

Glycemic Control in Diabetes: A Tale of Three Studies

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Much of the controversy at the American Diabetes Association Scientific Sessions, held 6–10 June 2008 in San Francisco, California, pertained to questions raised about the benefits of intensive glycemic control by three large clinical studies: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the Action in Diabetes and Vascular Disease (ADVANCE) trial, and the Veterans' Administration Diabetes Trial (VADT). All three presented somewhat negative study results.

ACCORD

David Goff (Winston-Salem, NC) discussed the ACCORD study design. The goal of ACCORD was to determine whether cardiovascular disease (CVD) event rates could be reduced by intensively treating three important risk factors (hyperglycemia, dyslipidemia, and high blood pressure) in a double 2 × 2 factorial design. For glycemia, the question of A1C <6 vs. 7–7.9% was addressed. Goff reviewed previous studies that led to the decision to aim for the low A1C target. In the UK Prospective Diabetes Study (UKPDS), insulin and sulfonylurea treatment achieved a mean A1C level of 7%, with 7.9% in a control group. The 16% CVD reduction just missed statistical significance. Metformin treatment in this study achieved a mean A1C level of 7.4% with 8% in a control group, associated with a significant 39% CVD reduction. (Goff did not mention that, compared with sulfonylureas alone, the other UKPDS metformin substudy showed that metformin with a sulfonylurea was associated with 96, 60, and 9% increases in diabetes-related and all-cause mortality and in myocardial infarction [1].) A nonsignificant CVD risk reduction of ~50% was seen in the Kumamoto study, while there was also a nonsignificant CVD risk increase of ~50% in the Veterans' Affairs

Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VACSMD); both studies showed A1C 7.1% in the treatment group and 9.3–9.4% in the control group. Analysis of a number of observational studies suggests that for every 1% increase in A1C, there is an 18% increase in the risk of CVD. The ACCORD study was based on the hypothesis that a 1.5% difference in A1C would result in a 15% difference in event rates in a population of high-risk diabetic individuals having a 3% annual CVD event rate. Power calculations required a sample size of 10,000 individuals, with 10,251 actually participating and 5,128 randomized to intensive and 5,123 to standard glycemia goals. In addition, half of the participants were randomized to intensive blood pressure lowering to a systolic goal <120 mmHg (2,362 individuals) vs. <140 mmHg (2,371 individuals), and half were randomized to statin plus fibrate (2,753 individuals) vs. statin plus placebo (2,765 individuals). Eligibility required stable type 2 diabetes treatment for at least 3 months with A1C 7.5–9.0%, BMI ≤45 kg/m², creatinine ≤1.5 mg/dl, and age 40–79 years with, or 55–79 years without, established CVD—the latter group either having other anatomic evidence of atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two CVD risk factors.

The primary outcome was first occurrence of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death, and secondary outcomes included the above individual outcomes, total mortality, quality of life, cost, cognitive health, skeletal health, and microvascular outcomes. At baseline, the groups were well matched, with median age 62 years, diabetes duration 10 years, just over one-third of the subjects with a prior CVD event, mean BMI 32 kg/m², blood pressure 136/75 mmHg, A1C 8.3%, and LDL

cholesterol 105 mg/dl. Proportions of subjects undergoing diabetes treatment at baseline were as follows: 35% were on insulin, 60% on metformin, 19% on a thiazolidinedione, and 62% on a statin. At baseline and during the trial, 85 and 91% took a blood pressure-lowering medication, 53 and 70% an ACE inhibitor, 54 and 76% aspirin, and 29 and 48% a β-blocker.

Hertzel Gerstein (Hamilton, ON) presented the mortality and primary outcome results. All randomized patients were analyzed by intention to treat, with ~25 in each group lost to follow-up and just over 300 in each group discontinuing the intervention. The target was an essentially normal A1C, stressing lifestyle as well as comprehensive pharmacologic treatment, with attention paid to hypoglycemia in all patients. In the intensive group, A1C decreased from a median of 8.1 to 6.7% at 4 months, 6.5% at 8 months, and 6.3–6.4% from 1 year through 6 years, while the A1C of the standard-treatment group decreased to 7.5% at 4 months and remained at that level for the duration of the study. Intensive treatment was associated with significant excess in nonhypoglycemia serious adverse events versus the number in those undergoing standard treatment (in 113 vs. 82 subjects, respectively), with significant excess in fluid retention (3,541 vs. 3,378 participants) and with significantly less elevation in transaminase levels.

