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Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials

A position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association

JAY S. SKYLER, MD, MACP[1]
RICHARD BERGENSTAL, MD[2]
ROBERT O. BONOW, MD, MACC, FAHA[3]
JOHN BUSE, MD, PHD[4]
PRAKASH DEEDWANIA, MD, FACC, FAHA[5]
EDWIN A.M. GALE, MD[6]
BARBARA V. HOWARD, PHD[6,7]
M. SUE KIRKMAN, MD[8]
MIKHAIL KOSIBOROD, MD, FACC[9]
PETER REAVEN, MD[10]
ROBERT S. SHERWIN, MD[11]

Diabetes is defined by its association with hyperglycemia-specific microvascular complications; however, it also imparts a two- to fourfold risk of cardiovascular disease (CVD). Although microvascular complications can lead to significant morbidity and premature mortality, by far the greatest cause of death in people with diabetes is CVD.

Results from randomized controlled trials have demonstrated conclusively that the risk of microvascular complications can be reduced by intensive glycemic control in patients with type 1 (1,2) and type 2 diabetes (3–5). In the Diabetes Control and Complications Trial (DCCT), there was an ~60% reduction in development or progression of diabetic retinopathy, nephropathy, and neuropathy between the intensively treated group (goal A1C <6.05%, mean achieved A1C ~7%) and the standard group (A1C ~9%) over an average of 6.5 years. The relationship between glucose control (as reflected by the mean on-study A1C value) and risk of complications was log-linear and extended down to the normal A1C range (<6%) with no threshold noted.

In the UK Prospective Diabetes Study (UKPDS), participants newly diagnosed with type 2 diabetes were followed for 10 years, and intensive control (median A1C 7.0%) was found to reduce the overall microvascular complication rate by 25% compared with conventional treatment (median A1C 7.9%). Here, too, secondary analyses showed a continuous relationship between the risk of microvascular complications and glycemia extending into the normal range of A1C, with no glycemic threshold.

On the basis of these two large controlled trials, along with smaller studies and numerous epidemiologic reports, the consistent findings related to microvascular risk reduction with intensive glycemic control have led the American Diabetes Association (ADA) to recommend an A1C goal of <7% for most adults with diabetes (6), recognizing that more or less stringent goals may be appropriate for certain patients. Whereas many epidemiologic studies and meta-analyses (7,8) have clearly shown a direct relationship between A1C and CVD, the potential of intensive glycemic control to reduce CVD events has been less clearly defined. In the DCCT, there was a trend toward lower risk of CVD events with intensive control (risk reduction 41% [95% CI 10–68]), but the number of events was small. However, 9-year post-DCCT follow-up of the cohort has shown that participants previously randomized to the intensive arm had a 42% reduction ($P = 0.02$) in CVD outcomes and a 57% reduction ($P = 0.02$) in the risk of nonfatal myocardial infarction (MI), stroke, or CVD death compared with those previously in the standard arm (9).

The UKPDS of type 2 diabetes observed a 16% reduction in cardiovascular complications (combined fatal or nonfatal MI and sudden death) in the intensive glycemic control arm, although this difference was not statistically significant ($P = 0.052$), and there was no suggestion of benefit on other CVD outcomes such as stroke. However, in an epidemiologic analysis of the study cohort, a continuous association was observed such that for every percentage point of lower median on-study A1C (e.g., 8–7%) there was a statistically significant 18% reduction in CVD events, again with no glycemic threshold.

Because of ongoing uncertainty regarding whether intensive glycemic control can reduce the increased risk of CVD in people with type 2 diabetes, several large long-term trials were launched in the past decade to compare the effects of intensive versus standard glycemic con-

From the [1]University of Miami, Miami, Florida; the [2]International Diabetes Center at Park Nicollet, Minneapolis, Minnesota; the [3]Northwestern University Feinberg School of Medicine, Chicago, Illinois; the [4]University of North Carolina, Chapel Hill, North Carolina; the [5]VA Central California Healthcare System, University of California San Francisco, Fresno, California; the [6]University of Bristol, Bristol, U.K.; [7]MedStar Research Institute, Hyattsville, Maryland; the [8]American Diabetes Association, Alexandria, Virginia; the [9]Mid America Heart Institute of Saint Luke's Hospital and the University of Missouri-Kansas City, Kansas City, Missouri; the [10]Carl T. Hayden VA Medical Center, Phoenix, Arizona; and [11]Yale University School of Medicine, New Haven, Connecticut.
Corresponding author: M. Sue Kirkman, skirkman@diabetes.org.
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Table 1—*Comparison of the three trials of intensive glycemic control and CVD outcomes*

