# How Should Diabetes Be Treated to Minimize the Risk of Cardiovascular Complications?

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## Abstract

Recognizing the great need to finally resolve the issue of whether lowering blood pressure with intensive treatment will decrease cardiovascular disease (CVD) events in type 2 diabetes, three randomized clinical trials were recently completed. ACCORD, VADT, and ADVANCE all found no significant benefit on primary CVD outcomes and ACCORD reported a 20% increase in total and CVD mortality with intensive treatment. A post-trial observational study by the UKPDS finally noted a decrease of 15% in myocardial infarction and 13% decrease in total mortality over a follow-up of 25 years from the diagnosis of diabetes. The BARI 2D trial found no significant overall advantage of insulin-sensitizing over insulin-providing drugs in these outcomes, although insulin-sensitizing augmented the benefit of coronary bypass surgery over medical therapy. Lowering blood pressure, low-density lipoprotein cholesterol, triglycerides, excessive body fat, and tobacco intake and raising high-density lipoprotein cholesterol may simply overwhelm the small additional benefit gained from reducing glycemia. Metformin has the largest body of evidence supporting its use for decreasing CVD events while reducing glycemia, but uncertainty still surrounds thiazolidinediones.

## Keywords

Type 2 diabetes, cardiovascular disease, clinical trials, hypoglycemic drugs, metformin, thiazolidinediones, diabetes duration, meta-analyses

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Cardiovascular disease (CVD) and diabetes, especially type 2, are closely intertwined and growing health threats in the US and many other regions of the world.[1,2] Fully one-third of coronary artery disease (CAD) is attributed to or at least accompanied by diabetes, and in turn it is responsible for 60–80% of mortality in type 2 diabetes.[3,4] Death from CAD is markedly increased by diabetes in both men[5] and women.[6]

The cause and effect relationship between CVD and type 2 diabetes remains uncertain, but there is enough reason to think of CVD as a complication of diabetes. There have therefore been major efforts to determine whether better glycemic control would reduce the incidence of CVD. If this were unequivocally shown to be the case, it would add enormously to the necessity for intensive treatment of hyperglycemia in most patients. Moreover, because the pathogenesis of hyperglycemia is complex and as new drugs with novel mechanisms of action that target various pathways leading to hyperglycemia appear, how best to lower blood glucose from the CVD standpoint has become an increasingly prominent question. There is considerable evidence from epidemiological studies that hyperglycemia, expressed as fasting plasma glucose,[7] post-glucose challenge plasma glucose,[7,8] or glycated hemoglobin ($HbA_{1c}$),[9–11] is a risk factor for CVD. Even the strongest of these studies can only prove an association and then infer that hyperglycemia causes atherosclerosis, myocardial infarction (MI), strokes, and peripheral vascular obstructive events. To make it a clinical dictum that physicians should work with patients to lower blood glucose in order to prevent CVD complications requires a convincing demonstration that this benefit will in fact ensue. To prove that one blood glucose therapy is superior to others in this respect requires equally rigorous randomized clinical trial evidence. This article examines recent major clinical trial evidence bearing on these issues. Has the evidence satisfactorily answered the critical questions? If not, what therapeutic guidance has it provided physicians who care for the 24,000,000 patients with diabetes in the US and the many millions more elsewhere in the world?

## Trials Comparing Effects of Intensive versus Standard Glycemic Control on Cardiovascular Disease Events

### The DCCT-EDIC Study

The incidence of CVD in both types of diabetes is similar,[12] thus this landmark study in type 1 diabetes, which clearly incriminates hyperglycemia as a likely causative contributor to CVD, may be applicable to type 2 diabetes as well. The DCCT was a randomized clinical trial conducted in 1,441 volunteers with type 1 diabetes with no or minimal evidence of microvascular complications and 5.5 years of diabetes at baseline.[13] Patients were randomly assigned to either intensive glycemic treatment targeted at $HbA_{1c}$ <6.0% or to continuation

of conventional treatment. Over 6.5 years of DCCT follow-up, median $HbA_{1c}$ levels were 7.0% in the intensive group and 8.9% in the standard group. The intensive group had striking reductions in the development or progression of retinopathy, nephropathy and neuropathy.[13] During further observational follow-up of 11 years in EDIC, mean $HbA_{1c}$ converged in the original two treatment groups at about 8.0%. The risk reductions in retinopathy, nephropathy, and neuropathy in the original intensive group, however, have persisted—a phenomenon referred to as 'metabolic memory.'[14] Moreover, at a mean diabetes duration of 24 years, a critical composite of CVD death, non-fatal MI, and non-fatal stroke was reduced by 57% (p=0.02).[15] Most of this intensive treatment effect was accounted for by the lowering of $HbA_{1c}$ during the DCCT period—another example of metabolic memory.[15]

