

# Cardiovascular Disease and Glycemic Treatment

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At the 57th Annual Advanced Postgraduate Course of the American Diabetes Association (ADA) held 5–7 February 2010 in San Francisco, California, Peter Raven (Phoenix, AZ) addressed the question of which patients should be targeted for glucose control as pertains to cardiovascular disease (CVD). He termed “the big question [for] tight glucose control . . . [whether] the benefits of tight glycemic control, cardiovascular but, of course, also microvascular, outweigh the risks of hypoglycemia, mortality, time, and quality of life.” The Diabetes Control and Complications Trial (DCCT) (1) and the Stockholm Diabetes Intervention Study (2) in persons with type 1 diabetes and the University Group Diabetes Program (UGDP) (3), UK Prospective Diabetes Study (UKPDS) (4), Kumamoto (5), and the Veterans Affairs Cooperative Study (6) in type 2 diabetes were followed by the Action to Control Cardiovascular Risk in Diabetes (ACCORD) (7), the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) (8), and the Veterans Affairs Diabetes Trial (VADT) (9) that addressed a glycemic goal of A1C from ~7% and going to even lower levels.

Comparing the older with newer studies, although we have a good understanding of the relationship between control and microvascular risk, Reaven suggested that the DCCT and UKPDS appear to show that the relationship of glycemia to outcome for microvascular disease shows a steeper slope than that for macrovascular disease, making it more difficult to determine the importance of the latter. In the DCCT itself, there was no significant cardiovascular benefit, although the trial was not intended for this. This was similarly the case for Kumamoto; in UKPDS, the 16% decrease in myocardial infarction was not statistically significant at the completion of the trial,

although all three trials showed reduction in microvascular disease. UKPDS also had a metformin arm, which did show significant cardiovascular reduction with monotherapy, although not when the agent was given in combination with a sulfonylurea (10). In these studies, however, blood pressure and lipids were not as aggressively treated as is currently done, which may limit our ability to extrapolate to current benefits.

The DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up did show cardiovascular benefit (11), leading to the concepts that this may require long periods of time and that there may be benefit to early control. The UKPDS follow-up similarly showed significant cardiovascular benefit a decade following the end of intensive treatment (12). There is, then, possible long-term cardiovascular benefit of glycemic treatment in type 1 and type 2 diabetes, but it appears to be slow in onset, with little data showing cardiovascular benefit of achieving A1C levels <7%. A recent analysis of type 2 diabetic persons from the U.K. General Practice Research Database, 27,965 whose treatment had been intensified from oral monotherapy to combination therapy and 20,005 who had changed to regimens that included insulin, suggested that either above or, more worryingly, below an A1C level of 7.5%, mortality increased (13).

In the three more recent trials, ACCORD, ADVANCE, and VADT, that included persons with longer diabetes duration and higher CVD prevalence and that had more aggressive A1C goals, the outcomes for cardiovascular reduction were modest, with reductions ranging from 6 to 12%, which were not statistically significant. Furthermore, there was a significant 22% increase in total mortality, with increased cardiovascular mortality, in the intensive treatment group of

ACCORD. Prespecified subgroup analysis showed, however, that those who had not had prior cardiovascular events and those who had baseline A1C  $\leq$ 8% seemed to have benefit in reduction of primary outcome, with mortality also appearing to show this pattern.

In ADVANCE, macrovascular event rates were not different despite the 0.7% difference in A1C. In the VADT, 1,791 patients were treated in 20 centers in a prospective, randomized fashion, with blood pressure, lipids, diet and lifestyle approaches identical in the intensive versus conventional glucose control arms, over an average follow-up of 5.6 years, with A1C 6.4 vs. 8.4%. There was a non-significant 12% lower rate of the primary composite outcome of cardiovascular death, myocardial infarction, stroke, heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene. Hypoglycemia rates tripled, however, in all types from mild to more severe, and this was a strong predictor of cardiovascular death for both the standard and intensive care groups. There was a trend ( $P = 0.07$ ) to decreased 2-step retinopathy progression, a reduction in progression from normal to micro- or macroalbuminuria, no difference in mononeuropathy or peripheral neuropathy, and a trend ( $P = 0.07$ ) to worsening of autonomic neuropathy.

