Curr Diab Rep (2012) 12:255–264
DOI 10.1007/s11892-012-0268-5

Glycemic Control and Cardiovascular Disease: What's a Doctor to Do?

Preeti Kishore · Sharon H. Kim · Jill P. Crandall

Published online: 1 April 2012

Abstract Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in individuals with diabetes mellitus. Moreover, rates of CVD mortality are two to four times higher in diabetes than in those without diabetes. It was conventional thinking that achieving near-normoglycemia would help reduce CVD risk and overall mortality in type 2 diabetes mellitus. Several recent large trials attempted to answer this question using a randomized control trial design with a conventional therapy and an intensive control arm. Surprisingly, these trials did not demonstrate neither mortality nor a CVD advantage with intensive glycemic control. Moreover, some studies (e.g., the ACCORD [Action to Control Cardiovascular Risk in Diabetes] study) showed increased mortality in the intensive control arm. In this review, our goal is to summarize the findings of the major trials in this field and to explore the potential reasons for why these trials had largely negative results. We conclude with some lessons that may be applied to the clinical management of patients with diabetes.

Keywords Type 2 diabetes · Cardiovascular disease · Glycemic control

Introduction

Cardiovascular disease (CVD) remains the single greatest cause of morbidity and mortality for patients with type 2 diabetes mellitus (T2DM) [1]. Ever since the UGDP (University Group Diabetes Program) study in the 1960s [2], defining the role of glucose control in modulating CVD risk has been akin to the "holy grail" in the field of clinical diabetes. The reports of several recent large and "definitive" clinical trials have generated more controversy (and scores of publications), largely because these trials failed to confirm what many in the field already believed—that achieving near-normoglycemia would provide clear benefits in reducing CVD events and mortality. This was not unreasonable, given the microvascular benefits demonstrated in the UKPDS (United Kingdom Prospective Diabetes Study) and the unequivocal cardiovascular results in type 1 diabetes mellitus (T1DM) in DCCT/EDIC (Diabetes Interventions and Complications/Epidemiology of Diabetes Interventions and Complications) [3, 4]. The unexpected findings of the more recent trials provide an opportunity to revisit existing assumptions and the approach to patients at risk. We provide a brief review of the relevant trials and discussion of how and what should be applied to current standards of clinical care in T2DM.

P. Kishore · S. H. Kim · J. P. Crandall (✉)
Division of Endocrinology and Diabetes Research Center,
Albert Einstein College of Medicine,
1300 Morris Park Avenue, Belfer 701,
Bronx, NY 10461, USA
e-mail: jill.crandall@einstein.yu.edu

Hyperglycemia and Cardiovascular Risk

Overall mortality in T2DM has decreased significantly [5] over the years, presumably due to intense risk factor modification, but T2DM is still the 7th leading cause of death in the United States [1] and rates of mortality and cardiovascular events remain unacceptably high. The overall death rate in T2DM is twice as high and CVD death rate is two to four times as high as those without T2DM [1]. In population-based studies, including diabetic and nondiabetic cohorts, hemoglobin A_{1c} (HbA_{1c}) has been reported as an independent predictor of all-cause and CVD mortality [6–8]. Among individuals with diabetes, every 1% rise in HbA_{1c} is associated with a 30% increase in all-cause mortality and a 40% increase in CVD mortality [9]. In the Atherosclerosis Risk in Communities study, higher HbA_{1c} in community-dwelling, nondiabetic adults was also associated with higher risk of CVD and death [10].

Clinical Trials of Glycemic Control in Prevention of Cardiovascular Disease

Below is a brief description of the major trials designed to test the role of intensive glycemic control and CVD risk in T2DM. Although these trials share a central hypothesis and treatment strategy (intensive vs conventional treatment), they differ in terms of patient characteristics and baseline CVD risk. Relevant details of the studies, including CVD risk factors (at baseline and at study end) and a summary of study outcomes, are shown in Table 1.

UGDP

This early trial, conducted in the 1960s, was the first to directly address the role of glucose control in preventing

Table 1 Summary of baseline characteristics, study interventions, and major outcomes of the UKPDS, ACCORD, ADVANCE, and VADT trials