### The UKPDS

The United Kingdom Prospective Diabetes Study (UKPDS) randomized 4,209 volunteers with type 2 diabetes (median age 54 years), three months from diagnosis, to intensive treatment with insulin, a sulfonylurea, or conventional treatment with a 'dietary policy.'[16] Mean $HbA_{1c}$ over an 11-year follow-up was 7.0% with intensive and 7.9% with conventional treatment. Microvascular complications were significantly reduced by 25% (p<0.01) and MI was reduced by 16% (p=0.052).[16] After the randomized trial, the UKPDS cohorts were followed observationally for an additional 10 years, with no significant difference in $HbA_{1c}$ between the original treatment groups. The reduction in microvascular outcomes was maintained, referred to as a 'legacy effect.'[17] Importantly, however, the reduction in risk of MI remained 15% and became statistically significant (p=0.01). Thus, there is substantial evidence that the incidence of MI can be decreased by lowering $HbA_{1c}$ to 7.0% or less for seven to 10 years, although it takes another 10–11 years to detect a statistically significant benefit. This last point is important when choosing glycemic targets for elderly patients or those with otherwise limited life expectancies.

### The VADT

The Veterans Affairs Diabetes Trial (VADT) randomly assigned 1,791 patients with type 2 diabetes (97% male, mean age 60 years) to intensive versus standard glycemic control for a median follow-up of five to six years, during which median $HbA_{1c}$ levels were 6.9 and 8.5%, respectively.[18] There was a non-significant 12% reduction in the primary composite CVD outcome (p=0.14), no significant difference in MI, a 32% increase in CVD mortality (p=0.24), a 7% increase in total mortality (p=0.64) with intensive treatment, and severe episodes of hypoglycemia were three times as frequent.[18] Of note, the difference in CVD event rates between the treatment groups was inversely proportional to the duration of diabetes at baseline.

### The ACCORD Trial

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was a double 2x2 factorially designed trial. It randomized 10,251 patients with type 2 diabetes (62% male, mean age 62 years) to intensive (target $HbA_{1c}$ <6%) versus standard (target $HbA_{1c}$ range 7.0–7.9%) treatment for a planned follow-up of 5.5 years.[19] All US Food and Drug Administration (FDA)-approved drugs were used in both treatment groups. The primary outcome was a composite of CVD death and non-fatal MI and stroke. The intensive glycemic treatment group experienced a 22% increase in total mortality (p=0.04) and a 35% increase in CVD mortality (p=0.02) after 3.5 years.[20] This prompted a transfer of this patient group to standard therapy for the remainder of the trial. The increased mortality with intensive treatment was not associated with severe hypoglycemic episodes or lower $HbA_{1c}$, but with a failure to reduce $HbA_{1c}$ promptly. Up to this point, the median $HbA_{1c}$ was 6.4% in the intensive and 7.5% in the standard group. The intensive treatment group had a 24% reduction in non-fatal MI (p=0.004).[20] Moreover, in subgroup analyses, patients with no previous CVD events and patients with $HbA_{1c}$ ≤8.0% at baseline had reductions in the primary outcome compared with those with the opposite characteristics. Intensive therapy was again associated with three times the number of severe hypoglycemic episodes as standard therapy.[20]

### The ADVANCE Trial

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial was factorially designed. It randomized 11,140 patients with type 2 diabetes (mean age 66 years, 42% female) to open-label intensive treatment ($HbA_{1c}$ target ≤6.5%) or standard treatment ($HbA_{1c}$ target as per 'local guidelines').[21] Modified-release gliclazide (a sulfonylurea) was added to the usual regimen of the intensive group. Both groups received further hypoglycemic agents, including insulin, if needed to reach their glycemic targets. During the five-year follow-up period, mean $HbA_{1c}$ was 0.7% lower in the intensive group. For the primary macrovascular outcome, a composite of CVD death, non-fatal MI, or stroke was evaluated. Intensive treatment led to a non-significant reduction of 6% (p=0.32).[21] Severe hypoglycemia was more common in the intensive group (2.7 versus 1.5%; p<0.001).

