Diabetes Treatment and Cardiovascular Safety

ZACHARY T. BLOOMGARDEN, MD

This is the third of a series of articles based on presentations at the American Diabetes Association (ADA) 70th Scientific Sessions, held 25–29 June 2010 in Orlando, Florida, pertaining to the need for large-scale cardiovascular (CV) safety requirements for the treatment of diabetes. The term "contrarian" is defined in various ways as "a person who takes an opposing view," as "one who rejects the majority opinion" (1), or as "an investor who goes against current market trends" (2). What might be characterized as a "contrarian" debate on diabetes discussed the new requirement for large-scale CV safety studies on all new glucose-lowering medications. There was also a discussion of an increasingly recognized issue, potential inaccuracies of capillary glucose test meters, and of point-of-care A1C testing technologies.

CV SAFETY REQUIREMENTS FOR NEW DIABETES TREATMENTS

—At the symposium, Steven Nissen (Cleveland Clinic, Cleveland, OH) addressed the question of whether diabetes drugs should have a higher bar for CV safety than other drugs. He began with an acknowledgment of relationships with multiple pharmaceutical companies, although stating that all income from such went to "charity." He then complained about the "ridiculous title for a debate," to suggest that the outcome (presumably his) would be a foregone conclusion. He stated that "all drugs must be required to show a health outcomes benefit," and that "diabetes drugs are being held to [a] standard that is neither greater nor less than other fields." He acknowledged microvascular benefits of reduction in glycemia but stated that "some of the drugs that lower blood sugar actually increase the risk of macrovascular complications" and suggested this to override microvascular disease, as "CVD is the cause of death in most diabetic patients." Furthermore, he questioned the use of biomarkers as "surrogate for real outcomes data" and termed the blood glucose concentration as simply a "biomarker." "Blood glucose measurements," he suggested, "are just the latest failure to gain widespread attention (even though this surrogate failed long ago)." This was certainly a way to draw audience attention at the ADA meeting!

Nissen reviewed the findings of the University Group Diabetes Program and the controversy that ensued over its finding of increased all-cause and CV mortality with tolbutamide (3). He strongly implied intellectual dishonesty on the part of some of those who criticized the study, citing a statement by Theodore Schwartz and Curtis Meinert, "Academicians, paid in cash or in grant awards, were hired as consultants by the Upjohn Company. . .writing highly critical assessments. . . challenging the honesty of the University Group Diabetes Program investigators" (4). Perhaps, he implied, one might similarly attribute base motives to those currently criticizing claims of adverse CV effects of diabetes treatments. An effect of sulfonylureas was observed on ischemic preconditioning (5), offering a mechanism by which tolbutamide might indeed have caused adverse outcome. As a more recent case, Nissen described studies of muraglitazar, which lowers A1C and triglyceride and raises HDL cholesterol levels, leading to the argument that there was "lack of biologic plausibility for CV risk," with the agent leading a U.S. Food and Drug Administration (FDA) advisory panel to recommend approval. However, Nissen reported increased mortality and major CV event rates shortly after the panel's meeting, with trends to increase in all-cause mortality and in congestive heart failure (CHF) and increase significantly in some commonly used composite CV end points (6), leading the FDA to request additional CV safety data. Thus, Nissen concluded that "a risky agent came close to approval because the surrogate end points of glucose and lipids did not predict CV outcomes." Next, Nissen discussed rosiglitazone, pointing out that it is associated with an increase in LDL cholesterol, particularly among individuals with lower baseline levels, as well as weight gain. In the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial, he stated that there was a trend to a 37% increase in the composite end point of myocardial infarction, stroke, CV death, CHF, new angina, and revascularization (7, 8). [Only the increase in CHF was statistically significant.] He noted that many small studies were performed with rosiglitazone, with a total of 14,237 patients enrolled in 42 randomized trials completed by 2007, although he characterized the Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral agent combination theRapy for type 2 Diabetes (RECORD) trial (9) as "hopelessly underpowered," so that meta-analysis was the only approach feasible in determining whether there was "a safety signal." He reported such a meta-analysis, finding rosiglitazone to be associated with a significant 43% increase in myocardial infarction (10). [For a review of questions pertaining to this meta-analysis, see Bloomgarden (11).] In contrast, he termed the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE) trial (12) "a large, reasonably well-powered CV outcome trial" showing a trend to improvement in the primary end point and a significant reduction in the secondary end point of death, myocardial infarction, and stroke, albeit with significantly increased rates of CHF hospitalization. Nissen himself performed a meta-analysis that supported the PROACTIVE finding of reduction in these outcomes (13), and he commented that "pioglitazone appears to have a more favorable effect on lipids, particularly triglycerides." What of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (14)? There was significant and sustained glycemic separation between the

