shift cannot be achieved when insulin resistance opposes the uptake of glucose by the myocardium by reducing insulin resistance; TZDs increase myocardial glucose uptake and decrease cardiac workload.[76] In addition, insulin resistance is associated with an increased myocardial triglyceride load, which results in the accumulation of lipotoxic compounds (particularly ceramide), which lead to increased free radical production, accelerated myocardial apoptosis, myocardial fibrosis, and impaired ventricular function. TZDs, by reducing the myocardial triglyceride load, reduce ceramide levels, free radical production, and apoptosis and improve ventricular function.[77,78]

Prevention of restenosis following coronary artery angioplasty has also been reported with TZDs.[79] The use of pioglitazone with a bare metal stent has been statistically shown over a 3-year period not to be inferior to the utilization of a drug-eluting stent without a TZD in patients with diabetes and CAD. Also, those who were treated with a bare metal stent and pioglitazone had similar risks of death, revascularization, MI, and stent thrombosis when compared with those treated with a drug-eluting stent without pioglitazone.[80] The probable reason for the lack of restenosis with TZDs is that they reduce the in-stent neointimal proliferation that occurs when the arterial wall is traumatized during angioplasty.[81]

Rosiglitazone is now only available through certified mail-order pharmacies because an association with an increased risk of MI and cardiac mortality has been documented.[82,83] A meta-analysis comparing the effect of pioglitazone and rosiglitazone on CV events showed significant decreases in the frequency of MI, HF, and death in subjects treated with pioglitazone.[84] The difference in CV events is probably due to the activation of different genes by different TZDs, which results in differing effects on the lipid profile. Rosiglitazone and pioglitazone commonly activate 23 genes, whereas rosiglitazone uniquely activates 5 genes, and pioglitazone uniquely activates 12 genes.[85] Presumably, as a result of these differences in gene activation, the lipid profiles seen with pioglitazone and rosiglitazone are very different. Although pioglitazone is superior to rosiglitazone in lowering triglycerides and total cholesterol levels, and increasing HDL levels and LDL particle size, the major difference between these TZDs is

that the apolipoprotein B level and number of LDL particles are lowered by pioglitazone and elevated by rosiglitazone.[86] Furthermore, these differences persist even when statins are concurrently used.[87] Therefore, the increased number of CV events that occur with rosiglitazone is most likely due to the significant increase in the number of LDL particles. Pioglitazone has been associated with a small but statistically significant increased risk of bladder cancer.

Quick-release Bromocriptine

Because of the increased CV events that occurred with rosiglitazone, which eventually led to its withdrawal, the FDA established new CV safety standards for all new antidiabetic therapies prior to approval. The safety study performed with quick-release bromocriptine showed a significant 40% lower rate of CV events when compared with comparators and placebo, and if only the combination of death, MI, and stroke was assessed, there was a 55% reduction.[88,89] This is not surprising because long-acting bromocriptine, when used to treat hyperprolactinemia and Parkinson disease, had been found to be cardioprotective.[90]

By reducing plasma catecholamine levels in anaesthetized dogs, long-acting bromocriptine raised the threshold for atrial fibrillation by 50%.[91] In humans, as a result of decreased catecholamine release, bromocriptine is associated with a decrease in blood pressure that may even result in orthostatic hypotension.[92] When bromocriptine was used to treat Parkinson disease, CV events were decreased, and a reduction in left ventricular hypertrophy was observed when bromocriptine was used to decrease prolactin levels and treat galactorrhea in dialysis patients.[93,94] In the patient with diabetes and especially in the hypertensive patient, with diabetes, sympathetic activity is increased and a sustained reduction of sympathetic activity should result in a decrease in nocturnal "non-dipping" and a decrease in nocturnal CV events.[95,96] Prior to widespread use of RAS inhibitors and β-blockers, bromocriptine was successfully used in the therapy of HF by decreasing sympathetic activity; more recently, bromocriptine has been shown to be effective in the therapy of acute severe peripartum cardiomyopathy.[97-99] Whether the success of bromocriptine therapy in peripartum cardiomyopathy is due to lowering prolactin levels, as is currently believed, or is due to an effect of bromocriptine on the RAS and sympathetic nervous systems is not known. Aldosterone release is tonically inhibited by dopamine and because spironolactone and eperolone have been shown to decrease mortality in severe HF by blocking the effects of aldosterone, the suppressed release of aldosterone by bromocriptine could also at least partially explain the positive effect of bromocriptine in HF.[100] Quick-release bromocriptine decreases insulin resistance and its associated cardiac risk factors, as well as suppresses postprandial glucose elevations; the accumulated reductions in all of these risk factors could at least partially explain why quick-release bromocriptine has been shown in a safety study by O'Keefe and Bell to decrease CV events.[101] Therefore, suppression of the sympathetic nervous system, inhibition of aldosterone release, and lowering of insulin resistance and postprandial glucose levels could all be explanations for why quick-release bromocriptine decreases CV events.[90]