Baseline data	UKPDS 33 (n=3867)	UKPDS 34 (n=753)	ACCORD (n=10,251)	ADVANCE (n=11,140)	VADT (n=1791)
Age, *y*	53 (9)	53 (8)	62 (7)	66 (6)	60 (9)
Duration of diabetes, *y*	< 1	< 1	10.0	7.9 (6.3)	11.5 (7.5)
HbA_{1c} at baseline, %	7.1 (1.5)	7.2 (1.5)	8.3 (1.1)	7.5 (1.6)	9.4 (1.5)
History of CVD, %	NR (*)	NR (*)	35	32	40
BMI, kg/m^2	27.2 (5.0)	31.7 (4.6)	32.2 (5.5)	28.3 (5.2)	31.3 (3.5)
Systolic BP, *mm Hg*	135 (20)	140 (18)	136 (17)	145 (22)	132 (17)
Diastolic BP, *mm Hg*	82 (10)	85 (10)	75(11)	81 (11)	76 (10)
Triglyceride, *mg/dL*	207 **	254 **	155 **	173 (114)	212 (257)
HDL, *mg/dL*	42 (9)	41 (9)	43 (12)	50 (15)	36 (10)
LDL, *mg/dL*	135 (37)	141 (42)	104 (35)	120 (39)	108 (31)
Current smoker, %	31	25	14	14	17
Intervention					
Glucose target (INT vs STD)	FPG<108 mg/dL vs FPG 110–270 mg/dL	FPG<108 mg/dL vs FPG 110–270 mg/dL	HbA_{1c}<6.0% vs HbA_{1c} 7%–7.9%	HbA_{1c}≤6.5% vs HbA_{1c}>6.5%	HbA_{1c} absolute reduction 1.5%
Duration of follow-up, *y*	10.0	10.7	3.4	5.0	5.6
Medical treatment at study completion (INT vs STD), %					
Insulin	38 vs16	NR (†)	77 vs 55	41 vs 24	89 vs 74
Metformin	10 vs 0	NR (†)	95 vs 87	74 vs 67	65 vs 58
Secretagogue (SU or glinide)	54 vs 25	NR (†)	87 vs 74	94 vs 62	57 vs 42
TZD	Not used	Not used	92 vs 58	17 vs 11	53 vs 42
Outcome (INT vs STD)					
HbA_{1c} post-intervention, %	7.0 vs 7.9 (**)	7.4 vs 8.0 (**)	6.4 vs 7.5	6.4 vs 7.0	6.9 vs 8.4
Weight changes, *kg*	+2.7 vs +0.9	−1.0 vs 0.0	+3.5 vs +0.4	−0.1 vs −1.0	+8.2 vs +4.1
Hypoglycemia, severe, %	1.3 vs 0.7	0.6 vs 0.7	15.9 vs 5.0	2.7 vs 1.5	8.5 vs 3.1
Primary outcome	Any diabetes-related end point; diabetes-related death (MI, stroke, PVD, renal disease, hyper/hypoglycemia, sudden death); all-cause mortality	Any diabetes-related end point; diabetes-related death (MI, stroke, PVD, renal disease, hyper/hypoglycemia, sudden death); all-cause mortality	Nonfatal MI, nonfatal stroke, or death from CVD	Macrovascular (nonfatal MI, nonfatal stroke, or death from CVD) and microvascular (new/worsening nephropathy, or retinopathy)	MI, stroke, death from CVD, CHF, surgery for vascular disease, inoperable CAD, or amputation for ischemic gangrene
HR for primary CV outcome [CI]	0.88 (0.79–0.99)	0.68 (0.53–0.87)	0.90 [0.78–1.04]	0.90 [0.82–0.98] (#) 0.94 [0.84–1.06] (# #)	0.88 [0.74–1.05]
HR for all-cause mortality [CI]	0.94 (0.80–1.10)	0.64 (0.45–0.91)	1.22 [1.01–1.46]	0.93 [0.83–1.06]	1.07 [0.81–1.42]

Means (SD), except for (**) median or geometric mean; (*) recent MI, angina, CHF, or > 1 vascular event exclusionary for UKPDS

(#) Combined micro- and macrovascular, (# #) macrovascular; (†) 44% of conventional group received SU, insulin, and/or metformin; hypoglycemia for UKPDS reported as %/year.

ACCORD Action to Control Cardiovascular Risk in Diabetes, *ADVANCE* Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation, *BMI* body mass index, *BP* blood pressure, *CAD* coronary artery disease, *CHF* congestive heart failure, *CV* cardiovascular, *CVD* cardiovascular disease, *FPG* fasting plasma glucose, *HbA_{1c}* hemoglobin A_{1c}, *HDL* high-density lipoprotein, *HR* hazard ratio, *INT* intensive, *LDL* low-density lipoprotein, *MI* myocardial infarction, *NR* not reported, *PVD* peripheral vascular disease, *STD* standard treatment design, *SU* sulfonylurea, *TZD* thiazolidinedione, *UKPDS* United Kingdom Prospective Diabetes Study, *VADT* Veterans Affairs Diabetes Trial.

diabetic complications. Patients with recently diagnosed T2DM were assigned to a standard, fixed low-dose insulin regimen, a more "intensive" treatment using variable insulin dosing (designed to achieve fasting glucose < 110 mg/dL, and less than 210 mg/dL following oral glucose challenge), or treatment with a sulfonylurea (SU), a biguanide (phenformin), or placebo. The unexpected findings of increased CVD mortality in the SU-treated patients generated a landslide of controversy, which has persisted for decades. It is also of note that CVD mortality was similar in both insulin groups and placebo, despite the lower glucose levels achieved in the variable insulin-treated group [2].

UKPDS

The UKPDS was the first of the recent large-scale multicenter trials designed to investigate the role of glycemic control in macrovascular and microvascular complications of T2DM. Over 4000 participants with newly diagnosed diabetes were recruited and followed for 10 years after randomization to an intensified regimen (based on SU or insulin), or to conventional therapy (based on diet management). Despite achieving a significant difference in glycemic control (median HbA_{1c} 7.0% vs 7.9% in the intensive and conventional groups, respectively), primary analysis failed to show a statistically significant risk reduction for myocardial infarction (MI). The occurrence of any diabetes-related end point was reduced, primarily due to a 25% risk reduction in microvascular end points [11]. In contrast, in a subset of the UKPDS, 753 overweight individuals randomly assigned to metformin versus conventional management did show a clinical benefit of intensive glucose control, with risk reductions of 42% for diabetes-related death, 39% for fatal/nonfatal MI, and 36% for all-cause mortality [12].

At study completion, patients were returned to their usual source of medical care. Baseline differences in HbA_{1c} were lost by 1 year, and after 5 years, there were no significant differences in HbA_{1c} (7.8%), body weight, lipid levels, or blood pressure among the groups. Despite this, reductions in the relative risk of diabetes-related end points were maintained 10 years after completion of the intervention trial, and now included a 15% reduction in MI and a 13% reduction in all-cause mortality in the main (UKPDS 33) trial [13].

ACCORD

In the ACCORD trial, over 10,000 patients with established T2DM and at high risk for CVD were randomly assigned to an intensive treatment group (HbA_{1c} goal<6%) or to a standard treatment group (HbA_{1c} goal 7% to 7.9%). Treatment was guided by an algorithm employing multiple antidiabetic drugs (including oral medications and insulin) in both arms. Both treatment groups achieved a stable HbA_{1c} level (6.4% and 7.5%, in the intensive and standard groups, respectively) within 1 year of randomization. After a mean follow-up of 3.5 years, the study was halted due to the unexpected finding of increased all-cause mortality in the intensive therapy group. In contrast to the increase in mortality, there was a nonsignificant trend toward a reduction in the primary outcome (a composite of nonfatal MI, nonfatal stroke, or cardiovascular death) within the intensive group, mainly due to a reduction in nonfatal MI [14].