A meta-analysis of ACCORD, ADVANCE, UKPDS, and VADT, with a total of 27,049 participants with 2,370 major vascular events, showed a significant 9% reduction in these events, driven by a 15% reduction in myocardial infarction, with nonsignificant 10 and 4% increases in cardiovascular and total mortality, respectively. Hypoglycemia rates were 2.5-fold more common with intensive treatment. There was heterogeneity between the trials, with ADVANCE suggesting a reduction in cardiovascular mortality, the UKPDS being neutral, and ACCORD and VADT having trends to increased cardiovascular mortality. In the meta-analysis, those with no history of macrovascular disease had a significant 16% reduction in CVD, while there was no cardiovascular benefit in those who had such a history—the interaction based

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on the presence or absence of prior CVD being statistically significant (14).

Prospective coronary artery calcium (CAC) scans were done in 301 participants in the VADT. Those with Agatston score  $>100$  did not have significant benefit, while those with score  $<100$  had a marked reduction in events with intensive glycemic control, with nearly a 10-fold difference in the benefit ratio (15). Reaven stated that “how you enter the trial in terms of your vascular status may influence how you do.” This may, he suggested, explain the negative findings of the overall study because nearly two-thirds of the VADT cohort likely had CAC  $>100$ . It may be, then, that those with advanced CVD may not have cardiovascular benefit from intensive glycemic treatment. Indeed, in a study of 2,613 type 2 diabetic patients, those with low-to-moderate scores had 40% better cardiovascular outcome with A1C  $\leq 6.5\%$  than at higher levels, while those with high comorbidity scores had a nonsignificant 9% reduction in CVD (16). Early disease, Reaven concluded, may be particularly benefited from intensive glycemic treatment, whereas there may be little benefit, or benefit outweighed by harm from hypoglycemia, in persons with diabetes and advanced CVD. Another possibility is that the time required for benefit to occur in those persons may be so long that adverse effects of treatment predominate during the period of a typical clinical trial. We continue to need to treat other cardiovascular risk factors aggressively, Reaven pointed out, but it may be appropriate to avoid very aggressive A1C lowering in older persons and in those with diabetes of longer duration, frequent or severe hypoglycemia, extensive microvascular disease, or with more CVD (imaging might be useful in assessing this).

### Hypoglycemia

I further discussed questions of hypoglycemia and other adverse consequences of glucose-lowering therapies in the three recent trials and reviewed the conceptual dilemma that although analysis showed no significant association of severe hypoglycemia with the increased mortality in ACCORD, there are many reasons to think that it may have played a role as severe hypoglycemia was significantly associated with higher mortality and as there is no doubt that the very aggressive treatment approach undertaken in the trial led to markedly increased rates of hypoglycemia in the intervention group. It is

worthwhile to examine the definition of a severe hypoglycemia episode used in ACCORD: hypoglycemia requiring medical or paramedical attention with either documented blood glucose  $<50$  mg/dl or prompt recovery with administration of oral carbohydrate, parenteral glucose, or subcutaneous glucagon. Each participant’s “Glucose Diary” was reviewed at each clinic visit to identify the occurrence of one of these hypoglycemic events. Using these criteria, hypoglycemia occurred in 10.3 vs. 3.4% of the intensive versus control group in ACCORD (17); severe hypoglycemia not necessarily requiring medical attention occurred in 16.2 vs. 5.1%, with presumably related rates of weight gain exceeding 10 kg of 27.8 vs. 14.1%, respectively (7). The rates of documented blood glucose  $<50$  mg/dl for the respective groups in VADT were 203 vs. 52 per 100 patient-years (9); this occurred much less frequently in ADVANCE, in 2.7 vs. 1.5% of the respective groups during the period of observation (8). Severe hypoglycemia was itself a strong risk factor for mortality; those persons with one or more episodes requiring medical assistance had annual mortality rates of 2.8% in the intensive control arm—less than the rate of 4.9% in the standard control arm—a paradoxical finding in view of the overall increase in mortality reported in the former group. Indeed, among those not experiencing any hypoglycemic events requiring assistance, annual mortality rates were 1.2% with intensive treatment and 1.0% with standard treatment (17). Although the ACCORD investigators concluded that “the increased risk of death seen in the ACCORD trial among participants in the intensive glycaemia control arm cannot be attributed to the increased rate of severe hypoglycemia in intensive arm participants (17),” it appears that there was no systematic attempt to capture overall rates of asymptomatic hypoglycemia with analysis of downloaded glucose meter data. One wonders whether, if such information were available, it might be found that the increase in mortality in the intensive control group among those not experiencing documented severe hypoglycemia might actually reflect what could be termed asymptomatic severe hypoglycemia. This suspicion may be bolstered by analysis of the causes of death in ACCORD: 86 of 136 cardiovascular deaths in the intensive group and 67 of 94 in the standard treatment group were sudden/unexpected, of the sort that might