When bromocriptine was used to treat Parkinson disease, CV events were decreased, and a reduction in left ventricular hypertrophy was observed when bromocriptine was used to decrease prolactin levels and treat galactorrhea in dialysis patients.

Other Drugs That Lower Postprandial Glucose

α-Glucosidase Inhibitors

Postprandial hyperglycemia has been shown to be associated with increases in CV events in both subjects with and without diabetes.[101] Postprandial hyperglycemia is accompanied by increased triglyceride and free fatty acid levels, with the resulting postprandial dysmetabolism leading to inflammation, oxidative stress, and endothelial dysfunction, all of which may lead to an increase in accumulation of atheroma and an increase in CV events. This may occur even when the fasting glucose level is in the normal range, as was shown in a study of glucose-tolerant women with CAD in whom progression was proportional to the 2-hour glucose level but not the fasting glucose level.[102,103] This study of postmenopausal women without diabetes but with 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 the fasting glucose levels (Figure 3). In a study of subjects with type 1 diabetes, the amylin derivative pramlintide, which lowers postprandial glucose through suppression of glucagon release, hepatic glucose production, and gastric emptying, has been shown to reduce measures of oxidative stress (reduced plasma nitrotyrosine, oxidized LDL cholesterol, and improved radical trapping ability).[104]

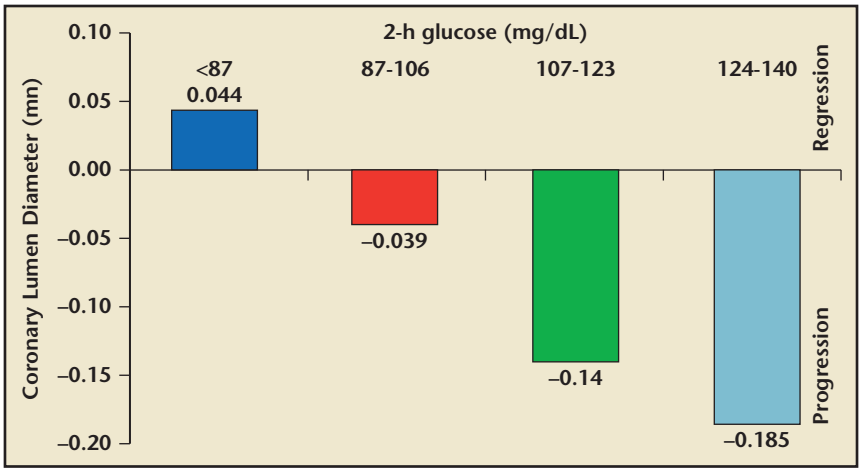

Figure 3. Postchallenge glucose and coronary atherosclerosis progression. Only women with postchallenge glucose values of < 87 mg/dL had regression in coronary atherosclerosis. Data from O'Keefe and Bell[101] and Mellen et al.[103]

Lowering postprandial glucose therefore decreases both cardiac risk factors and the rate of accumulation of atheroma, but the question remains whether this translates into a decrease in CV events. Evidence for a reduction of CV events was shown, albeit retrospectively, in the Study to Prevent Non–Insulin-Dependent Diabetes Mellitus (STOP-NIDDM), which assessed the effect of the α-glucosidase inhibitor acarbose on the development of T2DM in subjects with impaired glucose tolerance. Acarbose was associated not only with a 25% reduction in progression to diabetes, but also a 49% reduction in CV events over 3.3 years.[105] Due to side effects such as flatulence, the dropout rate was greater in the acarbose-treated group than in the placebo-treated group, but even after correction for this imbalance, the decrease in CV events with acarbose was still statistically significant.[105]