	ACCORD	ADVANCE	VADT
Participant characteristics			
n	10,251	11,140	1,791
Mean age (years)	62	66	60
Duration of diabetes (years)	10	8	11.5
Sex (% male/female)	39/61	42/58	97/3
History of CVD (%)	35	32	40
BMI (kg/m^2)	32	28	31
Median baseline A1C (%)	8.1	7.2	9.4
On insulin at baseline (%)	35	1.5	52
Protocol characteristics			
A1C goals (%) (I vs. S)*	<6.0 vs. 7.0–7.9	≤6.5 vs. "based on local guidelines"	<6.0 (action if >6.5) vs. planned separation of 1.5
Protocol for glycemic control (I vs. S)*	Multiple drugs in both arms	Multiple drugs added to gliclizide vs. multiple drugs with no gliclizide	Multiple drugs in both arms
Management of other risk factors	Embedded blood pressure and lipid trials	Embedded blood pressure trial	Protocol for intensive treatment in both arms
On-study characteristics			
Median duration of follow-up (years)	3.5 (terminated early)	5	5.6
Achieved median A1C (%) (I vs. S)*	6.4 vs. 7.5	6.3 vs. 7.0	6.9 vs. 8.5
On insulin at study end (%) (I vs. S)*	77 vs. 55*	40 vs. 24	89 vs. 74
On TZD at study end (%) (I vs. S)*	91 vs. 58*	17 vs. 11	53 vs. 42
On statin at study end (%) (I vs. S)*	88 vs. 88*	46 vs. 48	85 vs. 83
On aspirin at study end (%) (I vs. S)*	76 vs. 76*	57 vs. 55	88 vs. 86
Smokers at study end (%)	10	8	8
Mean blood pressure at study end (mmHg)			
Intensive glycemic control arm	126/67	136/74	127/68
Standard glycemic control arm	127/68	138/74	125/69
Weight changes (kg)			
Intensive glycemic control arm	+3.5	−0.1	+7.8
Standard glycemic control arm	+0.4	−1.0	+3.4
Severe hypoglycemia (participants with one or more episodes during study) (%)			
Intensive glycemic control arm	16.2	2.7	21.2
Standard glycemic control arm	5.1	1.5	9.9
Outcomes			
Definition of primary outcome	Nonfatal MI, nonfatal stroke, CVD death	Microvascular plus macrovascular (nonfatal MI, nonfatal stroke, CVD death) outcomes	Nonfatal MI, nonfatal stroke, CVD death, hospitalization for heart failure, revascularization
HR for primary outcome (95% CI)	0.90 (0.78–1.04)	0.9 (0.82–0.98); macrovascular 0.94 (0.84–1.06)	0.88 (0.74–1.05)
HR for mortality findings (95% CI)	1.22 (1.01–1.46)	0.93 (0.83–1.06)	1.07 (0.81–1.42)

*Medication rates for ACCORD are for any use during the study. I, intensive glycemic control; S, standard glycemic control; TZD, thiazolidinedione.

trol on CVD outcomes in relatively high-risk participants with established type 2 diabetes. In 2008, two of these trials, Action in Diabetes and Vascular Disease—Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and the Veterans Affairs Diabetes Trial (VADT), were completed and showed no significant reduction in cardiovascular outcomes with intensive glycemic control. A third trial, Action to Control Cardiovascular Risk in Diabetes (ACCORD), terminated its glycemic control study early due to the finding of increased mortality in participants randomized to a strategy of very intensive glycemic control with a target A1C of <6%. The findings of these three major trials led the ADA, with representatives of the American Heart Association (AHA) and the American College of Cardiology (ACC), to reexamine the recommendations for glycemic targets in patients with diabetes, the majority of whom have type 2 diabetes.