ADVANCE

The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial assessed the effects of intensive glycemic therapy on major vascular outcomes in patients with established T2DM and high risk for CVD [15]. Over 11,000 patients were randomized to an intensive glucose-control strategy using an SU (gliclazide) and additional medications as required to achieve the target HbA_{1c} level ($\leq$ 6.5%) versus a standard treatment group. The primary end point was a composite of major macrovascular events (death from CVD causes, nonfatal MI, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy). After a median follow-up of 5 years, the mean HbA_{1c} level was lower in the intensive control group (6.5%) compared to the standard control group (7.3%). Compared with standard therapy, intensive therapy was associated with a decrease in the incidence of the primary end point (hazard ratio [HR] 0.90, 95% CI 0.82–0.98, P=0.01), primarily due to a reduction in microvascular outcomes (HR 0.86, 95% CI 0.77–0.97, P=0.01). Intensive therapy had no significant effect on the incidence of macrovascular events (HR 0.94, 95% CI 0.84–1.06, P=0.32), or all-cause or CVD mortality.

VADT

The VADT (Veterans Affairs Diabetes Trial) was a multicenter trial designed to assess cardiovascular outcomes in response to intensive versus standard glucose-lowering therapy in 1791 patients with long-standing T2DM and suboptimal glycemic control. A variety of glucose-lowering medications were used to achieve a goal of 1.5% reduction in HbA_{1c} beyond that achieved by standard therapy. The primary outcome of the study was the time from randomization to the first occurrence of a major cardiovascular event (a composite of MI, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene). Although significant glycemic separation was achieved (mean HbA_{1c} 6.9% vs 8.4%,) after a mean follow-up of 5.6 years, the primary outcome (as well as individual components) was not significantly lower in the intensive therapy arm versus the standard

therapy arm (HR 0.88, 95% CI 0.74–1.05, P=0.12). Compared to conventional therapy, there was no difference between groups in death from CVD causes (HR 1.32, 95% CI 0.81–2.14) or death from any cause (HR 1.07, 95% CI 0.81–1.42) [16].

Meta-Analyses of Major Trials

Despite the largely negative results in the individual trials described above, two recent systematic reviews that combined the results from several studies concluded that intensive management may, in fact, reduce the risk of coronary events in T2DM. In a meta-analysis performed by Ray et al., which included data from the UKPDS, ACCORD, ADVANCE, VADT and PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) studies [17], intensive glycemic control resulted in a 17% reduction in nonfatal MI and 15% reduction in coronary heart disease events [18•]. Importantly, there was no significant heterogeneity of this result across the studies, which differed with respect to baseline subject characteristics and drug regimen employed. Intensive management had no significant effect on stroke or all-cause mortality in this study. A separate analysis of the same trials (excluding PROactive) demonstrated a similar 16% risk reduction for nonfatal MI and no effect on cardiovascular or all-cause mortality [19•]. A larger group of studies (including the UGDP and PROactive) was subjected to meta-analysis by Boussageon et al., but resulted in similar conclusions [20•].

Why Did Recent Trials Fail to Demonstrate the Expected CVD Benefit of Intensive Glucose Control?

Taken as a whole, these recent studies suggest that intensive glycemic control in T2DM plays, at best, a modest role in CVD prevention and may in fact be harmful. Here, we consider some possible scenarios that may explain these unexpected results:

Glycemic Control Does Not Directly Modulate CVD Risk/Events in T2DM

Despite the strong epidemiological evidence of the association between T2DM and CVD, it may be that glycemia per se is not the key metabolic factor in its pathogenesis [21]. In contrast to T1DM (for which there is clear evidence of the benefit of intensive glucose control on CVD [4]), T2DM is a more complex metabolic disorder characterized by dyslipidemia, insulin resistance, and obesity—all of which are directly implicated in atherothrombosis. In support of this is the observation that increased CVD risk exists in prediabetic states: dyslipidemia, hypertension, insulin resistance, and obesity often precede overt hyperglycemia [22, 23], although in some studies, progression to overt diabetes does seem to further increase CVD risk [24]. Of note, it has been difficult to separate effects of hyperglycemia from hyperlipidemia in experimental models and there is controversy whether "pure" hyperglycemia is atherogenic, at least in animals [25].

The lipid-centric view of atherogenesis proposes that dyslipidemia is the primary pathogenetic factor responsible for accelerated atherosclerosis in patients with diabetes [26]. The characteristic diabetic dyslipidemia—low high-density lipoprotein cholesterol, elevated triglycerides, and small, dense low-density lipoprotein particles—has been associated with accelerated atherosclerosis in epidemiologic studies. The fact that treatment of hyperlipidemia has consistently (and relatively robustly) been shown to reduce CVD events in patients with diabetes supports this view [27–29]. Further, multiple risk factor intervention, as in the Steno trial, which targeted reductions in blood pressure and lipids, antiplatelet therapy, and smoking cessation in addition to glucose control, resulted in a dramatic 57% reduction in CVD mortality after 13 years of follow-up [30]. The intensive treatment group in this study had a glycemic target of less than 6.5%, and achieved HbA_{1c} of 7.9% at the end of active intervention, compared to 9.0% in the conventional therapy group, although the independent contribution of glycemic control could not be determined in this study.

Glycemic Control Does Modulate CVD, but Issues Related to Study Design and Specific Drug Regimens Have Obscured This Relationship

Drug Toxicity

Certain antidiabetic drugs or combinations of drugs used in recent trials may themselves have adverse cardiovascular effects, which could have obscured the actual benefits of improved glycemic control. It also should be noted that these trials relied virtually exclusively on pharmacologic interventions and did not include any serious effort at lifestyle change (weight loss, increased physical activity), which might be expected to have cardiovascular benefits.