be brought about by a severe hypoglycemic episode, so that although only one documented death occurred with severe hypoglycemia, glucose measures were not available near the times of death for most cases. Similarly, in the VADT, there were 29 cardiovascular deaths in the standard versus 36 in the intensive glycemic treatment groups, with sudden death in 4 vs. 11, accounting for all of the excess mortality, and recent severe hypoglycemia was associated with a fourfold increase in cardiovascular mortality (18). Indeed, it is fascinating that hyperglycemia remained a mortality predictor in ACCORD; those participants with baseline A1C  $>8.5\%$  had greater mortality (19), and every 1% lower A1C was associated with more than a 50% reduction in mortality, so that an in-study A1C above 7% was associated with higher mortality (20). One would be tempted, then, to conclude that a contributor to mortality was the state of difficult-to-control diabetes, leading the investigators to fruitlessly increase their efforts to lower glucose levels in patients who for one or another reason responded poorly to such efforts.

I reviewed corroborative evidence from the Treating To Target in Type 2 Diabetes (4-T) study of 708 patients not optimally controlled with sulfonylureas plus metformin, where the less aggressive basal insulin first approach reduced weight gain and severe hypoglycemia, leading to a substantial difference in adverse events, with cardiovascular death in one, four, and nine persons randomized to initial use of basal, biphasic, and prandial bolus insulin, respectively (21). Documented severe hypoglycemia is likely to represent a tiny fraction of overall hypoglycemia. In a study comparing basal insulin glargine to prandial insulin lispro in 415 type 2 diabetic patients who received oral agents, the groups had 5.21 and 24.00 total hypoglycemic episodes per patient per year, but 0.03 and 0.08 severe hypoglycemic episodes per patient per year (22). It is likely then that severe but asymptomatic hypoglycemic episodes do occur, and there is no reason to suppose that such episodes do not have cardiovascular consequence, perhaps even more so than those for which the patient is able to obtain assistance. Further suggestion that treatments likely to cause hypoglycemia (insulin and sulfonylureas) might have particularly adverse cardiovascular consequence over approaches not intrinsically causing hypoglycemia (metformin and rosiglitazone) comes from the Bypass

Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial of 2,368 type 2 diabetic persons with angiographically documented coronary artery disease (23). The former treatment strategy led to 38 and 56% increases in total and in severe hypoglycemia, with a trend to increasing major cardiovascular events in those patients undergoing coronary artery bypass surgery. In considering very intensive glycemic treatment we should, I concluded, remember Elliott Joslin's dictum: "Insulin is a remedy primarily for the wise and not for the foolish, whether they be patients or doctors" (reported in [24]).

### Blood pressure and lipid treatment

David Kendall (Alexandria, VA), Chief Scientific and Medical Officer of ADA, discussed the treatment of other cardiovascular risk factors in diabetes. "It is quite clear," he said, "that diabetes, in particular type 2 diabetes, is associated with a myriad of risk factors . . . that contribute to the increased cardiovascular risk." Much of the discussion of A1C targets is based on microvascular disease risk, and this has also been true for blood pressure targets. ADA's "Standards of Medical Care in Diabetes—2010" does not state that glycemic control reduces cardiovascular risk but urges that more randomized controlled trials be carried out to assess the hypothesis (25). Kendall stated, "Epidemiology often exaggerates but . . . it rarely lies," suggesting that ultimately it will be shown that all the treatable factors associated with macrovascular disease in type 2 diabetes, LDL and HDL cholesterol, A1C, blood pressure, and cigarette use (26), will be found to be worth treating.

Examining the history of cardiovascular risk targets, the LDL target was originally 160 mg/dl, the community target for systolic blood pressure was 150 mmHg, and the A1C target was 8–9%. Over time, the LDL target fell to <130 and then to <100, with current guidelines <70 mg/dl in the highest-risk individuals. For blood pressure, systolic blood pressure goals for diabetic persons decreased to <140 and then to <130 mmHg. Similarly, A1C targets decreased to 7–8 in the 1990s and to 6–7% over the past decade, although the latter goal requires careful individualization.