Following the revelation that acarbose decreased CV events, a retrospective meta-analysis of seven studies of acarbose in patients with T2DM showed that, compared with other antidiabetic medications, acarbose was associated with a 35% reduction in CV events—a finding that was largely due to a 64% decrease in the incidence of MI.[106] In a subgroup of STOP-NIDDM subjects, acarbose was also shown to reduce the progression of CIMT (a surrogate measure of atheroma accumulation) by 50% when compared with the placebo group. This deceleration of atheroma formation was not permanent because there was regression to the original CIMT when acarbose was discontinued.[107]

However, not all agents that reduce postprandial glucose are associated with decreases in CV events. In the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial, the short-acting secretagogue nateglinide was not effective in lowering CV events in glucose-intolerant subjects. However—for unknown reasons—on glucose tolerance testing, nateglinide did not lower glucose levels in these subjects.[108]

Incretin Mimetics and DPP4 Inhibitors

Incretins lower postprandial glucose by slowing gastric emptying, increasing insulin release, and suppressing the release of glucagon; thus, drugs that increase incretin levels should be associated with decreases in CV events.[105] Subjects who had had an MI and an angioplasty and received a 3-day intravenous infusion of the incretin glucagon-like peptide-1 (GLP-1), improved their ejection fractions from 29% to 39%, and also significantly improved the indices of regional wall movements.[109] GLP-1 has also been shown to have a diuretic effect and to dilate the pulmonary arteries.[110] In patients with HF, intravenous GLP-1 not only improved ejection fraction, but also improved exercise tolerance.[111]

To date, incretin mimetics (eg, exenatide, liraglutide) when used in the treatment of subjects with diabetes, have not been associated with significant decreases in CV events. However, in a meta-analysis, exenatide was shown to nonsignificantly reduce CV events by 30% (95% CI, 0.38-1.39) in 2316 subjects compared with 1629 placebo- or insulin-treated subjects in 12 clinical trials that lasted from 12 to 52 weeks.[112] In a similar meta-analysis, liraglutide has been shown to nonsignificantly reduce CV events by 27% (95% CI, 0.38-1.4) in 4257 subjects when compared with 2381 comparator subjects treated with metformin, glimepiride, rosiglitazone, insulin glargine, or placebo.[113] In a prospective randomized study, liraglutide, when added to metformin therapy, reduced not only the HbA_{1c} level, but also levels of asymmetric dimethylarginine (a measure of improved endothelial function), and improved markers of inflammation and fibrinolysis.[114] A study using a large database in which exenatide-treated subjects started with a disadvantage of more CV comorbidities (including ischemic heart disease), showed that, when compared with those taking other diabetic therapies, subjects who were prescribed exenatide had a 29% decrease in CV events ($P = .01$), a 12% decrease in CV hospitalizations ($P = .02$), and a 6%

reduction ($P = .001$) in all-cause hospitalizations.[115] This improvement in CV events is probably due to the rapid onset and potent anti-inflammatory effect of exenatide, which occur at both the cellular and molecular levels.[116] Independent of weight loss, incretin mimetics have an anti-inflammatory effect and therefore have the potential to be antiatherogenic. Both high-sensitivity C-reactive protein levels and systolic blood pressure are reduced with exenatide, and postprandial endothelial dysfunction has been shown to improve.[117-120]

DPP4 inhibitors, which do not increase GLP-1 activity as much as the incretin mimetics exenatide and liraglutide do, have nevertheless been shown to significantly lower CV events. In a meta-analysis of 19 double-blind clinical trials in which sitagliptin was assigned to 5429 subjects and 4817 subjects assigned to other diabetic medications, there was a 33% nonsignificant decrease in CV events favoring sitagliptin.[121] In a prospective safety study, saxagliptin showed a 57% significant (95% CI, 0.23-0.80) decrease in CV events when compared with placebo and other diabetes therapies, with the differences in CV events seen as early as 3 months after the initiation of therapy.[122] A similar prospective safety study of linagliptin compared 3319 linagliptin-treated subjects with 1920 subjects taking other antidiabetic drugs and showed that CV events were reduced by 66% (95% CI, 0.15-0.75) in the linagliptin-treated group.[123] Retrospective safety studies of alogliptin have also shown a 34% decrease in CV events in those without established CAD and a 20% decrease in those with pre-existing CV risk.[124]