### Meta-analysis of Trials

A recent meta-analysis[22] included data from the UKPDS, VADT, ACCORD, ADVANCE, and PROspective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE). A total of 33,040 patients with type 2 diabetes were included (mean age 62 years, 62% male, mean diabetes duration ranging from less than one to 12 years and mean baseline $HbA_{1c}$ 7.1–9.4%). Mean $HbA_{1c}$ during follow-up was 6.6% on intensive treatment and 7.5% on standard treatment. Intensive compared with standard treatment was associated with reductions in non-fatal MI (odds ratio [OR] 0.83, 95% confidence interval [CI] 0.75–0.93) and non-fatal MI or all cardiac mortality (OR 0.85, 95% CI 0.77–0.93), but not in stroke or total mortality. This meta-analysis, however, is limited by lack of access to individual patient data, wide diversity of the trial cohorts in duration of diabetes and intensive treatment regimens, and great variation in baseline $HbA_{1c}$. Also, the inclusion of PROACTIVE is debatable, since all participants in that study were to be treated to a $HbA_{1c}$ target <6.5% and were not separated into intensive and standard treatment groups.

## Trials Investigating the Effects of Specific Blood-glucose-lowering Strategies on Cardiovascular Disease Events

### Metformin

A subset of 753 obese UKPDS participants were randomly assigned to intensive therapy with metformin or standard therapy with diet policy.[23] Mean $HbA_{1c}$ during follow-up was 7.4 and 8.0%, respectively. Metformin

treatment led to a 39% reduction in MI (p=0.01) and a 36% reduction in total mortality (p=0.01); there was no increase in severe hypoglycemia.[23] Importantly, during the subsequent 10-year observational follow-up, the reduction in MI (33%; p=0.005) and total mortality (27%; p=0.002) with metformin persisted.[17]

The Hyperinsulinaemia: the Outcome of Its Metabolic Effects (HOME) trial randomized 390 insulin-treated patients with type 2 diabetes to metformin or placebo for a mean follow-up of 4.3 years.[24] Although the same glycemic level was targeted, mean $HbA_{1c}$ was 0.4% lower in the metformin group. Mean daily insulin dose was 20 units less with a corresponding lower plasma insulin level. The addition of metformin to insulin treatment resulted in no difference in the primary outcome, a composite of macro- and microvascular events. There was, however, a substantial reduction in the macrovascular outcome (hazard ratio [HR] 0.60, 95% CI 0.40–0.92; p=0.04).[24]

## Thiazolidinedione Drugs

The two currently marketed agents in this class are rosiglitazone (Avandia) and pioglitazone (Actos). There is some debate about their relative effectiveness and safety with regard to CVD.[25–30]

### Pioglitazone

PROACTIVE included 5,238 patients with type 2 diabetes (mean age 62 years, 67% male), all with prior evidence of CVD. Patients were randomly assigned to titrated doses of pioglitazone or placebo in addition to their usual glycemic therapy. They were followed for three years.[31]

Median baseline $HbA_{1c}$ (7.8%) decreased by -0.8% with pioglitazone and by -0.3% with placebo. Pioglitazone had no significant effect on the primary outcome—a composite of total mortality, non-fatal MI, stroke, acute coronary syndrome, revascularization of coronary or leg arteries, and above-ankle amputation (HR 0.90, 95% CI 0.80–1.02) compared with placebo. For a secondary end-point of total mortality, non-fatal MI, and stroke, there was a significant reduction (HR 0.84, 95% CI 0.72–0.98; p=0.027).[31]

In subgroup analyses, pioglitazone reduced the pre-specified outcome of fatal and non-fatal MI by 28% (p=0.045) and acute coronary syndrome by 37% (p=0.035) in 2,445 patients with a previous MI.[32] Moreover, in patients with a previous history of stroke, pioglitazone reduced recurrent stroke (HR 0.53, 95% CI 0.34–0.85; p=0.009) and a composite end-point of CVD death, non-fatal MI, or stroke (HR 0.72, 95% CI 0.53–1.00; p=0.047).[33] Pioglitazone increased high-density lipoprotein (HDL) cholesterol, which along with lowering $HbA_{1c}$ may have contributed to its beneficial effect. It did, however, increase the risk of heart failure, with or without hospitalization (HR 1.43, 95% CI 1.20–1.70; p<0.001). There was no effect on total mortality.[31]