The glycemia comparison was stopped by a 10-individual monitoring board on 8 January 2008 after a 22% increase in all-cause mortality was found in 1.41% of intensively treated patients versus 1.14% of standard-treatment patients, with the comparison statistically significant at $P = 0.04$. CVD mortality also increased, occurring 35% more often in 2.63 vs. 1.83% of the respective groups over a mean 3.5 years of observation (statistically significant at $P = 0.02$). Interestingly, despite the extremely careful adjudication process, the largest single category of deaths was one termed “unexpected/presumed CVD,” affecting 86 intensively treated vs. 67 standard-treatment patients (Table 1). The attribution of the increase in mortality among intensively treated individuals to

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Table 1—Causes of death in the ACCORD trial

Cause of death	Intensive-treatment group	Standard-treatment group
Unexpected/presumed CVD	86	67
Myocardial infarction	19	13
Congestive heart failure	23	16
Cardiovascular procedure	10	3
Arrhythmia	4	10
Noncardiovascular procedure	1	3
Stroke	9	11
Other CVD	8	10
Cancer	65	63
Non-cancer/CVD	50	35
Indeterminate	7	11
Total	282	242

Data are n. Data available from http://diabetesconnect.org/storetemplate/webcast_viewer/preview.aspx?type=0&lid=3934. Accessed 6 July 2008.

CVD, then, is presumptive. Fascinatingly, there was at the same time a statistically significant ($P = 0.004$) reduction in nonfatal myocardial infarction occurring in 3.63 vs. 4.59% of patients randomized to intensive versus standard treatment, respectively.

Subgroup analysis failed to show differences between men and women or between nonwhite and white participants. There were nonsignificant trends toward a greater effect of intensive treatment on mortality among individuals with versus without prior CVD, with baseline A1C $>8\%$ (versus $\leq 8\%$), and with baseline age ≤ 65 years (versus >65 years). The primary outcome—first occurrence of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death—occurred significantly less often in the intensively treated subgroup without prior CVD and less often among the subgroup with baseline A1C $\leq 8\%$. Gerstein regarded these as hypothesis-generating findings and stated that, although ongoing follow-up and analysis will be important, the conclusion of the study was that “in people with type 2 diabetes at high risk for CVD, with an A1C of 7.5% or more, a therapeutic strategy that targets an A1C $<6\%$ vs. 7–7.9% increases mortality over 3.5 years.”

Robert P. Byington (Winston-Salem, NC) discussed the relationship between hypoglycemia and mortality outcome. In attempting to identify causes and mechanisms of the increased mortality, a number of exploratory analyses were carried out. Severe hypoglycemia occurred in three times as many intensive- as standard-treatment patients, with annual 3.3 vs. 1.1% rates, respectively. This, he

stated, was anticipated, but “what was not expected was that [intensive treatment] participants . . . would have a mortality higher than the standard group.” He presented an analysis of the relationship between mortality and severe hypoglycemia, defined by requirement for medical or paramedical intervention, with documented glucose <50 mg/dl and relief by parenteral or oral glucose or by glucagon. Review of a glucose diary and specific questioning about such episodes of severe hypoglycemia were carried out at each visit. Byington noted that stratification by a postrandomization characteristic such as hypoglycemia is inherently confounded by treatment group assignment, as it may be mediated by the intensive strategy per se, and that findings of such analyses should therefore be regarded as hypothesis generating. Given this caveat, he reported that 93% of patients did not experience severe hypoglycemia and had a mortality of 1.2% per year, while for the 705 participants who experienced at least one episode of severe hypoglycemia, the mortality was significantly greater (3.1% per year). Both among individuals randomized to intensive strategy, with 2.8 vs. 1.2% respective annual mortality rates, and in the standard-treatment group the same association between hypoglycemia and mortality was seen. Intriguingly, among participants not experiencing severe hypoglycemia, 223 vs. 186 deaths occurred, representing a 24% increase, which is similar to that found in the overall group. However, in those who did experience severe hypoglycemia, 34 vs. 17 deaths occurred, with annual mortality rates (given the larger number of such pa-

tients among those assigned to intensive treatment) of 2.8 vs. 4.8%. Intensive treatment among those experiencing severe hypoglycemia, then, was associated with unadjusted risk of 0.4, and the risk—adjusted by age, sex, race, education, standard cardiovascular risk factors, diabetes duration, A1C, creatinine, albuminuria, and other known or presumed mortality predictors—in the intensively treated group was 0.52 as great as that in the standard-treatment group. The difference between the overall 1.22-fold mortality and the 0.52-fold adjusted mortality ratio in the group experiencing severe hypoglycemia was statistically significant. Repeating the analysis with a broader definition of severe hypoglycemia to include any assistance by another individual did not change the conclusion. Byington acknowledged, however, that there was no systematic analysis or collection of low glucose levels other than that of severe hypoglycemia as defined above, such that although the investigators concluded that severe hypoglycemia was not related to the higher mortality, full assessment of the relationship between hypoglycemia and the outcome of ACCORD may not be possible.