Rosiglitazone. Since the publication of the first Nissen report in 2007 [31], evidence has been mounting that rosiglitazone is associated with increased CVD risk and use of this agent is now limited. A recent meta-analysis of 56 trials published over 11 years found that rosiglitazone use was associated with increased risk of MI, (odds ratio 1.28, 95% CI 1.02–1.61, P=0.04), although not cardiovascular mortality [32•]. In the ACCORD trial, 92% of subjects in the intensive arm were being treated with rosiglitazone at the end of the

study, compared with 58% subjects in the standard therapy group. While preliminary analysis could not attribute the excess mortality risk in the intensive treatment group to the use of any particular agent, more detailed analysis is ongoing [33]. In the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetics) trial, an open-label study designed (and powered) to examine the CVD effects of rosiglitazone, there was no increased risk for CVD death, MI, or stroke in subjects randomized to rosiglitazone when compared to non-thiazolidinedione (TZD) treatment regimens, although heart failure risk was increased [34]. Rosiglitazone was also used extensively in the BARI 2D (Bypass Angioplasty Revascularization Investigation—Type 2 Diabetes) study, which compared early revascularization versus intensive medical management in patients with stable coronary artery disease. Among subjects assigned to a strategy of insulin sensitization, 55% received rosiglitazone (often in combination with metformin) and no differences in survival or major CVD events were apparent after 5 years of follow-up [35]. Use of TZDs (including rosiglitazone) in VADT was common in both treatment groups (53% for intensive vs 42% for standard therapy). TZDs were not used in UKPDS and used infrequently in ADVANCE (17 and 11% in the intensive and standard groups, respectively).

Sulfonylureas. The UGDP was the first study to raise the possibility that use of a SU (in this case, tolbutamide) was associated with higher mortality compared to with insulin or diet [2]. Subsequently, several studies also provided evidence that SU use may be associated with increased CVD risk [36, 37]. Furthermore, a greater risk of death has been reported with increased use of higher doses of first-generation SUs, suggesting a dose-dependent effect [38]. The proposed mechanism for SU cardiac toxicity is related to the effect of KATP channel inhibition on myocardial ischemic preconditioning, but the clinical relevance of this remains to be proven. It is also unclear whether newer SUs have a better safety profile [39]. SU use was more common in the intensive treatment arms of ACCORD (78% vs 68%), ADVANCE (93% vs 59%), and VADT (57% vs 42%) compared to the standard treatment groups. However, the UKPDS, which was designed (and powered) to address the question of SU cardiotoxicity, reported no difference in MI or diabetes-related death between SU, insulin, and conventional treatment groups [11].

Insulin. Since insulin resistance (and the accompanying hyperinsulinemia) is associated with increased CVD risk, questions have been raised about the role of insulin therapy in promoting CVD. Insulin's opposing vascular actions as a vasodilator (via enhanced synthesis of nitric oxide) and also a mitogen and vasoconstrictor (via increased production of endothelin) suggest it plays a complex role in vascular health [40]. Signaling via the phosphatidylinositol 3-kinase pathway, which regulates endothelial nitric oxide synthase activity, is impaired in insulin-resistant states, but activity in the mitogen-activated protein kinase system is not, and in the setting of hyperinsulinemia, may be increased. This tends to shift the balance to favor insulin's proatherosclerotic effects, including cell proliferation and vasoconstriction. Presumably, in the setting of insulin resistance, the high levels of exogenous insulin required to achieve glycemic control could have similar proatherosclerotic effects. Further, the weight gain that often accompanies intensive insulin therapy may itself contribute to increased CVD risk.

Results from epidemiological studies suggest that insulin treatment is associated with increased CVD risk. For example, the Euro Heart Survey registry study reported that insulin treatment was associated with an adjusted HR of 2.23 for mortality (95% CI 1.24–4.03) and 1.27 for all CVD events (95% CI 0.85–1.87), compared to treatment with oral hypoglycemic drugs [41]. However, observational studies are confounded because insulin use may simply be a proxy for more severe diabetes. Patients with longer duration of diabetes and greater insulin resistance are more likely to be treated with insulin and also to have coexisting CVD, making it difficult to assign causality. Insulin treatment was more common in the intensive treatment arms of ACCORD (77% vs 55%), ADVANCE (41% vs 24%), and VADT (89% vs 74%). Unfortunately, no analysis has been reported of insulin doses in relationship to CVD outcomes in these studies.

Hypoglycemia

Iatrogenic hypoglycemia is a well-recognized consequence of intensive glucose management, particularly when insulin-based regimens are used. Hypoglycemic episodes induce sympathetic nervous system activation and can result in arrhythmia, myocardial ischemia, and sudden death [42–44] and may be particularly dangerous in the presence of cardiac autonomic neuropathy [45]. In all the recent trials, intensive treatment was associated with significantly increased rates of hypoglycemia, including severe episodes (defined as requiring assistance of another person). In ACCORD, 15.9% of participants in the intensive treatment group experienced at least one episode of hypoglycemia requiring any assistance, compared with 5.0% in the conventional treatment group, and 10.3% versus 3.4% had hypoglycemia requiring medical intervention [14]. Detailed analysis by the ACCORD research group confirmed that the occurrence of severe hypoglycemia was associated with increased mortality risk in both treatment arms and may have contributed to 5% to 6% of deaths during the trial. However, of the 74 participants who reported an episode of severe hypoglycemia and subsequently died, only

6 of these deaths occurred within 30 days of the hypoglycemic event and the investigators concluded that hypoglycemia did not explain the increased mortality seen in the intensive treatment group [46]. Further, in a post hoc analysis, higher (not lower) mean on-treatment HbA_{1c} was a significant predictor of mortality, an effect that appeared to be greater in the intensive treatment group [47].