What did the ACCORD, ADVANCE, and VA Diabetes trials show? — Table 1 provides a summary of baseline characteristics, glycemic treatment strategies

and goals, concomitant risk factor control, achieved glycemic control, and primary results of each of the three studies. The ACCORD study randomized 10,251 participants with either history of a CVD event (aged 40–79 years) or significant CVD risk (aged 55–79 years with anatomical CVD, albuminuria, left ventricular hypertrophy, or at least two other CVD risk factors) to a strategy of intensive glycemic control (target A1C <6.0%) or standard glycemic control (target A1C 7.0–7.9%). Investigators used multiple glycemic medications in both arms. ACCORD participants were on average 62 years of age and had a mean duration of diabetes of 10 years, with 35% already treated with insulin at baseline. From a baseline median A1C of 8.1%, the intensive arm reached a median A1C of 6.4% within 12 months of randomization, while the standard group reached a median A1C of 7.5%. Other risk factors were treated aggressively and equally in both groups. The intensive glycemic control group had more use of insulin in combination with multiple oral agents, significantly more weight gain, and more episodes of severe hypoglycemia than the standard group.

In February 2008, the glycemic control study of ACCORD was halted (embedded blood pressure and lipid studies are ongoing) on the recommendation of the study's data safety monitoring board due to the finding of an increased rate of mortality in the intensive arm compared with the standard arm (1.41 vs. 1.14% per year; 257 vs. 203 deaths over a mean 3.5 years of follow-up; hazard ratio [HR] 1.22 [95% CI 1.01–1.46]); there was a similar increase in cardiovascular deaths. The primary outcome of ACCORD (MI, stroke, or cardiovascular death) was reduced in the intensive glycemic control group due to a reduction in nonfatal MI, although this finding was not statistically significant when the study was terminated (0.90 [0.78–1.04], $P = 0.16$).

Exploratory analyses of the mortality findings of ACCORD (evaluating variables including weight gain, use of any specific drug or drug combination, and hypoglycemia) were unable to identify an explanation for the excess mortality in the intensive arm (10). In both study arms, participants with severe hypoglycemia had higher mortality than those without severe hypoglycemia. However, there was a complex interaction between hypoglycemia, study arm, and mortality: Among participants with at least one episode of severe hypoglycemia, mortality was higher in those in the standard treatment arm, while among participants with no history of severe hypoglycemia, mortality was higher in those in the intensive treatment arm. Other prespecified subset analyses showed that participants with no previous CVD event and those who had a baseline A1C <8% had a statistically significant reduction in the primary CVD outcome.

The ADVANCE study randomized 11,140 participants at sites in Europe, Australia/New Zealand, Canada, and Asia to a strategy of intensive glycemic control (with primary therapy being the sulfonylurea gliclizide and additional medications as needed to achieve a target A1C of ≤6.5%) or to standard therapy (in which any medication but gliclizide could be used, with the glycemic target set according to "local guidelines"). ADVANCE participants (required to be at least 55 years of age with either known vascular disease or at least one other vascular risk factor) were slightly older and of a high CVD risk similar to that in ACCORD participants. However, they had an average duration of diabetes 2 years shorter, lower baseline A1C (median 7.2%), and almost no use of insulin at enrollment. The median A1C levels achieved in the intensive and standard arms were 6.3 and 7.0%, respectively, and maximal separation between the arms took several years to achieve. Use of other drugs that favorably impact CVD risk (aspirin, statins, ACE inhibitors) was lower in ADVANCE than in ACCORD or VADT.

The primary outcome of ADVANCE was a combination of microvascular events (nephropathy and retinopathy) and major adverse cardiovascular events (MI, stroke, and cardiovascular death). Intensive glycemic control significantly reduced the primary end point (HR 0.90 [95% CI 0.82–0.98], $P = 0.01$), although this was due to a significant reduction in the microvascular outcome (0.86 [0.77–0.97], $P = 0.01$), primarily development of macroalbuminuria, with no significant reduction in the macrovascular outcome (0.94 [0.84–1.06], $P = 0.32$). There was no increase in overall or cardiovascular mortality in the intensive compared with the standard glycemic control arms (11).