Zachary T. Bloomgarden, MD, is a practicing endocrinologist in New York, New York, and is affiliated with the Division of Endocrinology, Mount Sinai School of Medicine, New York, New York.
DOI: 10.2337/dc11-0201

standard and intensive therapy groups but a significant increase in total and CV mortality, although with significant reduction in nonfatal myocardial infarction. "A regimen in which more patients received repaglinide, rosiglitazone, insulin and/or an α-glucosidase inhibitor," he concluded, "showed increased mortality risk."

Why, Nissen asked, are there "no well-designed, adequately powered comparative effectiveness trials evaluating macrovascular outcomes for diabetes drugs," although oral hypoglycemic agents have been available for more than 50 years? He reviewed a comparative effectiveness and safety study for glucose-lowering drugs (15), suggesting that the levels of evidence that diabetes drugs reduce all-cause mortality, CVD mortality, nonfatal myocardial infarction or stroke, peripheral vascular disease, or even microvascular outcomes are "low to very low!" [This study, however, specifically excluded the UK Prospective Diabetes Study from parts of its analysis, and a subsequent analysis from the same group did report significant reduction in CV end points with metformin (16).] Nissen went on to claim that neither meta-analyses nor what he termed "post hoc data dredging of randomized trials not designed to determine the benefits or risks of specific therapies" will be useful in determining the cause of the excess mortality in ACCORD and stated further that "no amount of torturing of the data will enable risk assessment when specific drugs are not randomized," although such a statement fails to recognize that there is progressive deterioration in glycemic control in type 2 diabetes, so that treatment must be augmented over time to maintain stable glycemic control. However, Nissen termed this a "knowledge gap" based on "current regulatory policy that emphasizes the importance of glucose lowering, not health outcomes, as a therapeutic goal," which he proposed to represent "glucocentricity," an "irrational belief that lowering blood glucose using virtually any pharmacologic means will produce a reliable reduction in adverse outcomes." He acknowledged that there is "the need to bring new diabetes agents to patients" but suggested that robust outcome data are absolutely necessary and commented favorably on the new FDA recommendation that preapproval clinical trials must rule out a >1.8-fold increase in hazards ratio (HR), with subsequent outcomes trials considered "sufficient to rule out a HR >1.3" (17). Nissen acknowledged that the latter outcome trials would typically require 5–7 years. Using such an approach, Nissen showed power calculations for populations with 2% and 3% annual combined death, myocardial infarction, and stroke event rates, with approximately 5,000 patient-years of observation required to exclude a HR>1.8. [It should be noted that "rule out" is defined strongly, as requiring that the 95% confidence limits not include the HR in question, even if the actual HR itself is <1.0.] Furthermore, the population estimates of Nissen's calculation are predicated on annual event rates ≥2.0%. This represents a very different population from that usually enrolled in diabetes trials, with expected event rates at ~0.5% (18), for which >20,000 patient-years of observation might be required for exclusion of a 1.8-fold increase in risk and >100,000 for exclusion of a 1.3-fold increase. Nissen termed the requirement for such studies as positive, and opined that patients at higher CV risk must be included in the testing of new diabetes agents, suggesting that it would only "modestly slow development programs...delaying introduction of new diabetes medications by 6–12 months."

David Orloff (Medpace, Cincinnati, OH) was the director of metabolic and endocrine drugs at the FDA from 2000 to 2005 and is now employed by a clinical research organization contracting with the pharmaceutical industry. He began by observing that he directs all income from his consultation with the pharmaceutical industry to his organization. He reviewed the rationale for the new FDA guidance and argued that one must have a more rational notion of risk management in diabetes and must take into account what he termed "black swans." He then discussed the protean nature of diabetes, in a sense taking and expanding on Nissen's notion of "glucocentricity" before discussing diabetes drug development from a patient's perspective. He concluded by reminding the audience that the FDA must play roles not only in regulation but also in encouraging innovation.

"The question of the day," he said, is whether all new diabetes drugs should be required to demonstrate CV safety. The FDA decision is in the affirmative, "so it's not hypothetical." Of course, he said, one must accept the notion that having more information is better and "that safe is better than sorry." However, he said that the need did not consider the CV safety profiles of all existing agents as germane to the evaluation of all possible new drugs, unless one thought that lowering glucose itself represented a CV risk. If that were the case, then to be considered a safe treatment, an approach would require an additional factor that offset the putative adverse effect of glucose lowering. There is not, he stated, any evidence that glucose lowering is itself atherogenic, so this position is not tenable.