### Rosiglitazone

*The RECORD Trial*

Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) was an open-label randomized trial. It included 2,222 patients already taking metformin and 2,225 on a sulfonylurea (mean age 59 years, 50% male, mean $HbA_{1c}$ 7.9%).[34]

Patients on metformin were randomized to rosiglitazone or a sulfonylurea and patients on a sulfonylurea were randomized to rosiglitazone or metformin. The analytical structure was a non-inferiority trial with an upper HR boundary of 1.20, comparing rosiglitazone with a combined active control group of metformin and sulfonylurea. The primary outcome was CVD hospitalization or death.

After 5.5 years of follow-up, rosiglitazone was not inferior to the control group (HR <1.20) for the primary outcome, MI, or stroke.[34] Nor was any CVD benefit shown for rosiglitazone, though HDL cholesterol was increased and $HbA_{1c}$ was decreased by 0.3%. Both heart failure and lower-limb fractures were increased by rosiglitazone.[34]

*BARI 2D*

Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) tested a cardiology and glycemic management question simultaneously in a factorial design with total mortality as the primary outcome and a composite of death, MI, or stroke as a principal secondary outcome.[35] The investigation included 2,368 patients with type 2 diabetes (mean age 62 years, 70% male, diabetic duration 10 years, baseline $HbA_{1c}$ 7.7%). All patients included had angiographically documented CAD and clinical or stress test evidence of ischemia.

Patients were randomly assigned to primary treatment, targeted at $HbA_{1c}$ <7.0%, with insulin-sensitizing drugs (metformin and/or rosiglitazone) or insulin-providing drugs (insulin, sulfonylureas, meglitinides). They were simultaneously randomly assigned to either aggressive medical therapy for CAD or the addition of prompt revascularization by coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI). The revascularization group was stratified by the cardiologist's choice of CABG or PCI prior to randomization, the CABG group having more severe CAD by angiographic and clinical characteristics. There was no direct comparison of CABG versus PCI in like patients.

No difference emerged in the primary or principal secondary outcomes over a five-year follow-up period between the insulin-sensitization and insulin-provision groups or between the revascularization and medical therapy control groups.[35] In the CABG stratum, however, there was a 12% reduction in the composite of death, MI, or stroke compared with medical therapy (p=0.01). This was largely accounted for by a significant 49% reduction in non-fatal MI.[35] Strikingly, the composite outcome was reduced by 42% (p=0.002) in the insulin-sensitization group of those randomized to CABG, but only 10% in the insulin-provision group (p=0.58). Within the CABG stratum, the composite outcome was 18.7% for insulin sensitization versus 26% for insulin provision (p=0.066). Severe hypoglycemia was 36% less frequent with insulin-sensitization than with insulin-provision treatment (p=0.003), and was largely accounted for by the addition of insulin to improve $HbA_{1c}$.[35] The mechanism for the unique beneficial interaction between CABG and insulin sensitization remains to be elucidated, but this interaction suggests a pathogenetic relationship between metabolic and anatomical abnormalities in diabetic CAD.

## Meta-analysis

### Pioglitazone

Nineteen trials involving 16,390 patients with type 2 diabetes followed for between four months and 3.5 years were analyzed.[36] For the primary

outcome of death, MI, or stroke, there were fewer events with pioglitazone then with placebo or an active comparator (HR 0.82, 95% CI 0.72–0.94; p=0.005), and each component CVD event was similarly reduced. By contrast, serious heart failure was increased by pioglitazone (HR 1.41, 95% CI 1.14–1.76; p=0.002).

### Rosiglitazone

Four major meta-analyses of rosiglitazone trials have been published, with non-uniform results.

The original meta-analysis, which set off a controversy over the role of this thiazolidinedione (TZD), involved 42 trials with follow-up times of six months to three years. Patients with type 2 diabetes or in a pre-diabetic state (n=27,843) were randomly assigned to rosiglitazone or either placebo or comparator drugs.[37] Mean baseline $HbA_{1c}$ was 8.2%. Rosiglitazone was associated with an increased incidence of MI (86 versus 72 events, OR 1.43, 95% CI 1.03–1.98; p=0.03) and CVD death (OR 1.64, 95% CI 0.98–2.74; p=0.06).[37] Important limitations pointed out in an editorial[38] were:

- no access to individual patient data;
- use of non-adjudicated CVD events;
- a small number of events;
- the inclusion of trials with zero events in one of the two arms; and
- a heterogeneous population.