Meta-analyses of DPP4 inhibitor studies have shown results that are similar to the prospective safety studies of individual DPP4 inhibitors. A meta-analysis of 53 clinical trials involving 33,000 subjects showed a 31.3% relative risk reduction in major CV events with DPP4 inhibitors.[125] A meta-analysis of 18 randomized controlled trials in which 4998 patients randomized to monotherapy with a DPP4 inhibitor were compared with 3546 patients randomized to monotherapy with another oral hypoglycemic, and showed a 52% significant decrease in CV events and a 60% significant decrease in nonfatal MI or acute coronary syndromes with DPP4 inhibitors.[126]

If decreases in CV events with incretin mimetics and DPP4 inhibitors were due to the activity of GLP-1, then a greater decrease in CV events would be expected to occur with the greater increase in GLP-1 activity that is associated with the incretin mimetics exenatide and liraglutide. It is therefore likely that the greater decreases in CV events that, to date, have been shown to occur with DPP4 inhibitors is not mediated solely through improved GLP-1 activity and that other mechanisms must be involved.

One candidate for the added decrease in CV events that occur with DPP4 inhibitors is increased levels of high-mobility group box 1 ($HMGB_1$) protein. $HMBG_1$ protein is a cytokine that is released from practically all nucleated cells with necrosis and is also secreted by immune cells such as monocytes and macrophages. Release of $HMGB_1$ induces not only an inflammatory response but also promotes tissue repair and improves angiogenesis. Tissues from subjects with diabetes have been shown to contain lower $HMGB_1$ levels and this may be why, in the patient with diabetes, angiogenesis is defective and the outcomes of ischemic events are worse.[127] In a murine model, $HMGB_1$ has been shown to improve left ventricular function following an experimentally induced MI through enhancing angiogenesis and regenerating cardiomyocytes.[128,129] $HMGB_1$ contains cleavage sites for the DPP4 enzyme so that DPP4 lowers $HMGB_1$ levels and activity and therefore inhibits angiogenesis and tissue repair. When DPP4 inhibitors are used, the activity of $HMGB_1$ is increased to levels found in subjects without diabetes, which leads to improvement in angiogenesis and tissue repair.[130] Therefore, the increase in $HMGB_1$ levels that occurs with DPP4 inhibitors is a possible explanation as to why DPP4 inhibitors decrease CV events more than incretin mimetics in patients with T2DM.

In a murine model, $HMGB_1$ has been shown to improve left ventricular function following an experimentally induced MI through enhancing angiogenesis and regenerating cardiomyocytes.

Recently, the first sodium-glucose cotransporter 2 (SGLT2) inhibitor canagliflozin was approved by the FDA. By blocking the activity of SGLT2 in the proximal renal tubule, canagliflozin induces glycosuria, weight loss, osmotic diuresis, lowering of systolic blood pressure, and reduction of both fasting and postprandial glucose levels without inducing hypoglycemia. However, for unknown reasons, canagliflozin increases the calculated LDL level.

In the first 30 days of the ongoing Canagliflozin Cardiovascular Assessment Study (CANVAS), a prospective, double-blind, placebo-controlled study of T2DM subjects with a history of or a high risk for CV disease, there was a nonsignificant increase in CV events were observed in those

subjects taking canagliflozin: 13 (0.45%) versus 1 (0.07%) in those on placebo (HR 6.5; 95% CI, 0.85-49.66).[131,132] The CV events were mainly strokes and may have been precipitated by syncope caused by dehydration from an osmotic diuresis. However, after 30 days, there was no increase in CV events, and overall, there was a nonsignificant decrease in CV events. Furthermore, a meta-analysis of nine canagliflozin studies did not show an increase in CV events. Results of the CANVAS study are not likely to be available until 2015.