Certainly, he agreed with the notion of regulation of industry, and he suggested that the FDA has played an important role in development of high-quality pharmacologic treatments. Although "regulators and industry will not always see eye to eye" and the regulators must make the final call, the FDA must be allowed discretion, he said, to balance the desire for a "level playing field" with the need for case-by-case decisions. With that understanding, should a uniform approach be applied to the development plan of all diabetes treatment agents? The guidance requires demonstration that a drug not be associated with the increases in CV risk outlined by Nissen, which indeed might require 4–6,000 treatment years of follow-up of high-CV risk patients. The ≥2% annual event rate supposition is, however, based on the notion of diabetes as a CV risk equivalent. As CV risks decline in diabetic patients [see discussion in Bloomgarden (19)], Orloff suggested that ever larger and larger studies will be required for the 95% HR confidence intervals not to include a 1.8- and then a 1.3-fold increase in risk as described above. What will be the burden of demonstrating "beyond a reasonable doubt" that risk is not increased?

Orloff emphasized that the FDA guidance does not require demonstration of a reduction in CV risk. Certainly, CVD is a huge issue for diabetic and prediabetic patients, and reduction in atherosclerosis certainly is desirable, but such a study would only demonstrate benefit, he suggested, if a diabetes agent led to reduction in risk similar to that of statins. A further issue, he said, is the paucity of comparisons of CV risk among drugs. [It is noteworthy that there is evidence that the thiazolidinediones available prior to 2001 may, similarly to metformin, be associated with lower postmyocardial infarction mortality than other glucose-lowering drugs (20).] Drug safety is not an incorrect goal, he said, "but [to require that] all . . . new diabetes drugs should be taken through the same battery of tests," becomes a hugely expensive undertaking.

Risk management may be considered the reduction in adverse events and maximization of opportunities. From the time of drug discovery through the lifetime of a drug, one must make evidence-based judgment regarding benefits, and one must do so "with a prepared mind," aware of all potential adverse effects. Orloff stressed the need to follow evidence, which he contrasted with "signals," which by definition do not represent statistically significant risks. This is particularly important if one is to consider the need for rational expenditure of resources in the development of new agents. The question for a new drug that is unlikely to show adverse CV effects then is whether the remote possibility of such an effect should be allowed to constitute the single most important aspect of the evaluation of that agent, requiring its developers to undertake an immensely complex and expensive trial.

Orloff discussed the notion of black swans, popularized by the recent book by Nassim Nicholas Taleb (21), suggesting such a phenomenon to be an important aspect of sudden changes in the global economy. Juvenal, who had written approximately in the 1st century B.C., coined the expression, and it became for centuries a standard simile in referring to impossibilities. Actual black swans then were discovered in Australia, seeming to render the figure of speech meaningless!

"Black swans," however, remain rare in the universe of swans. Orloff asked, then, whether those of us who have labored under the misconception (or hope) that glycemic control improves CV outcome and those who have felt comfortable that diabetes treatment is safe, or at least neutral in terms of CV effect, should now be expected to take this opposite view. If there is a diabetes drug that exacerbates CV risk, must one ask the question: given the "absolute certainty that not all diabetes drugs will be atherosclerosis-safe, does it follow that all diabetes drugs [might] be atherosclerosis-promoting? That's the black swan," he said.

Orloff said that diabetes certainly is protean in its effects, and he acknowledged the pitfalls in being "glucocentric," but it is difficult to argue against glycemic control being life-saving. Yes, he said, diabetes is certainly far more than a disease of insulin action and altered glucose, and it is a disease of lipids, liver, brain, gut, and many other organs and metabolic systems. We do have great deal to be done in developing appropriate treatments. Diabetes drugs then should not be viewed as simply glucose-lowering agents, but "perhaps we need to approach it from a different angle," that a diabetes drug "is simply a drug for a patient with diabetes." In that sense, drugs for CVD, developed separately from drugs for dysglycemia, might be a huge step forward. "It is not clear," he explained, that adverse CV effects must "become the prime safety concern." We need to address all complications and endeavor to ameliorate them all, and we should be aware of any adverse effects, "but obligatory focus on any single aspect" may not be proper "rational prioritization of resources."