Severe hypoglycemia was also relatively frequent in the VADT study and was a powerful predictor of cardiovascular death (HR 4.04, P=0.02) [48]. A recent analysis from the ADVANCE trial also showed an association between severe hypoglycemia and adverse study outcomes in both treatment groups, including cardiovascular and noncardiovascular outcomes and all-cause mortality [49]. Adverse CVD outcomes or death occurred 1.05–1.56 years after the most recently reported severe hypoglycemic episode. These finding support the view, also proposed by others [50], that the occurrence of severe hypoglycemia is a marker of patient vulnerability and may not be causally related to CVD and mortality outcomes. However, in all of the trials, plasma glucose level at the time of death was generally not known. Further, the presence of hypoglycemia unawareness (which may occur as a consequence of frequent hypoglycemia) may also tend to obscure the temporal relationship between severe hypoglycemic events and adverse outcomes. Interestingly, a recent analysis from ACCORD demonstrated an unexpected inverse relationship between the frequency of minor hypoglycemic episodes (defined as self-monitored blood glucose < 70 mg/dL or "minor but uncomfortable" hypoglycemia symptoms) and mortality risk in the intensive treatment group. The possible blunting of counterregulatory responses (including increases in catecholamines) in the setting of frequent hypoglycemia was offered as a possible explanation [51•].

Other Study Design Issues

Inadequate Power. As mentioned above, as compared to the period of 1950–1975, all-cause and cardiovascular mortality declined in individuals with and without diabetes in the period of 1976–2001 [5]. Thus, event rates in many of the recent large trials were lower than anticipated, and consistent with national trends and multiple risk factors targeting in current T2DM treatment. In the ACCORD study, the rate of all-cause mortality was 14.3 and 11.3 per 1000 patient-years in the intensive and conventional arms, respectively—approximately half of what was predicted. This suggests the study was underpowered to detect treatment group differences, especially given the relatively short follow-up period of 3.5 years. In VADT, ADVANCE, and UKPDS the event rates were somewhat higher than in ACCORD, varying between 18.2 and 20.6 per 1000 patient-years in the various arms of the studies, but still may have been inadequate to detect treatment group differences. Further, the average duration of follow-up in ACCORD, ADVANCE, and VADT (3.5, 5, and 5.6 years, respectively) was relatively short. In fact, the premature termination of ACCORD may have precluded the emergence of a statistically significant effect of intensive treatment in reducing the primary outcome, which showed an HR of 0.90 (95% CI 0.78–1.04) at the time the trial was stopped. In contrast, the EDIC and UKPDS demonstrated a reduction in CVD outcomes with average total follow-up periods of 16–18 years. Taken together, it appears that larger and longer-duration studies may be required to detect a benefit of intensive glycemic control on mortality and CVD outcomes. Nonetheless, current evidence supports the conclusion that any benefit of intensive management on CVD outcomes is likely to be modest.

Too Rapid Correction of Hyperglycemia. It has also been proposed that a too rapid rate of glycemia reduction could be a factor in adverse CVD outcomes. Temporary worsening of diabetic retinopathy following initiation of intensive glucose control is well recognized and is usually attributed to a reduction of retinal blood flow, resulting in capillary closure or retinal microhemorrhages [52, 53]. In a similar fashion, acute reduction of hyperglycemia could result in adverse hemodynamic changes that precipitate cardiac events, although this has not been established. In ACCORD, subjects in the intensive arm experienced a rapid decline in HbA_{1c} (8% to ~6.7% in the first year), although cardiovascular event rates were highest in years 2 to 7 [47].

Selection of the Wrong Glucose Target. Postprandial (after a meal) or postchallenge (after an oral glucose challenge) hyperglycemia has been strongly associated with CVD risk in observational studies and may be a better predictor of mortality than is fasting hyperglycemia [54, 55]. Moreover, postchallenge hyperglycemia tends to correlate strongly with CVD markers and subclinical atherosclerosis [56, 57]. However, in most clinical trials, lower HbA_{1c} (and in some cases, lower fasting glucose) was the glycemic target and no specific effort was made to reduce postprandial hyperglycemia. Interestingly, in the STOP-NIDDM (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus) trial, conducted in a prediabetic population with impaired glucose tolerance, treatment with the drug acarbose, which blunts postprandial glucose elevations, there was a 49% reduction in CVD end points compared with placebo [58]. However, in a similar population, treatment with another prandial glucose regulator, nateglinide, failed to show cardiovascular benefits [59].

Glycemic variability per se has been proposed to have a unique and underappreciated role in the pathogenesis of diabetic vascular complications [60, 61], potentially via induction of oxidative stress. In an animal model, oscillating glucose levels appear to accelerate atherosclerotic processes,

including monocyte adhesion, more than constant levels of hyperglycemia [62]. However, glycemic variability is difficult to quantify in clinical situations [63•] and has not been carefully assessed, nor specifically targeted in clinical trials to date.

Study Interventions Occurred Too Late in the Course of Diabetes: Control of Glycemia May be Effective for Primary Prevention, But Not Once CVD is Established

Although the role of glycemic control in the prevention of microvascular complications has been firmly established, it is also known that glucose control contributes much less to the progression of established complications. A similar paradigm may be at play with macrovascular disease—that aggressive glucose lowering in the setting of established atherosclerosis may be ineffective, or even harmful. Evidence from recent trials tends to support this hypothesis. However, since subclinical atherosclerosis probably exists in a substantial proportion of patients with T2DM but was not directly assessed in these studies, misclassification of subjects confounds efforts to confirm this. Nonetheless, duration of diabetes can be viewed as a proxy for atherosclerotic burden, in that patients with long-standing diabetes probably have more subclinical (as well as clinical) CVD.