Conclusions

Drugs that reduce postprandial glucose (α-glucosidase inhibitors, incretin mimetics, quick-release bromocriptine, colesevelam, and DPP4 inhibitors) are associated with a decrease in CV events. Drugs that directly reduce insulin resistance (pioglitazone and metformin) are also associated with lesser but still significant decreases in CV events. Mechanisms that may reduce CV events in addition to lowering insulin resistance and postprandial glucose are the decrease in sympathetic activity that occurs with bromocriptine, the increased $HMGB_1$ levels that occur with DPP4 inhibitors, the decreased inflammation and increased cardiac ejection fraction that occurs with incretin mimetics, and the increased 5'-AMPK levels associated with metformin use. Rosiglitazone (but not pioglitazone), insulin, sulfonylureas (especially with glyburide and particularly in combination with metformin), are associated with increases in CV events. The increase in CV events with insulin and sulfonylureas is likely due to induction of hypoglycemia, which increases sympathetic activity and inflammation, and leads to cardiac arrhythmias and events. Sulfonylureas, with the exception of glimepiride and gliclazide, also block the K^+ATPase channels in the myocardiocyte, which leads to a loss of ischemic reconditioning; this may also be a factor in the increased CV event rates that are associated with these drugs.

When considering the therapies we use to treat T2DM, the prudent physician should preferentially prescribe antidiabetic medications that have been associated with decreases in CV events (metformin, pioglitazone, quick-release bromocriptine, incretin mimetics, and DPP4 inhibitors) and restrict the use of drugs that increase CV events (sulfonylureas and insulin) until the preferred medications are no longer effective in maintaining glycemic control and additional medications are needed. At that time, sulfonylureas (glimepiride or gliclazide) should be added to the existing combination of drugs that have been shown to decrease—or not increase—CV events, although are no longer proficient in maintaining glycemic control. Insulin should not be used as monotherapy to treat early T2DM, and should only be used when safer agents are no longer effective. Large doses of basal insulin without fast-acting insulins should be avoided so that the risk of hypoglycemia is decreased and the benefits of lower postprandial glucose levels are achieved, and the risk of cardiac arrhythmias and MI is minimized.

The drugs that seem to be most efficient in lowering CV events are drugs that lower postprandial glucose irrespective of the mechanism involved in this effect. Recently, the bile acid sequestrant colesevelam has been shown to lower HbA_{1c} by decreasing postprandial glucose through the slowing of gastric emptying due to increased cholecystokinin production.[130] Of course, separating the lipid-lowering effect of colesevelam from its effect of lowering postprandial glucose in the prevention of CV events would be extremely difficult. ■

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MAIN POINTS

- Diabetes mellitus is a potent independent risk factor for major adverse cardiovascular events (MACE), and this risk increases in proportion to the elevation of hemoglobin A_{1c}. Available data suggest that tight glycemic control in patients with diabetes reduces microvascular complications, but has limited effect or may even increase the risk of MACE and other macrovascular complications.
- For individuals with type 2 diabetes mellitus (T2DM), drugs that reduce postprandial glucose (α-glucosidase inhibitors, incretin mimetics, quick-acting bromocriptine, dipeptidyl peptidase-4 [DPP4] inhibitors, and colesevelam) are associated with a decrease in cardiovascular (CV) events. Drugs that directly reduce insulin resistance (pioglitazone and metformin) are also associated with lesser but still significant decreases in MACE. Insulin, rosiglitazone (but not pioglitazone), and sulfonylureas (especially with glyburide and particularly glyburide + metformin in combination) are associated with increases in MACE.
- Drugs that reduce postprandial glucose and improve insulin resistance without predisposing patients to hypoglycemia appear to both control hyperglycemia and improve CV prognosis. However, many of the traditional agents used for treating T2DM, such as insulin and sulfonylureas, do not improve CV prognosis despite improving hyperglycemia.
- When considering the therapies we use to treat T2DM, the prudent physician should preferentially prescribe antidiabetic medications that have been associated with decreases in CV events (metformin, pioglitazone, quick-release bromocriptine, incretin mimetics, and DPP4 inhibitors) and restrict the use of drugs that increase CV events (sulfonylureas and insulin) until the preferred medications are no longer effective in maintaining glycemic control and additional medications are needed.

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