From the patient's perspective, Orloff suggested that one must know how an agent will be helpful in improving outcome and how it will compare with other options, including doing nothing. It is best to have multiple choices, in case a given agent has particular adverse effects for a given person. What if a given individual does not "fit" into the profile of the clinical trial database? If a patient is told that a given agent is unlikely to increase CV risk, will he be comforted? If a patient has a 1% CV risk over the present year, would a possible increase to no more than 1.5% be comforting?

Innovation "is the bane of existence of regulators, doctors, patients, and industry," and Orloff suggested that "perhaps our most nerve-wracking" task is knowing what is safe. However, developing new therapies is a crucial responsibility of the regulatory agency, as Orloff stated, not just the goal of industry, "and in the end, whether intentional or not, the agency's stances can either quash or stimulate." We must then make sure that "the costs and risks of development" do not become prohibitive, which would drive pharmaceutical companies away from the development of new approaches to diabetes and would certainly cause further increases in costs of those medications that do come to market. "We should direct our energies and our spending as appropriate," he concluded, "from case to case." This argument seems to carry weight, and it will be fascinating to see whether the FDA responds to voices such as Orloff's argument that extensive CV safety studies must not become indispensable in diabetes drug development.

POINT-OF-CARE DEVICES FOR MANAGEMENT OF DIABETES

—Continuing an annual series of combined American Diabetes Association (ADA)–American Association of Clinical Chemists Symposia, a pair of talks were entitled "Point-of-Care (POC) Devices for Glucose and HbA_{1c}–Are They Up to the Task?" Mitchell G. Scott (Washington University School of Medicine, St. Louis, MO) discussed the need for greater accuracy with glucose meters, reviewing common interfering substances, comparing different criteria for acceptable performance of meters, and discussing whether different outcomes of tight glycemic control studies might in part be the result of errors from use of such devices in estimating glucose levels. Currently available meters are smaller than those in the past, and more than 30 different devices are now available. Over the past few years "no wipe" strips, smaller sample sizes, faster analytic responses, and data storage and capture have become standard, and alternate site testing has become available but with a time lag issue (22). Many hospital systems use measures to "lockout" results if quality standards are not met. POC glucose testing has become a huge ($6 billion/year) market, comprising nearly one third of laboratory-testing costs.

Interferences are not uncommon. Because the values are standardized for plasma glucose on almost all meters currently in use, anemia increases and polycythemia decreases glucose values (23,24). Reducing agents, such as ascorbic acid at levels seen with commonly taken doses (25) and acetaminophen with some methodologies (26), will lower measured glucose levels, although some new meters can correct for hematocrit and reducing agents (27). Glucose dehydrogenase methods are affected by maltose-containing substances, such as intravenous immunoglobulin, or by isodextrin, which is found in peritoneal dialysis fluids (28); since the mid-1990s, Scott noted that there have been 13 documented deaths from such interference. User errors are another important issue, as strip manipulation readily alters glucose readings with some meters.

In critical care settings, most centers have adopted protocols to maintain the blood glucose below 130 mg/dL, requiring frequent glucose testing and insulin infusion rate adjustment. This has markedly increased the use of strips in hospitals, with Scott noting that the annual number of test strips used at his institution increased from approximately 250,000 to 550,000 from 2000 to 2009, with nearly half of strips used in critical care units. Tight glycemic control in

intensive care, however, did not reduce mortality or morbidity in a meta-analysis of 27 studies, while being associated with increased likelihood of hypoglycemia (29). In particular, the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial showed decreased survival with tight glycemic control in association with increased hypoglycemia (30). How can one reconcile the better outcome in the original Van Den Berghe studies (31,32) with these reports? Scott pointed out that the original studies used arterial blood glucose measurement with blood gas instrument methods, giving highly precise values, whereas many of the studies showing null or negative effect seem to have used glucose meters. Unfortunately, few of these studies report the actual glucose measurement methodologies used, particularly when carried out at more than one center. Anemia is commonly found in critical care patients, potentially causing overestimation of glucose levels. Sampling site is of great importance. Scott reviewed a study of 20 CV surgery patients comparing arterial, venous, and capillary blood specimens, showing that, with use of strip methods, arterial samples led to an overestimate of 15 mg/dL, with even greater inaccuracy using venous blood samples (33). Scott and associates have suggested that it is likely that meter glucose measurements may lead to hypoglycemia (34) and that such measurements may not be sufficiently accurate for in-hospital use. Likewise, these measurements should not be used in diagnosis of diabetes, which leads to the question of whether we may incorrectly advise outpatient treatments when we rely on self-monitoring using such approaches. (One also might ask whether calibration of continuous glucose monitoring by capillary glucose measurements risks perpetuation of inaccurate measurements.)