Michael E. Miller (Winston-Salem, NC) discussed the relationship between prescribed medications and mortality in ACCORD. He pointed out that participants were not randomized to different medications, and the choice of medication in a given participant was based on clinical judgment and characteristics of participants. Adjustment for patient characteristics may, he stated, not be able to distinguish between treatment assignment and an actual medication effect. Analysis including self-reported adherence has not yet been carried out. The main medication differences between the intensive- and standard-treatment groups were in the former making greater use of repaglinide, rosiglitazone, and basal and bolus insulin and in the latter making greater use of premixed insulin, both in percentage ever prescribed and in the time of use of the medication. Insulin was given more often to those with prior CVD or longer duration of diabetes, while rosiglitazone was given less often to patients with baseline history of CVD. Exenatide was less likely to be given to participants using insulin, and both rosiglitazone and exenatide were given $\sim 25\%$ less often to the 23% of participants with diabetes duration ≥ 15 years. Taking medication use into account and adjusting for baseline

participant characteristics as well, the mortality ratio decreased from 1.22 to 1.19, which are similar figures but no longer statistically significant at the 95% confidence level. When addressing in particular the use of rosiglitazone in combination with insulin, the investigators found no evidence of adverse effect on mortality. Exenatide was associated with lower mortality but was not used frequently in the study, and both premixed and bolus insulin types were associated with greater mortality; however, premixed insulin was more used in the standard-treatment group and bolus insulin in the intensive-treatment group.

Jeffrey L. Probstfield (Seattle, WA) discussed the blood pressure and lipid trials. Hypertension and dyslipidemia are more common in diabetes and associated with disproportionate increase in CVD risk, with the combination multiplicative, but optimal treatment approaches have not been determined. The blood pressure study will have a 94% power to detect a 20% effect on outcome, and the lipid study will have an 87% power to detect such an effect; both of these trials continue and will complete in 2009, with reporting anticipated in 2010. There was no interaction of blood pressure or of lipid treatment with the adverse glycemia-treatment effect.

Denise Simons-Morton (Bethesda, MD) summarized the ACCORD findings, emphasizing that because the study was a strategy trial, specific treatment and patient characteristics may be difficult to relate to outcomes. The suggestions of reduced major cardiovascular events in the primary prevention group and among those with A1C <8% at baseline, she stated, may hint at important directions for further study, and ongoing analyses will include the microvascular outcome study, comparisons of outcomes, such as those in ECG abnormality and microvascular disease, of outcomes among those with lesser or greater change in body weight, creatinine, or edema. Epidemiologic analyses of the relationship between A1C and outcomes and the effects of specific medications on A1C and on outcomes are planned. At the present time, however, she stated, "maximum lowering of glycemia using an ACCORD-like strategy in ACCORD-like patients is not warranted because of undue risk."

ADVANCE

ADVANCE was a randomized controlled factorial trial of 11,140 patients with type

2 diabetes randomized to intensive blood pressure and glycemic treatment. Stephen MacMahon (Sydney, Australia) stated that this was an independent investigator-initiated trial sponsored by the National Health and Medical Research Council of Australia and by Servier, with the sponsors not participating in any of the editorial committees, involving some 200 collaborating sites from 20 countries, including Canada, Australia, China, Russia, and India. The study aim was to determine the effects of intensive glucose control (A1C \leq 6.5) and blood pressure-lowering with an ACE inhibitor plus a diuretic on macro- and microvascular outcomes. The UKPDS showed a 12% reduction in total diabetes-related end points, primarily microvascular, without a clear reduction in myocardial infarction or stroke, although a relationship could be shown between the achieved level of A1C during follow-up and macrovascular disease. The UKPDS in essence compared A1C of 8 vs. 7%, but, McMahon stated, "the guidelines have gone beyond the randomized evidence . . . using epidemiologic data." The question, then, is whether achieving an A1C level <6.5–7% actually provides additional protection for either micro- or macrovascular disease. The UKPDS also showed that tight blood pressure control reduced diabetes-related end points by ~25%, with epidemiologic analysis showing a continuous effect up to a systolic blood pressure of 115 mmHg, but again the study actually compared systolic blood pressure levels of 155 vs. 145 mmHg, although guidelines have extrapolated from these findings to suggest benefit of further blood pressure lowering. A second question, then, is whether lowering systolic blood pressure to <130–135 mmHg produces additional protection for either micro- or macrovascular outcomes.