VADT randomized 1,791 participants with type 2 diabetes uncontrolled on insulin or maximal-dose oral agents (median entry A1C 9.4%) to a strategy of intensive glycemic control (goal A1C <6.0%) or standard glycemic control, with a planned A1C separation of at least 1.5%. Medication treatment algorithms were used to achieve the specified glycemic goals, with a goal of using similar medications in both groups. Median A1C levels of 6.9 and 8.5% were achieved in the intensive and standard arms, respectively, within the first year of the study. Other CVD risk factors were treated aggressively and equally in both groups, with the trial achieving excellent blood pressure control, high levels of aspirin and statin usage, and a high degree of smoking cessation (12).

The primary outcome of VADT was a composite of CVD events (MI, stroke, cardiovascular death, revascularization, hospitalization for heart failure, and amputation for ischemia). During a median 5.6-year follow-up period, the cumulative incidence of the primary outcome was not significantly lower in the intensive arm (HR 0.88 [95% CI 0.74–1.05], $P = 0.12$). There were more CVD deaths in the intensive arm than in the standard arm (38 vs. 29, sudden deaths 11 vs. 4), but the difference was not statistically significant. Post hoc subgroup analyses suggested that duration of diabetes interacted with randomization such that participants with duration of diabetes less than about 12 years appeared to have a CVD benefit of intensive glycemic control, while those with longer duration of disease before study entry had a neutral or even adverse effect of intensive glycemic control. Other exploratory analyses suggested that severe hypoglycemia within the past 90 days was a strong predictor of the primary outcome and of CVD mortality, with an association of severe hypoglycemia with all-cause mortality apparent only for participants in the standard arm. An embedded ancillary study within the main VADT showed that baseline coronary or aortic calcium scores predicted future CVD events and that intensive glycemic control significantly reduced the primary CVD end point in those with low baseline coronary artery calcium scores but not in those with high baseline scores.

2. What are potential explanations for the increased CVD deaths with intensive glycemic control in ACCORD? — Numerous post hoc analyses have been unable to prove or disprove causes; in fact, the design of the study renders such "proof" elusive. Randomization to the intensive arm was associated with or led to many downstream

effects, such as higher rates of severe hypoglycemia; more frequent use of insulin, thiazolidinediones, other drugs, and drug combinations; and greater weight gain. Such factors may be associated statistically with the higher mortality rate in the intensive arm but may not be causative. It is biologically plausible that severe hypoglycemia could increase the risk of cardiovascular death in participants with high underlying CVD risk. This might be further confounded by the development of hypoglycemia unawareness, particularly in patients with coexisting cardiovascular autonomic neuropathy (a strong risk factor for sudden death). Death from a hypoglycemic event may be mistakenly ascribed to coronary artery disease, since there may not have been a blood glucose measurement and since there are no anatomical features of hypoglycemia detected postmortem. Other plausible mechanisms for the increase in mortality in ACCORD include weight gain, unmeasured drug effects or interactions, or the "intensity" of the ACCORD intervention (use of multiple oral glucose-lowering drugs along with multiple doses of insulin, frequent therapy adjustments to push A1C and self-monitored blood glucose to very low targets, and an intense effort to rapidly reduce A1C by ~2% in participants entering the trial with advanced diabetes and multiple comorbidities).

Since the ADVANCE trial did not show any increase in mortality in the intensive glycemic control arm, examining the differences between ADVANCE and ACCORD supports additional hypotheses. ADVANCE participants on average appeared to have earlier or less advanced diabetes, with shorter duration by 2–3 years and lower A1C at entry despite very little use of insulin at baseline. A1C was also lowered, even more gradually, in the ADVANCE trial, and there was no significant weight gain with intensive glycemic therapy. Although severe hypoglycemia was defined somewhat differently in the three trials, it appears that this occurred in fewer than 3% of intensively treated ADVANCE participants for the entire study duration (median 5 years) compared with ~16% of intensively treated subjects in ACCORD and 21% in VADT.