The current allowable error for laboratory oratory glucose measurements is 10% or 6 mg/dL for "main laboratory" or arterial blood glucose methods, a level considered sufficiently precise to be used in the diagnosis of diabetes. For meters, the ADA standard requires that total analytic error be <5%, but Scott pointed out that "there's not a meter around that will do this." Other testing programs have suggested that the minimal standard be the greater of 20% or 12 mg/dL; or 20% if >75 mg/dL, 15 mg/dL if <75 mg/dL, for 95% of values; or the standard suggested by the FDA, 20% for glucose ≥ 100 mg/dL and 12 mg/dL for <100, again for 95% of values (35). The Clarke Error Grid, a commonly used methodology for determining meter accuracy, may no longer be suitable for assuring that meters are sufficiently precise.

By use of the Hemo-Cue test as a reference method, in a 1973 study of capillary blood samples from pregnant women measured by a registered nurse, high variability was shown (36). In a comparison study of five meters with sample testing by a medical technician, using 93 individuals, with 12 samples obtained per patient, 2 with each meter, the coefficient of variability (c.v., defined as the SD × 100/mean) ranged from 6.3 to 11.3%, with the differences between meters varying with glucose concentration and meter pairs, showing a 1–32% bias (37). Another study, comparing four meters, found a c.v. of 1.4–8.7% in tests on 54 patients with nine operators and six replicates (38). The greatest inaccuracy, as reflected by c.v., was seen at low glucose levels. Scott observed that the Clarke Error Grid allowed what seemed to be unacceptable degrees of error in this study. Finally, a study comparing blood gas analyzer with main laboratory glucose showed only 1% of values having >20% error, suggesting that this approach is usually quite accurate, whereas in the same study, particularly with capillary sampling, meters often overestimated actual blood glucose (39).

In a 2009 survey by the College of American Pathologists, with four of the most commonly used meters, the c.v. averaged 5.3%, 6.0%, 4.7%, and 4.8% but varied from laboratory to laboratory. At Washington University School of Medicine, ~200 meters are used by >2,000 operators, testing ~1,400 values daily; the c.v. for low and high glucose values were 8.8% and 5.9%, respectively. Scott pointed out that few repeat glucose tests are done, perhaps because they are not billable, but that of those done recently, the mean absolute difference was 84 mg/dL, leading him to ask, "How many [inaccurate glucose values] are not being picked up that way?" New meters may be able to correct for anemia and reducing substances and may have 2–3% imprecision and relatively small bias.

Scott suggested that we require that values within 10% of actual glucose and within 10 mg/dL for glucose levels <100 mg/dL and argued that such an approach seems possible. A new error grid has been proposed, requiring that 95% of values be within 10% or 10 mg/dL and that 99% be within 15% or 12 mg/dL, so that <1% will exceed this level of abnormality (40,41). There currently is no direct comparison of meter versus blood gas analyzer in outcome, but Scott reviewed an analysis that uses a Monte Carlo modeling method, suggesting that simulation of the clinical effects of measurement error might be a useful approach to determining appropriate standards for these methodologies (and, presumably, for eventual use of continuous blood glucose-monitoring methods) (42).

Richard Hellman (Kansas City, KS) reviewed some of the same information on issues with use of POC devices for measuring blood glucose. A New York Times article brought to public attention the tremendous variability of out-of-hospital glucose measurements with available meters (43) and was followed by an FDA/Center for Devices and Radiological Health (CDRH) Public Meeting on the topic of Blood Glucose Meters, held on 16–17 March 2010 at the Hilton Washington DC North/Gaithersburg Hotel, examining whether there is need to change meter standards, with the consensus that improvement is needed.

In addition to the issues raised by Scott with in-hospital measurements, Hellman noted that hypotension leads glucose oxidase-based test strip methods to overestimate glucose levels, whereas glucose dehydrogenase methods may be either increased or decreased, with nearly two thirds of values showing >20% variance (28,44). Even small changes in meter precision or bias have the potential to cause adverse outcome, and Hellman observed that "outliers are dangerous," misleading both the patient and the provider and potentially causing harm, whether from high or low estimates. The dilemma, however, is that "we need the real-time information that the meters provide." If maltose-containing substances cause false elevation with glucose dehydrogenase, Hellman asked whether there is an effect of other dietary sugars? Might fruits, vegetables, herbs, and other dietary products containing xylose and galactose cause interference? The effects of anemia and polycythemia on meter accuracy are important as well. Many hospitals fail to implement comprehensive quality control testing for POC meters, and even more important, personnel who perform the testing rarely are taught the characteristics of the meters in accuracy, precision, and sensitivity to interference.