The glucose component of the ADVANCE study was based on an extended-release form of the sulfonylurea gliclazide, and the blood pressure component used the combination of perindopril with indapamide. Glucose treatment involved frequent visits and A1C monitoring, with drug titration beginning with gliclazide, then adding other orals including metformin, then adding long-acting insulin, and finally adding preprandial insulin bolus treatment. Rather than employing forced titration, the advancement of glycemic treatment was determined by the local study trial coordinator. Primary study outcomes were nonfatal stroke,

nonfatal myocardial infarction, or death from any cardiovascular cause (including sudden death and microvascular outcomes of new or worsening nephropathy, based on increased albuminuria, doubling of creatinine, development of proliferative retinopathy, macular edema, blindness, or need for photocoagulation). Sample size was calculated from an anticipated 1% A1C and 6 mmHg blood pressure reductions, both of which were assumed to decrease micro- and macrovascular events by 16% from expected 3% annual incidences. Most patients were recruited in 2002, with one-half from Europe and one-third from China. Mean age was 66 years, 43% were women, diabetes duration averaged 8 years, one-third of subjects had a history of macrovascular disease and one-tenth of microvascular disease, and 28% had microalbuminuria. Baseline blood pressure was 145/81 mmHg, fasting blood glucose (FBG) 153 mg/dl, and A1C 7.5%.

John Chalmers (Sydney, Australia) presented the blood pressure results. Patients in the intensive blood pressure-lowering arm were treated with 2 mg perindopril plus 0.625 mg indapamide for 3 months, with the dose doubled subsequently. At baseline, ACE inhibitors were used by 40% and aspirin by ~50% of the participants. At 4.3 years, 73% of patients adhered to treatment. Systolic blood pressure was lowered by 5.6 mmHg, and diastolic blood pressure was lowered by 2.2 mmHg, with the control versus intervention groups having levels of 140/77 vs. 135/75 mmHg. Mortality decreased by 14%, with an 18% reduction in cardiovascular mortality. There was a 9% reduction in the macro- and microvascular composite end point. Coronary outcomes decreased by 14%, and renal outcomes decreased by 21%, driven by a reduction in new-onset microalbuminuria. Albuminuria progression decreased by 22% and albuminuria regression increased by 16% with the perindopril/indapamide combination. There was no relationship of renal outcome to baseline blood pressure, age, sex, diabetes duration, or other blood pressure-lowering treatment, and epidemiologic analysis showed a linear relationship of renal disease reduction to a systolic blood pressure of 106 mmHg, implying, Chalmers stated, that "there's no lower threshold." There was no significant change in cerebrovascular disease or clinical retinopathy events; retinal photograph analysis has not been com-

pleted. At 5 years, assignment to perindopril/indapamide prevented one major vascular event for every 66, one death for every 79, and 1 coronary event for every 75 treated participants, which is important given what would typically be considered adequate existing blood pressure treatment in the majority of patients, with 65% of the placebo group receiving aspirin. Chalmers suggested that “in some respects present [existing] guidelines may even be conservative.”

Anushka Patel (Sydney, Australia) discussed the glucose control comparison. The intensive–glucose control arm used gliclazide MR in all participants, with unrestricted additional therapy to achieve target A1C \leq 6.5%, while in the standard arm a sulfonylurea other than gliclazide was used. All treatment assignment was at the discretion of the treating physician. The intensive–glucose treatment group had more frequent visits, emphasizing lifestyle, with drug titration based on A1C and FBG. At the time of randomization, 71% of patients received a sulfonylurea, 61% metformin, 4% a thiazolidinedione, 8% acarbose, and few were treated with a glinide or insulin. During the study, 40% of intensive treatment–group participants were treated with insulin, 74% with metformin, 17% with a thiazolidinedione, and 91% (by trial design) with a sulfonylurea, exceeding the treatment given the control group. A1C levels decreased from 7.5% (median 7.2) at onset to 7.3% (7.0) vs. 6.5% (6.4) in the control versus intensive groups, respectively, with the greatest decrease occurring during the initial 6 months. The average difference over the course of the trial was 0.7%, which is less than the 1% difference in the trial design. FBG decreased from 153 to 139 mg/dl in the standard-treatment group and to 112 mg/dl in the intensive-treatment group. At study conclusion, 21 and 44% of patients, respectively, had A1C 6–6.5%, and 8 vs. 20% had A1C $<$ 6%; i.e., the goal of extending the achieved A1C from the 7% mean level in UKPDS was achieved. Combined macro- and microvascular end points decreased 10%, without significant reduction in total macrovascular disease, nonfatal stroke, or myocardial infarction, although there was a trend toward reduction in cardiovascular mortality. Microvascular events decreased by 14%, with a 21% reduction in new or worsening neuropathy, perhaps in part related to a 1.6-mmHg lower systolic blood pressure with intensive glyce-