A number of trials have addressed blood pressure in diabetes: the Systolic Hypertension in the Elderly Program (SHEP), Hypertension Optimal Treatment (HOT), Systolic Hypertension in Europe (Syst-Eur), Fosinopril Versus Am-

lodipine Cardiovascular Events Randomized Trial (FACET), Appropriate Blood Pressure Control in Diabetes (ABCD), UKPDS, Heart Outcomes Prevention Evaluation (HOPE), Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), and ADVANCE, with most showing improvement in outcome, using a variety of treatment approaches. In UKPDS, each 10 mmHg decrease in systolic blood pressure was associated with reduction both of microvascular events and of myocardial infarction by ~15% (27). Kendall pointed out that U-shaped curves with adverse outcome at low as well as at high levels are shown in many blood pressure epidemiologic analyses, but whether this indicates adverse effect of treatment or coexisting illness is not clear. It is not clear whether the evidence supports a systolic blood pressure goal <130 mmHg, and none of the randomized controlled trials showed this. The ACCORD substudy targeting systolic blood pressure <120 mmHg was reported subsequent to Kendall's lecture, showing some adverse effects, although there was substantial reduction in stroke, which might be important in certain populations (28).

For lipids, LDL <100 mg/dl is the primary goal, with levels <70 mg/dl an option for those with overt CVD; much less is known about triglyceride and HDL. Statins have been shown of benefit, with a meta-analysis of 18,686 diabetic patients showing a 31% reduction in vascular mortality, 22% reduction in myocardial infarction or coronary death, 21% reduction in stroke, and 25% reduction in coronary revascularization for every 39 mg/dl reduction in LDL cholesterol (29). There is, however, substantial residual risk even with good LDL control, whether lipid-related or from other risk factors. Fibrates (30), niacin (31), and other agents have not been fully explored in diabetes, but may be of benefit. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, there was no significant benefit of addition of fenofibrate (32). The ACCORD statin plus fibrate substudy was reported subsequent to Kendall's lecture and also failed to show reduction in cardiovascular events (33), although there is some evidence from the study of improvement in retinopathy (34). What is needed, Kendall concluded, is comprehensive cardiovascular risk factor improvement, of the sort reported in the Steno-2 study, in which modest individual interventions on blood pressure,

lipids, glucose, aspirin use, and cigarette smoking reduced risk by half (35), with substantial long-term reduction in mortality (36). We should maintain "therapeutic optimism" for glycemic treatment, particularly early in the course of diabetes, with diabetes prevention as the goal, and lipid and blood pressure treatment is important as well.

### Lifestyle intervention

Gretchen Youssef (Washington, DC) discussed lifestyle interventions in a number of diabetes and CVD trials, DCCT and UKPDS, ACCORD, BARI 2D, VADT, and Look AHEAD (Action for Health in Diabetes). Diabetes self-management education (DSME) involves assessing the knowledge skills and then developing a plan for each individual patient in the content areas of healthy eating, being active, taking medications, monitoring, problem-solving, healthy coping, and reducing risks. Medical nutrition therapy provides nutrition assessment, planning, and support while reinforcing the DSME content areas with individualized modification of food plan/physical activity/medication for improved postmeal glycemic control and hypoglycemia prevention. It involves individualized modification of carbohydrate, protein, fat and sodium intake, with guidance to achieve lipid and blood pressure goals, and individualized weight loss planning and coaching.

The ADA standards suggest that every person with diabetes should receive DSME according to the national standards when diabetes is diagnosed and thereafter. Medicare allows reimbursement for 10 h of education (1 h individual, 9 h group) in the first year and 2 h of either group or individual in subsequent years of diabetes, with medical nutrition therapy (MNT) reimbursed for 3 h allowed in the first and 2 h in subsequent years. MNT is effective, Youssef said, with evidence of benefit of many types of nutrition intervention throughout the disease process, particularly at initial diagnosis, although multiple encounters are necessary (37). The American Dietetic Association recommends that MNT provided by a registered dietitian be offered to all individuals with diabetes, in a series of three to four encounters each lasting 45–90 min, after which additional MNT may be needed.