The degree of hematocrit interference with glucose tests strips shows lot-to-lot variation, with Hellman also wondering whether such variability might be related to the findings of adverse outcome of intensive glycemic control in NICE-SUGAR (45). Hypoglycemia is not, of course, the only issue for hospitalized diabetic patients; Hellman reviewed a Medicare identification of "things that should never happen but did," with 14,929 episodes of diabetic ketoacidosis and hyperosmolar coma developing among hospitalized patients in 2007. What he considered "the real problem in the hospital" was "untreated hyperglycemia both in the ICU and on the floors," so accurate glucose measurement is crucial. Out-of-hospital ketoacidosis also may occur in individuals having incorrectly low glucose readings (46). Many of the meters have better performance characteristics at one range than another, so that meters having falsely high levels in the low range will result in disproportionate risk for hypoglycemia.

Another issue, Hellman raised, is the consequence of not knowing which meter was being used. This has particularly become problematic when the choice of meter is dictated by the patient's pharmacy benefit plan. "The irony," Hellman emphasized, "is that the insurance [benefit provider] could take our patients and give them that [less accurate] meter because it's cheaper. We would like better meters, but they may cost more." Payers and pharmacy benefit managers should not be permitted to arbitrarily change patients' POC meters without input from the patient and provider, and any proposed new meter should have accuracy, precision, and ease of learning at least equivalent to the previous meter.

There are issues when the measurement is not properly performed by the patient. Failure to wash can cause both high and low glucose values. Failure to dry the hands causes hemodilution, and sluggish blood flow from hemoconcentration, vasospasm, or hyperviscosity may lead to inadequate sample size causing falsely low results. Most published data on accuracy and precision involve studies performed by highly trained technicians with properly stored new strips, with well cared for meters. Such results may not be found in usual patient care, where the c.v. is nearly 50% greater than that in the inpatient setting (47). In addition, there are lot-to-lot variations, with Hellman noting that more than half of the instruments studied show more hematocrit-induced error in glucose levels than acknowledged in the manufacturers' documentation. Storage for 30 min at low or high temperatures also lead to error, and we lack good studies on the useful life of meters. Without specific efforts to maintain patient proficiency, such as the use of mailed unknown samples from a central agency, inaccurate testing may occur over time even after appropriate patient education. Furthermore, many patients do not have effective education in self-monitoring, with older patients given written materials rather than in-person education being particularly likely not to test correctly.

We then need to find a balance between convenience, cost, size, and speed on the one hand and accuracy on the other hand. In critical care settings, Hellman stated, "accuracy and precision are life-saving," and must not be affected by change in hematocrit, hypotension, hypoxia, or interfering substances, so that it may not be appropriate to care for patients in these settings with instruments other than blood gas multichannel analyzers. Hellman suggested that for glucose levels ≥75 mg/dL, 95% of values should be within 10%, 99% of values within 15%, and 99.9% within 20% of actual, and for glucose levels <75, the respective accuracy criteria should be 10, 15, and 20 mg/dL. Strip lots, Hellman said, should be tested systematically by a FDA-approved entity for accuracy, and the results should be publically available. Manufacturers have a responsibility to provide effective educational materials on POC meters. Glucose meters should contain software so that date- and time-stamped glucose levels can be securely downloaded using an industry-standard interface to be available for patients and providers without charge. Most importantly, Hellman concluded that "health care providers should not use POC meters uncritically, especially when the clinical setting makes these values suspect."