mic treatment, which might be explained by the closer follow-up of this group. Heart failure, peripheral arterial disease, cognitive function, and neuropathy did not change. There was no heterogeneity across baseline A1C or FBG groups and no evidence of subgroups showing increased mortality.

Bruce Neal (Sydney, Australia) discussed the occurrence of hypoglycemia, defined as glucose $<$ 50 mg/dl and/or an episode with typical symptoms and signs. Hypoglycemia was considered severe if the individual required assistance or minor if the episode was self-treated, with the two forms occurring in 231 and \sim 4,500 individuals, respectively, at rates of 0.56 and 105 episodes per 100 patient-years. Severe and minor hypoglycemia occurred 86 and 41% more often with intensive glycemic treatment. There was one fatal hypoglycemic episode in the standard-treatment group and one episode leading to permanent disability each in the standard- and intensive-treatment groups. The Mini Mental State Examination showed greater decrease among individuals who had severe hypoglycemia, although this was quantitatively modest, and there was no evidence of adverse long-term sequelae.

Hospitalization occurred 7% more often with intensive treatment, in 2,146 vs. 2,039 individuals, leading to 5,645 vs. 5,039 total hospitalizations. It does not appear that the increase in hospitalization was related to hypoglycemia because this explained only 4% of the excess in hospitalization, and, similarly, initiation of insulin treatment explained only 2% of excess hospitalization. Closer patient follow-up or a broad-based adverse effect of intensive insulin treatment is possible, with Neal noting that the excess hospitalization comprised a broad range of categories, suggesting that “the possibility that the excess hospitalization . . . [was] simply due to the fact that . . . the patients were seen more often.” Body weight was stable in the intensive group while decreasing in the standard group, leading at 5 years to a 1.5-lb difference; weight gain was less in Asian than in non-Asian trial participants. Neal suggested that the longer duration of diabetes may explain the relative weight stability because in the UKPDS most of the mean 6.8-lb weight gain with intensive treatment was seen in the first few years after diagnosis. “Intensive glucose lowering was clearly safe,” Neal concluded, not

increasing mortality or causing weight gain and causing one severe hypoglycemic episode per 81 individuals but preventing one micro- or macrovascular event per 52 patients.

Mark Cooper (Melbourne, Australia) put the trial results in context, further exploring the question of benefit versus harm, the significance of the renal findings, and the trial’s clinical implications. There was benefit in the primary outcome, with particular reduction in microvascular disease. No “J curve” increase in adverse effect occurred at low blood pressure or glucose levels, with no evidence of a major issue related to hypoglycemia. The results of both the glucose and blood pressure interventions led Cooper to comment that “clearly this strategy is associated with a significant reduction in the development and progression of renal disease.” Macroalbuminuria was closely linked to CVD, with trial participants with macroalbuminuria having a fourfold increase in cardiovascular mortality. This suggests that the renal benefit would lead to cardiovascular benefit over time, which is a long-term effect that the trial was not designed to study. The renal impact of glycemic treatment is impressive, with a comment made in discussion after Cooper’s presentation that “5 years is normal for a trial but a short piece of the whole life.”

The UKPDS studied patients at the time of diagnosis of diabetes who were on average 10 years younger than those in ADVANCE, with lower blood pressure and lower baseline A1C. UKPDS, ADVANCE, and ACCORD had rather different patient populations, with ACCORD including many more patients receiving insulin at baseline and patients from different geographic areas. ACE inhibitors and statins are now more widely used than when the ADVANCE and ACCORD studies were designed. All-cause mortality was 1.8% in the UKPDS and 1.8% in ADVANCE but 1.2% in ACCORD, which Cooper speculated might be related to the lower baseline blood pressure in ACCORD. In both the ADVANCE and UKPDS studies, there was a nonsignificant mean 7% reduction in mortality with intensive treatment, but in the ACCORD study there was a 22% increase in mortality, although with significant heterogeneity between subgroups. BMI and A1C were higher in ACCORD, although none of these factors clearly explain the differences between the mortality findings. Cooper wondered whether the rate of re-