Youssef reviewed the use of MNT in clinical trials. The DCCT was a model, in which each person received a meal plan

based on guidelines, weight goals of 90–120% ideal body weight, with exercise encouraged, the intensive group seen monthly, and the standard group seen every 6 months. The food pyramid, exchange system, carbohydrate counting, and assessment of total available glucose were taught to participants (38). In UKPDS, MNT was individualized for all participants, contributing to the 1.9% decrease in A1C over the initial 3-month run-in phase. In ACCORD, individual recommendations were made, with the goal 10% or 5–9 kg weight loss, as well as Na restriction (see protocol at [www.accordtrial.org/public/protocol\\_2005-05-11.pdf](http://www.accordtrial.org/public/protocol_2005-05-11.pdf)). In BARI 2D, there were nutritionist visits reviewing nutrition, behavior change, and physical activity at 3 months and annually, with a goal loss of 10% of weight for BMI >25 kg/m<sup>2</sup>, with additional sessions for patients not meeting A1C, blood pressure, or lipid goals or with gain of 5% of original weight (see protocol, adapted from the Diabetes Prevention Program [DPP] approach, at [www.bari2d.org/researchers/manuals.html](http://www.bari2d.org/researchers/manuals.html)). The VADT approach followed ADA guidelines, with visits every 6 weeks for the first year and then quarterly. Finally, the Look AHEAD lifestyle intervention trial was also adapted from DPP, recording food intake, restricting calories, and developing portion control plans or replacing two and then one meals daily with liquid shake and using frozen entrées for dinner. The trial used two to four visits monthly over the first 4 years and achieved 8.6 vs. 0.7% weight loss and 0.7 vs. 0.1% decrease from a baseline A1C of 7.3%, with increased fitness and improvement in other measures (39).

Youssef concluded by stressing the importance of culturally appropriate meals, financial considerations, content appropriate for the health literacy level, the use of individual and group MNT, the need for multiple encounters and support, and the benefit of regular physical activity. She noted that consistency across study sites and consistency of implementation are not always assured in clinical trials, adding to the difficulty of translating studies into actual clinical use.

### Clinical practice considerations

Richard Bergenstal (Minneapolis, MN) reviewed the implications of the trials for clinical practice. “It really is about a whole spectrum” of interventions, he said, including self-management and lipid/blood pressure/glycemic interventions. The

practice must be organized for success, understanding factors predicting glycemic control, agreeing on treatment goals, and using appropriate tools. Factors predicting A1C include lifestyle, about which Bergenstal commented that “it’s never too late,” but a typical finding is that A1C is lowest in patients on diet alone, intermediate in those receiving oral agents, and highest in those treated with insulin (40), suggesting that insulin is started too late or that we do not really prescribe insulin properly. He noted the importance of patients and physicians agreeing on diabetes management goals: if the patient is interested in their depression and the physician in A1C, blood pressure, and lipids, it is difficult to make headway; a recent study showed that “30% of the time the doctor’s top three weren’t even on the patient’s list” (41).

Bergenstal suggested that after one gives the patient a plan (for example, taking aspirin; improving A1C, blood pressure, and lipids; stopping cigarette use; getting eye and foot exams; and checking renal function), it is not advisable to address each component at each visit, but rather that several should be worked on at each contact. Patients typically reported hypoglycemia in ACCORD to be caused by missed meals, which must be addressed by MNT. He cited Davidson’s indictment of “how our medical care system fails,” suggesting that disease management reminders and laboratory reports are not effective, with the only effective interventions using proven algorithms followed by specially trained staff to change treatment (42). Which algorithm is best? Bergenstal noted the ADA tier 1 and tier 2 recommendations, in which metformin, sulfonylureas, and insulin are given as first choices (with which this writer disagrees). He asked, what target? Should the A1C be as low as possible? Should one use eAG? Is it safe to drop the A1C quickly? There is microvascular benefit of glucose lowering in most studies, and Bergenstal gave his belief that there is cardiovascular “benefit in the long run,” but suggested that ACCORD aimed “too low,” resulting in adverse effect in those with intensive treatment who did not respond, which he pointed out to be “the group you have to back off on.” He further noted that “relying on A1C alone is causing part of the problem,” as the practitioner must target A1C and also self-monitored glucose patterns. Perhaps greater use of continuous glucose monitoring will allow better glycemic treat-

ment. He pointed out that not only A1C and self-monitoring but also “minimizing hypoglycemia and weight gain” are important, leading to consideration of use of  $\alpha$ -glucosidase inhibitors, amylin mimetics, incretin-based treatments, and bile acid sequestrants. Furthermore, he stressed the importance of the blood pressure, lipid, and A1C “triple goal” in optimizing outcome. We need, he said, aggressive early treatment “to undo 15 years of glucose exposure,” and we need to make sure “not to push when we’re not getting a response.”

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