There may be similar issues with POC A1C testing. At the National Glycohemoglobin Standardization Program (NGSP) Clinical Advisory Committee meeting at the ADA, David Sacks (Boston, MA) discussed this matter, noting that POC testing may incorporate immunoassay or boronate affinity chromatography, the latter infrequently used in clinical laboratories. Between laboratory A1C, c.v. values are typically <3.5%, and within a given laboratory, the c.v. may be <1.0%. The Clinical Laboratory Improvement Amendments (CLIA) act of 1988 allows waiver of "test systems [which] are simple…cleared by FDA for home use… so simple and accurate as to render the likelihood of erroneous results negligible, or pose no reasonable risk of harm." Based on this waiver, six POC A1C devices have been NGSP-certified. Advantages are these devices' rapidity, convenience, and the CLIA waiver, allowing testing to be performed in the physicians' office. There is evidence that immediate A1C feedback improves outcome. Disadvantages are greater expense and the lack of requirement for proficiency testing; thus, there is very limited objective data regarding performance in patient care and potential lack of precision in the hands of those who use them. How accurate, Sacks asked, should one expect the A1C measurement to be? If a specimen has A1C 6.5%, with a c.v. of 4%, the 2 SD range would be 5.98–7.02, with 3%, 6.11–6.89, and with 2%, 6.24–6.76. Is it necessary then for the c.v. to be <2% for acceptable precision? Sacks argued that if A1C is used for diagnosis and even if it is used for management, the between-laboratory c.v. should be low. Sacks reviewed a study of eight commercial POC A1C devices (48). Two of the manufacturers withdrew their devices after initial poor results, but only two of the others had c.v. <3%, and only one device met current NGSP criteria with two different lots. The bias of the devices ranged from −0.9% to +0.4%. Noting that a positive 0.4% A1C bias would more than double the number of individuals diagnosed with diabetes, Sacks reviewed current ADA guidelines, which suggest that POC devices not be used for the diagnosis of diabetes. Of course, one must be concerned about both positive and negative biases in use of these devices in clinical care.

Acknowledgments — Z.T.B. has served on speaker's bureaus of Merck, Novo Nordisk, Lilly, Amylin, Daiichi Sankyo, and GlaxoSmithKline; has served on advisory panels for Medtronic, Takeda, Merck, AtheroGenics, CV Therapeutics, Daiichi Sankyo, BMS, and AstraZeneca; holds stock in Abbott, Bard, Medtronic, Merck, Millipore, Novartis, and Roche; and has served as a consultant for Novartis, Dainippon Sumitomo Pharma America, Forest Laboratories, and Nastech. No other potential conflicts of interest relevant to this article were reported.