duction in A1C was excessively rapid in ACCORD, compared with the gradual reduction in ADVANCE, and pointed out that both studies may be contrasted with UKPDS in showing no tendency for A1C to subsequently rise. There was more use of insulin and thiazolidinediones in ACCORD and of sulfonylureas and metformin in ADVANCE, and Cooper stated that “the difference in the way glucose was reduced . . . could be a factor . . . but this has to be considered speculative.” Certainly, multifactorial intervention is required for individuals with diabetes, with benefit of blood pressure reduction in ADVANCE and with statins well recognized to be of benefit in macrovascular disease reduction. Although there was no reduction in all-cause mortality in ADVANCE, there was significant reduction in renal events, which may predict subsequent reduction in macrovascular disease. In STENO-2, Cooper stated, there was no significant change in mortality at 4 and 8 years, so “we cannot exclude that ACCORD . . . could ultimately translate to additional benefits.” Eighty percent of the intensive-treatment participants in ADVANCE achieved A1C <7%, and two-thirds achieved A1C <6.5%, leading Cooper to conclude that “we can achieve an A1C of 6.5% gradually, using a rather pragmatic approach which was not associated with adverse effects of weight gain . . . or mortality.” An interesting implication of the study pointed out in discussion is that sulfonylureas may be safer and more effective than generally recognized, such that it may be appropriate to compare different agents in trials to those in “the next generation of studies.”

The VADT

Carlos Abaira (Miami, FL) discussed the VADT background and design. In the preliminary feasibility trial, A1C was 9.2% in control subjects vs. 7.1% in those undergoing intensive glycemic treatment, but the latter group had an increase in adverse outcomes. Three glycemic treatment studies were available at that time: the DCCT, showing reduction in microvascular complications with intensive treatment of type 1 diabetes; the Kumamoto study showing this as well in lean, relatively young type 2 diabetic patients receiving insulin; and the UKPDS in type 2 diabetes, with reduction in photocoagulation and cataract extraction but without significant reduction in cardiovascular complications. In the UKPDS, however,

there was progressive worsening of glycemic control regardless of glycemic regimen, with both the control and intensive-treatment groups spending more time above than below the 7.5–8% level, which may be required for improvement in CVD. Blood pressure treatment appeared more than twice as potent as glucose treatment in reducing adverse outcome in this study. The Veterans' Administration investigators designed the VADT as a randomized controlled trial of 1,791 type 2 diabetic individuals with identical treatment for blood pressure, lipids, and lifestyle factors and with the primary outcome a composite of cardiovascular death, myocardial infarction, stroke, congestive heart failure, severe inoperable coronary artery disease, amputation for ischemia, and interventions for coronary and peripheral arterial disease. Retinopathy, nephropathy, and neuropathy outcomes are still being analyzed. Eligible patients had A1C >7.5%, were either already receiving insulin or on a maximal oral agent regimen, were aged >41 years, and had no major cardiovascular events during the 6 months before enrollment. Median follow-up was 6 years, with the study carried out from 1 December 2000 to 31 May 2008. The basic treatment scheme utilized rosiglitazone with either metformin or glimepiride in all participants and insulin and other oral agents as required. At study onset, mean age was 60 years, BMI 31 kg/m², diabetes duration 12 years, and A1C 9.4%. Seventeen percent of subjects smoked cigarettes, and 55% were former smokers, and 97% of participants were male because of the general makeup of the Veterans' Administration population. Blood pressure was 132/76 mmHg, with 80% receiving blood pressure treatment. Forty percent of participants had prior vascular events, 43% had neuropathy, and 62% had retinopathy (proliferative in 6%).

Glycemic control was stable at 8.4 vs. 6.9% in the control and intervention groups, respectively. During the study, 8.5% of patients withdrew: 4.3% of whom did so during the first year and 10% of whom died. Insulin was given to 70 vs. 85% of the two groups. Rosiglitazone and metformin were used more than glimepiride during the first year, but there was similar use of all three during the third through fifth years. Insulin doses gradually increased to 45 vs. 57 units/day. BMI increased in both groups, particu-

larly the intensive-treatment group, with a plateau at 3 years.