It is likely that the increase in mortality in ACCORD was related to the overall treatment strategies for intensifying glycemic control in the study population—not the achieved A1C per se. The ADVANCE study achieved a median A1C in its intensive arm similar to that in the ACCORD study, with no increased mortality hazard. Thus, the ACCORD mortality findings do not imply that patients with type 2 diabetes who can easily achieve or maintain low A1C levels with lifestyle modifications with or without pharmacotherapy are at risk and need to "raise" their A1C.

3. Why did none of the trials show a significant benefit of intensive glycemic control on CVD in type 2 diabetes—in contrast to many epidemiologic studies and the DCCT follow-up study? — Although randomized controlled trials often confirm hypotheses grounded in observational evidence or physiologic studies of surrogate end points, this is certainly not the first time that such trials have failed to do so. The results of ACCORD, ADVANCE, and VADT highlight the critical need for randomized controlled trials with meaningful clinical outcomes, such as in these trials, to help answer major clinical questions.

In the three glucose-lowering trials, other CVD risk factors were treated to a moderate or high degree, and likely due to this, all had lower rates of CVD in the standard arm than originally predicted. The evidence for CVD prevention by statin therapy, blood pressure treatment, aspirin therapy in high-risk participants, and other interventions is robust. In type 2 diabetes, where other CVD risk factors are highly prevalent, the additive benefits of intensive glycemic control might be difficult to demonstrate except in even larger or longer trials. It is likely that a real benefit of glucose lowering on CVD in type 2 diabetes, even if it could be proven, is modest compared with and incremental to treatment of other CVD risk factors.

Additionally, the three trials compared treatments to A1C levels in the "flatter" part of the observational glycemia-CVD risk curves (median A1C 6.4–6.9% in the intensive arms compared with 7.0–8.4% in the standard arms). Their results should not be extrapolated to imply that there would be no cardiovascular benefit of glucose lowering from very poor control (e.g., A1C >9%) to good control (e.g., A1C <7%).

All three trials were carried out in participants with established diabetes (mean duration 8–11 years) and either known CVD or multiple risk factors, suggesting the presence of established atherosclerosis. Subset analyses of the three trials suggested a significant benefit of intensive glycemic control on CVD in participants with shorter duration of diabetes, lower A1C at entry, and/or or absence of known CVD. The finding of the DCCT follow-up study, that intensive glycemic control initiated in relatively young participants free of CVD risk factors was associated with a 57% reduction in major CVD outcomes, supports the above hypothesis. Of note, the benefit on CVD in the DCCT-EDIC (Epidemiology of Diabetes Interventions and Complications) required 9 years of follow-up beyond the end of the DCCT to become statistically significant.

A recent report (13) of 10 years of follow-up of the UKPDS cohort describes, for the participants originally randomized to intensive glycemic control compared with those randomized to conventional glycemic control, long-term reductions in MI (15% with sulfonylurea or insulin as initial pharmacotherapy and 33% with metformin as initial pharmacotherapy, both statistically significant) and in all-cause mortality (13 and 27%, respectively, both statistically significant). These findings support the hypothesis that glycemic control early in the course of type 2 diabetes may have CVD benefit. As is the case with microvascular complications, it may be that glycemic control plays a greater role before macrovascular disease is well developed and a minimal or no role when it is advanced.

People with type 1 diabetes, in whom insulin resistance does not predominate, tend to have lower rates of coexisting obesity, hypertension, and dyslipidemia than those with type 2 diabetes and yet are also at high lifetime risk of CVD (14). It is possible that CVD is more strongly glycemia mediated in type 1 diabetes and that intervening on glycemia would ameliorate CVD to a greater extent in type 1 than in type 2 diabetes.

Finally, the inability of ACCORD, ADVANCE, and VADT to demonstrate significant reduction of CVD with intensive glycemic control could also suggest that current strategies for treating hyperglycemia in patients with more advanced type 2 diabetes may have counterbalancing consequences for CVD (such as hypoglycemia, weight gain, or other metabolic changes). Results of long-term CVD outcome trials utilizing specific antihyperglycemic drugs, intensive lifestyle therapy (such as the Look AHEAD [Ac-

tion for Health in Diabetes] study), bariatric surgery, or other emerging therapies may shed light on this issue.