A second meta-analysis included only four major trials comprising 14,291 diabetic and pre-diabetic patients followed for at least one year.[39] CVD events were mostly adjudicated, but time-to-event data were not available. Results for MI were similar to those recorded above: rosiglitazone increased MI incidence (94 versus 83 events, relative risk [RR] 1.42, 95% CI 1.06–1.91; p=0.02) but there was no significant increase in CVD death (RR 0.90; p=0.53). There was a clear increase in the risk of congestive heart failure (RR 2.09, 95% CI 1.52–2.88; p<0.001).[39]

Another meta-analysis concerned with the 'cardiac safety profile' of rosiglitazone included 164 trials with a duration of more than four weeks. It included 45,875 patients with diabetes, impaired glucose metabolism, and diseases characterized by insulin resistance, e.g. polycystic ovary syndrome.[40] ORs for all-cause mortality (0.93, 95% CI 0.76–1.14), for CVD mortality (0.94, 95% CI 0.68–1.29), and for non-fatal MI (1.14, 95% CI 0.90–1.45) showed no evidence of risk for rosiglitazone. The OR for congestive heart failure (1.64, 95% CI 1.21–2.36), on the other hand, confirmed this adverse effect of TZDs.[40]

A final meta-analysis focused on the effects of TZD treatment in type 2 diabetes and pre-diabetes on the outcomes of CVD death and congestive heart failure. A total of 20,191 patients were included: 72% enrolled in five rosiglitazone trials and 28% in two pioglitazone trials.[41] The risk of congestive heart failure was increased by TZDs (RR 1.72, 95% CI 1.21–2.42; p=0.02), but the risk of CVD death was not increased (RR 0.93, 95% CI 0.67–1.29; p=0.68).[41] There were no statistically significant differences in congestive heart failure event rates between rosiglitazone and pioglitazone, although the RR was higher with rosiglitazone (2.18 versus 1.32).

## Discussion

It should be clear from the above review of recent data that we still lack consistent evidence that lowering blood glucose ($HbA_{1c}$) reduces the risk of CVD. What are the possible reasons that randomized clinical trials have thus far failed to demonstrate this benefit conclusively?

- The direct association of $HbA_{1c}$ with CVD outcomes in observational studies may be just that: hyperglycemia may be only a marker for the real causative factor(s) that are not proportionately reduced when blood glucose is actively lowered.
- The effect of hyperglycemia reduction on CVD risk may be small compared with the effect on microvascular complications and therefore beneath the power of feasible studies to detect.
- Blood glucose may need to be kept down ($HbA_{1c}$ <7.0%) from early on in type 2 diabetes and for many years to reap a CVD benefit. The UKPDS results point to such a conclusion. If this is so, intensive treatment begun in elderly patients at greater CVD risk but with shorter life expectancies may be both ineffectual and, as per the ACCORD results, dangerous.
- The actual event rates in the control groups of recent major randomized clinical trials have turned out to be lower than projected, probably because of better management of other even more powerful risk factors, limiting study power.

In this context it may be asked whether any additional CVD benefit will be attainable by lowering blood glucose, given the effectiveness of reducing low-density lipoprotein (LDL) cholesterol and systolic blood pressure and the possible benefit of increasing HDL cholesterol and reducing triglycerides.[42] Patients with diabetes respond as well as those without to statin therapy in randomized clinical trials.[42,43] In a meta-analysis of statin therapy involving 90,000 patients, 21% of whom had diabetes, each mmol/l reduction (39mg/dl) in LDL cholesterol was associated with a 23% reduction in coronary death or MI and a similar reduction in need for coronary revascularization. Statin therapy was also associated with a 17% reduction in fatal or non-fatal stroke.[43] Moreover, a greater reduction in events can be achieved using a maximum statin dose that lowers LDL cholesterol to 77mg/dl.[44] Reducing systolic blood pressure—and with it diastolic blood pressure—also decreases the risk of CVD events, especially strokes, in patients with and without diabetes.[41] In a large meta-analysis involving 159,000 patients (21% with diabetes), more compared with less intensive blood-pressure-lowering significantly reduced stroke by 36%, major CVD events by 25%, and total mortality by 27%, but not coronary heart disease, in patients with diabetes.[45] Similar benefits have been individually noted in the UKPDS,[46] Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[47] and ADVANCE trials.[48]