Severe hypoglycemia occurred 0.04 vs. 0.12 times per patient per year in the standard- and intensive-treatment groups, respectively, and the total hypoglycemia frequency was 4.24 vs. 15.29 times per patient per year. Aspirin and statin use, cigarette smoking, and blood pressure control were identical, with blood pressure decreasing from 132/77 to 125/69 mmHg and median LDL cholesterol decreasing from 105 to 73 mg/dl during the course of the trial. HDL cholesterol increased and triglyceride decreased similarly in both groups during the trial. It was feasible, then, to achieve American Diabetes Association goals for A1C, blood pressure, and LDL cholesterol in these individuals with difficult-to-control type 2 diabetes.

Thomas Moritz (Chicago, IL) discussed statistical methods and specifically addressed the impact of rosiglitazone. The study assumed there would be a 21% treatment difference at 6 years, with cumulative survival rates of 40% in the standard- vs. 31.8% in the intensive-treatment groups, to give statistical power of 86% and a two-sided α level of 5% for a sample size of 1,700 participants. The final sample size of 1,791 individuals gave a power of 88% to detect such an effect. He noted that a 42% increase in myocardial infarction with rosiglitazone has been reported (2). In the VADT, only 5% of intensively treated patients did not receive rosiglitazone; 16% received 4 mg and 79% received 8 mg daily. On a per-visit basis, rosiglitazone was not used on 32% of standard- vs. 26% of intensive-treatment visits; 40 vs. 10%, respectively, received 4 mg, and 27 vs. 65% received 8 mg. The VADT studied relationships between rosiglitazone and time to first myocardial infarction, time to cardiovascular death, time to either, and time to new or worsening congestive heart failure. In a case-control analysis, 140 patients had myocardial infarction, with two control subjects used per case and matched for baseline use of insulin, prior macrovascular events, duration in study, age within 4.35 years, and total cholesterol within 23.5 mg/dl (one-half SD). Smoking, statin use, and HDL cholesterol levels were somewhat discordant between case and control subjects, but overall the matching was satisfactory. Moritz reported that rosiglitazone was actually used more often in the control group than among the case subjects in association with both myocar-

dial infarction and cardiovascular death; thus, not only was there no evidence of harm, but there was evidence that rosiglitazone actually decreased these events. Rosiglitazone also was less often used in individuals having congestive heart failure, suggesting a treatment choice phenomenon. A further time-dependent covariate analysis allowed for assessment of the effects of variables that changed over time and showed a 30% reduction in myocardial infarction with rosiglitazone at either 4- or 8-mg doses that remained significant for the 8-mg dose after adjustment for baseline variables. For cardiovascular death, all comparisons showed a reduction in risk of ~70%, and the combined myocardial infarction or cardiovascular death end point was significant for all comparisons. Moritz concluded, "We could not find any evidence that rosiglitazone was harming our patients."

Peter Reaven (Phoenix, AZ) discussed the relationships of coronary and abdominal arterial calcification (CAC and AAC, respectively) and other novel risk factors to cardiovascular events. Vascular calcium is a rapid noninvasive measure of atherosclerosis burden closely associated with CVD events (3). A recent meta-analysis suggests that CAC is a predictor of events in asymptomatic nondiabetic cohorts. There are considerably fewer data in diabetic patients on the prognostic value of CAC and AAC. In the VADT, 324 participants had CAC and AAC before study entry and at study end. The 88 individuals having a Veterans' Administration composite outcome event had longer diabetes duration, higher A1C, and lower HDL cholesterol. CAC Agatston scores of 0–10, 10–100, and 100–400 were each seen in ~20% of studied patients, and 40% of patients had a score exceeding 400 units, with event rates of 10, 15, 30, and 45%, respectively, in the four categories and with a more rapid time-to-event rate in the higher score groups. AAC was not as strong a risk separator. Comparing CAC scores >100 vs. <100, there was a fivefold increase in risk, while a history of a prior event was associated with a 2.5-fold increase in composite event risk. The CAC score was independent of standard cardiovascular risk factors and was an even stronger risk factor than having a prior event. Furthermore, Reaven showed evidence that the effect of the treatment assignment was modified by the baseline CAC score: the participants with a baseline CAC score <100 showed reduction in cardiovascular events with intensive

glycemic treatment, while glycemic treatment was not associated with reduction in cardiovascular events in those with a baseline CAC score >100.

William Duckworth (Phoenix, AZ) discussed the effect of the glycemic control treatment group on cardiovascular outcomes. He emphasized that the study enrolled "the toughest patients we could find" and that to focus on glucose effects they endeavored to achieve excellent control of other cardiovascular risk factors. The median A1C was 8.4% in the control group vs. 6.9% in the intensive glycemic treatment group, both groups showing significant improvement in A1C from baseline, but there was a nonsignificant 13% cardiovascular event reduction with the intervention. Baseline predictors were prior event, age, duration, blood pressure, LDL cholesterol, not being in an ethnic minority group, and A1C. Based on analysis after adjusting for baseline factors, there was minimal effect of the glycemia-control intervention. Predictors of a first primary event with treatment were age, duration, HDL cholesterol, and A1C at the time of study, with severe hypoglycemia during the 3 months before the event second in importance to having a prior event as a risk factor.