4. What are the implications of these findings for clinical care?— The benefits of intensive glycemic control on microvascular and neuropathic complications are well established for both type 1 and type 2 diabetes. The ADVANCE trial has added to that evidence base by demonstrating a significant reduction in the risk of new or worsening albuminuria when median A1C was lowered to 6.3% compared with standard glycemic control achieving an A1C of 7.0%. The lack of significant reduction in CVD events with intensive glycemic control in ACCORD, ADVANCE, and VADT should not lead clinicians to abandon the general target of an A1C <7.0% and thereby discount the benefit of good control on serious and debilitating microvascular complications.

The ADA's Standards of Medical Care in Diabetes (6) and the AHA and ADA's scientific statement on prevention (15) advocate controlling nonglycemic risk factors (through blood pressure control, lipid lowering with statin therapy, aspirin therapy, and lifestyle modifications) as the primary strategies for reducing the burden of CVD in people with diabetes. The lower-than-predicted CVD rates in ACCORD, ADVANCE, and VADT, as well as the recent long-term follow-up of the Steno-2 multiple risk factor intervention (16), provide strong confirmation of the concept that comprehensive care for diabetes involves treatment of all vascular risk factors—not just hyperglycemia.

The evidence for a cardiovascular benefit of intensive glycemic control remains strongest for those with type 1 diabetes. However, subset analyses of ACCORD, ADVANCE, and VADT suggest the hypothesis that patients with shorter duration of type 2 diabetes and without established atherosclerosis might reap cardiovascular benefit from intensive glycemic control. Conversely, it is possible that potential risks of intensive glycemic control may outweigh its benefits in other patients, such as those with a very long duration of diabetes, known history of severe hypoglycemia, advanced atherosclerosis, and advanced age/frailty. Certainly, providers should be vigilant in preventing severe hypoglycemia in patients with advanced disease and should not aggressively attempt to achieve near-normal A1C levels in patients in whom such a target cannot be reasonably easily and safely achieved.

The evidence obtained from ACCORD, ADVANCE, and VADT does not suggest the need for major changes in glycemic control targets but, rather, additional clarification of the language that has consistently stressed individualization:

- Microvascular disease: Lowering A1C to below or around 7% has been shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes. Therefore, the A1C goal for nonpregnant adults in general is <7%. ADA, A-level recommendation; ACC/AHA, class I recommendation (level of evidence A).
- Macrovascular disease: In type 1 and type 2 diabetes, randomized controlled trials of intensive versus standard glycemic control have not shown a significant reduction in CVD outcomes during the randomized portion of the trials. However, long-term follow-up of the DCCT and UKPDS cohorts suggests that treatment to A1C targets below or around 7% in the years soon after the diagnosis of diabetes is associated with long-term reduction in risk of macrovascular disease. Until more evidence becomes available, the general goal of <7% appears reasonable. ADA, B-level recommendation; ACC/AHA, class IIb recommendation (level of evidence A).

For some patients, individualized glycemic targets other than the above general goal may be appropriate:

- Subgroup analyses of clinical trials such as the DCCT and UKPDS and the microvascular evidence from the ADVANCE trial suggest a small but incremental benefit in microvascular outcomes with A1C values closer to normal. Therefore, for selected individual patients, providers might reasonably suggest even lower A1C goals than the general goal of <7% if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients might include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. ADA, B-level recommendation; ACC/AHA, class IIa recommendation (level of evidence C).
- Conversely, less stringent A1C goals than the general goal of <7% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, or extensive comorbid conditions or those with long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. ADA, C-level recommendation; ACC/AHA, class IIa recommendation (level of evidence C).

For primary and secondary CVD risk reduction in patients with diabetes, providers should continue to follow the evidence-based recommendations for blood pressure treatment, including lipid-lowering with statins, aspirin prophylaxis, smoking cessation, and healthy lifestyle behaviors delineated in the ADA Standards of Medical Care in Diabetes (6) and the AHA/ADA guidelines for primary CVD prevention (15).

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R.S.S. is the DSMB chair for MannKind* and Novartis* and has served on advisory boards for Amylin, Medtronic, Eli Lilly, Merck*, Astra Zeneca, Pfizer, Boehringer Ingelheim, DiObex, Metabolex, and Insulet.

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