Participants enrolled in UKPDS, which demonstrated reduced risk of MI and all-cause mortality after about 16 years follow-up, were relatively young (mean age 53 years) with known diabetes duration of less than 1 year. In contrast, ADVANCE, ACCORD, and VADT recruited participants who were older (mean ages 60–66 years, with an average duration of diabetes ranging from 7.9–11.5 years at baseline)—and failed to demonstrate significant cardiovascular benefit of intensive management. Subgroup analysis from ACCORD suggested that patients without a previous cardiovascular event and those with lower baseline HbA_{1c} did show benefit from intensive glucose management [14, 64].

In a post hoc analysis of the VADT study, intensive treatment resulted in a 26% reduction in cardiovascular events if initiated within 15 years of diabetes diagnosis ($P=0.006$), but was less beneficial and possibly harmful for subjects with longer-duration diabetes [65•]. In a VADT substudy, subjects with lower coronary artery calcium scores (reflecting less atherosclerotic burden) showed benefit from intensive treatment, whereas those with higher scores (> 100) did not [66]. In the ADVANCE study, the risk reduction for the combined major vascular outcome was greater for patients without known macrovascular disease at baseline (−14% vs −4%) [15, 46]. Further, in a meta-analysis of the four major trials, subjects with shorter duration of diabetes (< 5 years) and those without a prior history of micro- or macrovascular disease showed significant reduction in major CVD events with intensive therapy [67]. Additional evidence in support of the benefits of earlier initiation of intensive management comes from the DCCT/EDIC study in T1DM, in which the average age at randomization was 27 years, and a 57% reduction in major cardiovascular outcomes was observed [4].

From these studies, one could reasonably conclude that intensive glycemic control may be more effective in patients with earlier diabetes and less extensive atherosclerosis, although the mechanisms for this differential effect are not clear. It may be that metabolic factors (e.g., hyperglycemia) demonstrated to play a role in the development of atherosclerosis are less able to modulate the inflammatory process once it is well established. It has been proposed that glucose reduction in patients with established atherosclerosis may disrupt previously stable plaques and result in increased plaque rupture and clinical coronary events [68]. Further, hyperglycemia-induced tissue damage, including formation of advanced glycation end products, may not be readily reversible by restoration of normoglycemia and may contribute to the "legacy effect" (also called "metabolic memory"). The concept of glycemic legacy refers to the observation that the benefits of early glycemic control appear to persist for many years after glucose control reverts to that of a standard treatment control group, as in the DCCT/EDIC study [4, 69]. Viewed another way, a "bad glycemic legacy" from many years of poor glucose control may be what drives the risk of diabetes vascular complications and cannot be reversed by a relatively brief period (3–5 years) of improved glucose control [70].

Conclusions

Now that the dust has settled, it seems that intensive glucose control provides, at best, a modest benefit in preventing CVD events and mortality in selected patients. Much has already been written about the inconclusive and otherwise disappointing results of recent trials and how the information from these studies should be applied to clinical care of patients with T2DM. Selection of specific glycemic targets and drug regimens remains problematic. However, there are reasonable conclusions that can be drawn from the available results:

1. Aggressive multidrug and high-dose insulin regimens should probably be avoided in older T2DM patients and those with established CVD, although evidence suggests that strict glycemic control early in the course of diabetes may be beneficial. Specific glycemic targets should be selected with consideration of comorbidities and risk of microvascular complications, for which evidence of benefit remains clear.
2. Multiple risk factor intervention (glucose, lipids, blood pressure, etc.) has been shown to be effective and should be offered to most patients.

3. More attention should be paid to monitoring for and avoidance of hypoglycemia in patients being treated with insulin and/or insulin secretagogues, particularly if near-normoglycemia (HbA_{1c}<7%) is a target.

Future Research

More research is needed on the specific cardiovascular effects of diabetes medications, particularly drugs and drug classes that are new to the market. Recent US Food and Drug Administration requirements for defined cardiovascular trials, while criticized by some as an impediment to the drug development process, have the potential to provide critically needed information.

At this time, it seems unlikely that additional large cohort studies addressing the issue of glycemic control and CVD will be undertaken. However, existing cohorts and ongoing studies can be leveraged to provide new insights into this important question. Given the evidence for a "legacy effect" demonstrated in the UKPDS and DCCT/EDIC studies, it is hoped that the assembled ACCORD, ADVANCE, and VADT cohorts will be followed long term for the further development of CVD and mortality end points.

Finally, the potential CVD benefits of lifestyle change (weight loss and increased physical activity) have received comparatively little attention. Results of the ongoing Look AHEAD (Action for Health in Diabetes) trial, which is testing the efficacy of an intensive lifestyle program in patients with established diabetes, will provide welcome insight [71]. In addition, information about the vascular benefits of intervention (lifestyle change or metformin) early in the course of dysglycemia will be forthcoming from the Diabetes Prevention Program Outcome Study, conducted in a cohort with prediabetes [72]. In the meantime, glycemic targets for the prevention of CVD should be determined based on each patient's unique risk profile and appreciation for the complex pathophysiology of vascular outcomes in type 2 diabetes.

Disclosure No potential conflicts of interest relevant to this article were reported.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. CDC: National Diabetes Fact Sheet 2011. Available at www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Accessed February 2012.
2. The University Group Diabetes Program: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. Diabetes 1970;19 Suppl 2:747–830.
3. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977–86.
4. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353(25):2643–53.
5. Preis SR, Hwang S-J, Coady S, Pencin MJ, D'Agostino Sr RB, Savage PJ, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. Circulation. 2009;119(13):1728–35.
6. Gall MA, Borch-Johnsen K, Hougaard P, Nielsen FS, Parving HH. Albuminuria and poor glycemic control predict mortality in NIDDM. Diabetes. 1995;44(11):1303–9.
7. Agewall S, Wikstrand J, Ljungman S, Fagerberg B. Usefulness of microalbuminuria in predicting cardiovascular mortality in treated hypertensive men with and without diabetes mellitus. Am J Cardiol. 1997;80(2):164–9.
8. Goff Jr DC, Gerstein HC, Ginsberg HN, Cushman WC, Margolis KL, Byington RP, et al. Prevention of cardiovascular disease in persons with type 2 diabetes mellitus: current knowledge and rationale for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol. 2007;99(12A):4i–20i.
9. Khaw K-T, Wareham N, Luben R, Bingham S, Oakes S, Welch A, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). BMJ. 2001;322(7277):15–8.
10. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med. 2010;362(9):800–11.
11. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352(9131):837–53.
12. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352(9131):854–65.
13. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10 year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577–89.
14. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff Jr DC, Bigger JT, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545–59.
15. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560–72.
16. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360(2):129–39.
17. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes: a randomized trial of pioglitazone. The PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events). Lancet. 2005;366:1279–89.
18. • Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, et al. Effect of intensive control of glucose on

cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomized controlled trials. Lancet. 2009;373(9677):1765–72. These authors performed a meta-analysis including UKPDS, ACCORD, ADVANCE, VADT, and PROactive studies to demonstrate that intensive glycemic control resulted in a 17% reduction in nonfatal MI, and 15% reduction in CVD events.

19. • Kelly TN, Bazzano LA, Fonseca VA, Thethi TK, Reynolds K, He J. Systemic review: glucose control and cardiovascular disease in type 2 diabetes. Ann Intern Med. 2009;151(6):394–403. A separate analysis of the same trials as in Dormandy et al. [17] and Ray et al. [18•] (excluding PROactive) demonstrated a similar 16% risk reduction for nonfatal MI and no effect on cardiovascular or all-cause mortality.
20. • Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death and microvascular events in type 2 diabetes: meta-analysis of randomized controlled trials. BMJ. 2011;343:d4169. This is a recent meta-analysis in which an impressive 13 studies (with a Jadad score > 3) and 34,533 patients were included. It demonstrated no significant effect of intensive glycemic control on CVD or overall mortality with a slight risk reduction for nonfatal MI and a twofold higher risk of severe hypoglycemia and 47% risk for congestive heart failure.
21. Liu J, Grundy SM, Wang W, Smith Jr SC, Vega GL, Wu Z, et al. Ten-year risk of cardiovascular incidence related to diabetes, prediabetes and the metabolic syndrome. Am Heart J. 2007;153(4):552–8.
22. Hu FB, Stampfer MJ, Haffner SM, Solomon CG, Willett WC, Manson JE. Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. Diabetes Care. 2002;25(7):1129–34.
23. Milman S, Crandall JP. Mechanisms of vascular complications in prediabetes. Med Clin North Am. 2011;95(2):309–25.
24. DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med. 2001;161(3):397–405.
25. Goldberg IJ. Why does diabetes increase atherosclerosis? I don't know! J Clin Invest. 2004;114:613–15.
26. Chait A, Bornfeldt K. Diabetes and atheroslcerosis: is there a role for hyperglycemia? J Lipid Res. 2009;50(Suppl):S335–9.
27. Collins R, Armitage J, Parish S, Sleigh P, Peto R, Heart Protection Study Collaborative Group. MRC/BHF Heart protection Study of cholesterol lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet. 2003;361(9374):2005–16.
28. Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM, Blackwell L, Collins R, Keech A, Simes J, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008;371 (9607):117–25.
29. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364(9435):685–96.
30. Gaede P, Lund-Andersen H, Parving HH, et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358:580–91.
31. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007;356(24):2457–71. Erratum in: N Engl J Med. 2007;357 (1):100.
32. • Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. Arch Intern Med. 2010;170(14):1191–201. This recent meta-analysis combined recent articles on the issue of cardiac toxicity of rosiglitazone and came to the conclusion that rosiglitazone increased risk of MI but not cardiovascular or overall mortality.
33. Winterstein AG, Heckbert SR, Schambelan M. Intensive glucose lowering and cardiovascular outcomes. N Engl J Med. 2011;364 (23):2263. author reply 2264.
34. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009;373:2125–35.
35. BARI 2D Study Group, Frye RL, August P, Brooks MM, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med. 2009;360:2503–15.
36. Garratt KN, Brady PA, Hassinger NL, Grill DE, Terzic A, Holmes Jr DR. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. J Am Coll Cardiol. 1999;33(1):119–24.
37. Johnson JA, Majumdar SR, Simpson SH, Toth EL. Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. Diabetes Care. 2002;25 (12):2244–8.
38. Simpson SH, Majumdar SR, Tsuyuki RT, Eurich DT, Johnson JA. Dose–response relation between sulfonylurea drugs and mortality in type 2 diabetes mellitus: a population-based cohort study. CMAJ. 2006;174(2):169–74.
39. Bell DS. Do sulfonylurea drugs increase the risk of cardiac events? CMAJ. 2006;174(2):185–6.
40. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction. Circulation. 2006;113(15):1888–904.
41. Anselmino M, Ohrvik J, Malmberg K, Standl E, Rydén L, Euro Heart Survey Investigators. Glucose lowering treatment in patients with coronary artery disease is prognostically important not only in established but also in newly detected diabetes mellitus: a report from the Euro Heart Survey on Diabetes and the Heart. Eur Heart J. 2008;29(2):177–84.
42. Marques JL, George E, Peacey SR, Harris ND, Macdonald IA, Cochrane T, et al. Altered ventricular repolarization during hypoglycaemia in patients with diabetes. Diabet Med. 1997;14(8):648–54.
43. Landstedt-Hallin L, Englund A, Adamson U, Lins PE. Increased QT dispersion during hypoglycaemia in patients with type 2 diabetes mellitus. J Intern Med. 1999;246(3):299–307.
44. Johnston SS, Conner C, Aagren M, Smith DM, Bouchard J, Brett J. Evidence linking hypoglycemic events to an increased risk of acute cardiovascular events in patients with type 2 diabetes. Diabetes Care. 2011;34(5):1164–70.
45. Adler GK, Bonyhay I, Failing H, et al. Antecedant hypoglycemia impairs autonomic cardiovascular function: implications for rigorous glycemic control. Diabetes. 2009;58:360–66.
46. Bonds DE, Miller ME, Bergenstal RM, Buse JB, Byington RP, Cutler JA, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ. 2010;340:b4909.
47. Riddle MC, Ambrosius WT, Brillon DJ, Buse JB, Byington RP, Cohen RM, et al. Epidemiologic relationships between HbA1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. Diabetes Care. 2010;33(5):983–90.
48. Schernthaner G. Diabetes and Cardiovascular Disease: Is intensive glucose control beneficial or deadly? Lessons from ACCORD, ADVANCE, VADT, UKPDS, PROactive, and NICE-SUGAR. Wien Med Wochenschr. 2010;160(1–2):8–19.
49. Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, Billot L, et al. Severe hypoglycemia and risks of vascular events and death. N Engl J Med. 2010;363(15):1410–8.
50. Boucai L, Southern WN, Zonszein J. Hypoglycemia-associated mortality is not drug-associated but linked to comorbidities. Am J Med. 2011;124(11):1028–35.