Duration of diabetes showed an interaction with treatment in the intensive-treatment group but not in the standard-treatment group. There was an increasing benefit of the glycemia-control intervention in association with shorter diabetes duration and no benefit with diabetes duration of 12–16 years, and an adverse effect of intensive treatment was seen with ≥18 years duration of diabetes. The intensively treated patients had fewer coronary revascularizations. Predictors of cardiovascular death were prior event, age, A1C, and low HDL cholesterol. Again, having a recent severe hypoglycemia episode was associated with a fourfold increase in likelihood of cardiovascular death. Predictors of total mortality were prior event, age, cigarette use, baseline A1C, and, only in the standard-treatment group, hypoglycemia. Severe hypoglycemia was seen in 20% of intensive-treatment vs. 8.8% of standard-treatment participants. There were 29 cardiovascular deaths in the standard-treatment vs. 36 in the intensive-treatment group, with sudden death in 4 vs. 11 patients, respectively, accounting for all of the excess mortality. Predictors of sudden death were a prior macrovascular event, BMI, A1C at

baseline, weight gained during the study, and low HDL cholesterol. Duckworth concluded that in the studied population of older, difficult-to-control patients, cardiovascular risk factors and glucose control could be improved and the risk for cardiovascular events could be reduced. Recent severe hypoglycemia was a predictor of cardiovascular death and of the primary outcome and, in the standard-treatment group, of all-cause mortality. Duration was a significant predictor of the primary end point and showed a highly significant interaction with the treatment effect in the intensive-treatment group, suggesting that intensive treatment might be protective during the first decade of diabetes but that late intensive treatment in the fashion used in the VADT might be harmful.

Comparing the trials

Are there important similarities in the three trials? A striking finding of all three studies is the suggestion that a beneficial effect of the glycemia-control intervention is more likely in association with less disease duration. In the published report of the ACCORD study, trial participants entering with baseline A1C <8%, rather than having an adverse effect of intensive glycemic treatment on mortality, showed a significant reduction in the primary outcome favoring such treatment (4). Similarly, in the ADVANCE trial, the combined micro- and macrovascular primary outcome benefit of the glycemia-control intervention was seen in participants without a baseline history of macrovascular disease (5), and the CAC score and duration of diabetes findings in the VADT, described above, point in the same direction.

The effect of hypoglycemia appears to be of great importance. In the ACCORD study, although the investigators stated that this was not a mediator of the increased mortality associated with intensive treatment, they did find that hypoglycemia was associated with increased mortality and that the intensive intervention was associated with increased hypoglycemia, and they acknowledged not having collected full information pertaining to home glucose-monitoring results. It is intriguing in this regard that 19 of the 40 excess deaths in ACCORD are in the "unexpected/presumed CVD" category. If future analyses of ACCORD are able to more fully take into account participants' home

glucose measurements, show a relationship between weight gain and mortality, or show that mortality was associated with a higher degree of hemoglobin glycation for a given level of glycemia, it may be possible to gain a fuller understanding of these questions. Severe and nonsevere hypoglycemia did occur more often with intensive glycemic treatment in ADVANCE, although the investigators did not report this to be associated with any less benefit of the intervention. It is noteworthy that there was actually a trend toward a reduction in cardiovascular mortality in association with intensive glycemic treatment in this study. The VADT similarly reported that hypoglycemia occurred more often in association with intensive glycemic treatment and was associated with adverse outcome. This study found that the increase in mortality in the intensive-treatment

group was accounted for by an increase in sudden death, which, combined with the strikingly similar finding of the ACCORD study, suggests this to be an area requiring more attention to the potential adverse effects of glycemia-control treatment. The development of potent treatment approaches less likely to cause hypoglycemia should continue to be an important pharmacologic goal.

References

1. UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998
2. Nissen SE, Wolski K: Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 356:2457–2471, 2007
3. Reaven PD, Sacks J, the Investigators for the VADT: Coronary artery and abdominal aortic calcification are associated with cardiovascular disease in type 2 diabetes. *Diabetologia* 48:379–385, 2005
4. The Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT: Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 358:2545–2559, 2008
5. The ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F: Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 358:2560–2572, 2008