The ACCORD study is simultaneously testing an intensive systolic blood pressure target of <120mmHg versus <140mmHg in 4,733 hypertensive subjects and the addition of fenofibrate versus placebo added to statin therapy in 5,518 patients with dyslipidemia.[19] This double factorial design may enable separate determination of the influence of intensive glycemic control when added to optimal blood pressure control and the guideline level of LDL cholesterol control, with and without a supplemental increase in HDL cholesterol and decrease in triglycerides. These data should be publicly available within a few months. If a beneficial effect of intensive glycemic treatment is ultimately observed only in the conventional but

not in the intensive arms of the blood pressure and lipid ACCORD trials, this would answer the question raised above and provide very useful guidance for treating individual patients. Does it matter how we lower blood glucose? The evidence for a beneficial effect of metformin on CVD event rates is impressive and justifies its recommendation as first-line pharmacological treatment of type 2 diabetes.[49] The situation with the TZDs is less clear-cut, although this drug class has been shown to have numerous antiatherosclerotic, antiendothelial dysfunction, anti-thrombogenic, and pro-fibrinolytic actions.[3] On the other hand, TZDs double the risks of congestive heart failure and fractures.

Of the two TZDs, the bulk of the evidence gives the advantage to pioglitazone. In oral presentations at American Diabetes Association meetings, neither ACCORD nor BARI 2D reported an association between rosiglitazone—used much more often in each study than pioglitazone—and adverse CVD outcomes. Even when reported fully, however, these will be secondary epidemiological analyses with lesser weight in assessing safety. A consensus algorithm for treating type 2 diabetes relegates TZDs to a second tier and no longer recommends rosiglitazone.[49] The survival of the latter in the therapeutic armamentarium, which is debatable,[50–52] may depend on offering financial advantages that translate into greater cost-effectiveness.

The results of the BARI 2D trial showed a trend toward reduced CVD outcomes with a regimen that was based on insulin sensitization with metformin and/or TZDs. Most intriguing was the observation that CABG was superior to medical therapy alone, particularly in reducing the incidence of MI in the insulin-sensitization glycemic arm but not in the insulin-provision glycemic arm. These results indicate that patients about to undergo CABG whose $HbA_{1c}$ is >7.0% should have metformin and/or a TZD added to their glycemic management, rather than a beta-cell stimulant or an increased dose of insulin.

## Conclusion

There is still the need for more definitive randomized clinical trial evidence to determine whether lowering blood glucose reduces CVD late in type 2 diabetes and whether using a particular therapeutic approach to glycemic control provides an advantage. The necessary size, duration, and cost of such a trial, however, are formidable obstacles that may prevent its execution. Therefore, clinical strategy must proceed on the basis of what is known. In most patients, an $HbA_{1c}$ level ≤7.0% lowers the risks of retinopathy, nephropathy, and neuropathy substantially, if not completely, but requires special effort to decrease episodes of severe hypoglycemia with their dangerous consequences.

There is now more reason to hope that CVD complications will also diminish with this degree of glycemic control, if it is implemented at or soon after the time at which type 2 diabetes is diagnosed. Aiming for a target much below 7.0% may be dangerous, particularly in elderly patients who already have CVD or strong CVD risk factors. Failure to respond promptly to intensification of glycemic control should call for caution in further efforts to drive $HbA_{1c}$ below 7.0%. Reducing insulin resistance with metformin (in the liver) and TZDs adds to whatever effect lowering blood glucose may have. Metformin should be the first-line drug treatment of type 2 diabetes, when not excluded by renal insufficiency or persistent gastrointestinal toxicity. Some but not all opinion favors pioglitazone over rosiglitazone, but this issue has not been resolved by a head-to-head comparison of their efficacy and safety. There should be no hesitancy in using insulin itself to lower blood glucose, bearing in mind its increased risk of hypoglycemia. Other approved approaches to lowering blood glucose by increasing incretin effects with GLP-1 analogs or DPP-4 inhibitors have not as yet been adequately tested for CVD benefits or safety. ■

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