51. • Seaquist ER, Miller M, Bonds D, et al. The impact of frequent and unrecognized hypoglycemia on mortality in the ACCORD study. Diabetes Care. 2012;35:409–14. This analysis form the ACCORD group raises the provocative suggestion that frequent, mild hypoglycemia may in fact offer protection against fatal CVD events, possibly by blunting sympathetic nervous system counter-regulatory response.
52. Dahl-Jorgensen K, Brinchmann-Hanssen O, Hansen KF, Sandvik L, Aagenaes O, Aker Diabetes Group. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. Br Med J. 1985;290(6471):811–5.
53. Frier BM, HIlsted J. Does hypoglycemia aggravate the complications of diabetes? Lancet. 1985;2(8465):1175–7.
54. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe. Lancet 1999;354(9179):617–21.
55. Saydah SH, Miret M, Sung J, Varas C, Gause D, Brancati FL. Postchallenge hyperglycemia and mortality in a national sample of U.S. adults. Diabetes Care. 2001;24(8):1397–402.
56. Hanefeld M, Koehler C, Henkel E, Fuecker K, Schaper F, Temelkova-Kurktschiev T. Post-challenge hyperglycaemia relates more strongly than fasting hyperglycaemia with carotid intima-media thickness: the RIAD Study. Risk factors in impaired glucose tolerance for atherosclerosis and diabetes. Diabet Med. 2000;17 (12):835–40.
57. Ohshita K, Yamane K, Ishida K, Watanabe H, Okubo M, Kohno N. Post-challenge hyperglycaemia is an independent risk factor for arterial stiffness in Japanese men. Diabet Med. 2000;21 (6):636–9.
58. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance. JAMA. 2003;290(4):486–94.
59. NAVIGATOR Study Group, Holman RR, Haffner SM, McMurray JJ, Bethel MA, Holzhauer B, et al. Effect of nateglinide on the incidence of diabetes and cardiovascular events. N Engl J Med. 2010;362 (16):1463–76. Erratum in N Engl J Med. 2010;362(18):1748.
60. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA. 2006;295 (14):1681–7.
61. Brownlee M, Hirsch I. Glycemic variability: a hemoglobin A1c–independent risk factor for diabetic complications. JAMA. 2006;295(14):1707–8.
62. Mita T, Otsuka A, Azuma K, et al. Swings in blood glucose levels accelerate atherogenesis in apolipoprotein E deficient mice. Biochem Biophys Res Commun. 2007;358:679–85.
63. • Standl E, Schnell O, Ceriello A. Postprandial hyperglycemia and glycemic variability: should we care? Diabetes Care. 2011;34 Suppl 2:S120–127. This is a concise review of the evidence to support the role of glycemic variability per se in the pathogenesis of diabetic vascular complications. Methodologic issues (ie, our inability to accurately measure and effectively target glucose "spikes") are noted as important limitations of current research.
64. Calles-Escandón J, Lovato LC, Simons-Morton DG, Kendall DM, Pop-Busui R, Cohen RM, et al. Effect of intensive compared with standard glycemia treatment strategies on mortality by baseline subgroup characteristics: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care. 2010;33(4):721–7.
65. • Duckworth WC, Abraira C, Moritz TE, Davis SN, Emanuele N, Goldman S, et al. The duration of diabetes affects the response to intensive glucose control in type 2 subjects: the VA Diabetes Trial. J Diabetes Complications. 2011;25(6):355–61. This post hoc analysis proposes the hypothesis that intensive glucose control may have its greatest benefit if begun before 15 years duration of diabetes and may increase risks in those with longer duration.
66. Reaven PD, Moritz TE, Schwenke DC, Anderson RJ, Criqui M, Detrano R, et al. Intensive glucose-lowering therapy reduces cardiovascular disease events in Veterans Affairs Diabetes Trial participants with lower calcified coronary atherosclerosis. Diabetes. 2009;58 (11):2642–8.
67. Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia. 2009;52:2288–98.
68. Orchard TJ. Glycemic control and CAD risk: a heretical thought. Diabetes Care. 1999;22(7):1220.
69. White NH, Sun W, Cleary PA, Danis RP, Davis MD, Hainsworth DP, et al. Prolonged effect of intensive therapy on the risk of retinopathy complications in patients with type 1 diabetes mellitus: 10 years after the Diabetes Control and Complications Trial. Arch Opthalmol. 2008;126(12):1707–15.
70. Del Prato S. Megatrials in type 2 diabetes. From excitement to frustration? Diabetologia. 2009;52(7):1219–26.
71. Wing RR, Lang W, Wadden TA, Look AHEAD Research Group, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care. 2011;34:1481–6.
72. Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet. 2009;374(9702):1677–86. Epub 2009 Oct 29. Erratum in: Lancet. 2009 Dec 19;374(9707):2054.