References

1. Dictionary.reference.com/browse/contrarian, Accessed 29 January 2011

2. encarta.msn.com/dictionary_1861670806/contrarian.html, Accessed 29 January 2011
3. The University Group Diabetes Program. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. Diabetes 1970;19(Suppl. 2):747–839
4. Schwartz TB, Meinert CL. The UGDP controversy: thirty-four years of contentious ambiguity laid to rest. Perspect Biol Med 2004;47:564–574
5. Brady PA, Terzic A. The sulfonylurea controversy: more questions from the heart. J Am Coll Cardiol 1998;31:950–956
6. Nissen SE, Wolski K, Topol EJ. Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. JAMA 2005;294:2581–2586
7. Gerstein HC, Yusuf S, Bosch J, et al.; DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006;368:1096–1105
8. Nissen SE. The DREAM trial. Lancet 2006;368:2049; author reply 2050–2051
9. Home PD, Pocock SJ, Beck-Nielsen H, et al.; RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet 2009;373:2125–2135
10. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457–2471
11. Bloomgarden ZT. The Avandia debate. Diabetes Care 2007;30:2401–2408
12. Dormandy JA, Charbonnel B, Eckland DJ, et al.; PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279–1289
13. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 2007;298:1180–1188
14. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
15. Bolen S, Feldman L, Vassy J, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med 2007;147:386–399
16. Selvin E, Bolen S, Yeh H-C, et al. Cardiovascular outcomes in trials of oral diabetes medications: a systematic review. Arch Intern Med 2008;168:2070–2080
17. Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. Accessed 29 January 2011 from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf
18. Bansal S, Wackers FJ, Inzucchi SE, et al.; DIAD Study Investigators. Five-year outcomes in high-risk participants in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study: a post hoc analysis. Diabetes Care 2011;34:204–209
19. Bloomgarden ZT. Diabetes and Cardiovascular Disease. Diabetes Care 2011;34:e24–e30
20. Inzucchi SE, Masoudi FA, Wang Y, et al. Insulin-sensitizing antihyperglycemic drugs and mortality after acute myocardial infarction: insights from the National Heart Care Project. Diabetes Care 2005;28:1680–1689
21. Taleb NN. *The Black Swan: the Impact of the Highly Improbable*. Random House, New York, 2005
22. Bina DM, Anderson RL, Johnson ML, Bergenstal RM, Kendall DM. Clinical impact of prandial state, exercise, and site preparation on the equivalence of alternative-site blood glucose testing. Diabetes Care 2003;26:981–985
23. Louie RF, Tang Z, Sutton DV, Lee JH, Kost GJ. Point-of-care glucose testing: effects of critical care variables, influence of reference instruments, and a modular glucose meter design. Arch Pathol Lab Med 2000;124:257–266
24. Lyon ME, Baskin LB, Braakman S, Presti S, Dubois J, Shirey T. Interference studies with two hospital-grade and two home-grade glucose meters. Diabetes Technol Ther 2009;11:641–647
25. Karon BS, Griesmann L, Scott R, et al. Evaluation of the impact of hematocrit and other interference on the accuracy of hospital-based glucose meters. Diabetes Technol Ther 2008;10:111–120
26. Kaufmann-Raab I, Jonen HG, Jähnchen E, Kahl GF, Groth U. Interference by acetaminophen in the glucose oxidase-peroxidase method for blood glucose determination. Clin Chem 1976;22:1729–1731
27. Rao LV, Jakubiak F, Sidwell JS, Winkelman JW, Snyder ML. Accuracy evaluation of a new glucometer with automated hematocrit measurement and correction. Clin Chim Acta 2005;356:178–183
28. Dungan K, Chapman J, Braithwaite SS, Buse J. Glucose measurement: confounding issues in setting targets for inpatient management. Diabetes Care 2007;30:403–409
29. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA 2008;300:933–944
30. Finfer S, Chittock DR, Su SY, et al.; NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283–1297
31. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001;345:1359–1367
32. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med 2006;354:449–461
33. Karon BS, Gandhi GY, Nuttall GA, et al. Accuracy of roche accu-chek inform whole blood capillary, arterial, and venous glucose values in patients receiving intensive intravenous insulin therapy after cardiac surgery. Am J Clin Pathol 2007;127:919–926
34. Scott MG, Bruns DE, Boyd JC, Sacks DB. Tight glucose control in the intensive care unit: are glucose meters up to the task? Clin Chem 2009;55:18–20
35. Chen ET, Nichols JH, Duh SH, Hortin G. Performance evaluation of blood glucose monitoring devices. Diabetes Technol Ther 2003;5:749–768
36. Henry MJ, Major CA, Reinsch S. Accuracy of self-monitoring of blood glucose: impact on diabetes management decisions during pregnancy. Diabetes Educ 2001;27:521–529
37. Kimberly MM, Vesper HW, Caudill SP, et al. Variability among five over-the-counter blood glucose monitors. Clin Chim Acta 2006;364:292–297
38. Chen ET, Nichols JH, Duh SH, Hortin G. Performance evaluation of blood glucose monitoring devices. Diabetes Technol Ther 2003;5:749–768
39. Kanji S, Buffie J, Hutton B, et al. Reliability of point-of-care testing for glucose measurement in critically ill adults. Crit Care Med 2005;33:2778–2785
40. Krouwer JS, Cembrowski GS. A review of standards and statistics used to describe blood glucose monitor performance. J Diabetes Sci Tech 2010;4:75–83
41. Meynaar IA, van Spreuwel M, Tangkau PL, et al. Accuracy of AccuChek glucose measurement in intensive care patients. Crit Care Med 2009;37:2691–2696
42. Boyd JC, Bruns DE. Monte Carlo simulation in establishing analytical quality requirements for clinical laboratory tests meeting clinical needs. Methods Enzymol 2009;467:411–433
43. Gardiner Harris. "Standards Might Rise on Monitors for Diabetics." New York Times, July 18, 2009, Accessed 30 January 2011 from http://www.nytimes.com/2009/07/19/health/policy/19monitor.html
44. Atkin SH, Dasmahapatra A, Jaker MA, Chorost MI, Reddy S. Fingerstick glucose determination in shock. Ann Intern Med 1991;114:1020–1024

45. Cembrowski GS, Tran DV, Slater-Maclean L, Chin D, Gibney RT, Jacka M. Could susceptibility to low hematocrit interference have compromised the results of the NICE-SUGAR trial? Clin Chem 2010;56:1193–1195
46. Blank FS, Miller M, Nichols J, Smithline H, Crabb G, Pekow P. Blood glucose measurement in patients with suspected diabetic ketoacidosis: a comparison of Abbott MediSense PCx point-of-care meter values to reference laboratory values. J Emerg Nurs 2009;35:93–96
47. Kristensen GB, Monsen G, Skeie S, Sandberg S. Standardized evaluation of nine instruments for self-monitoring of blood glucose. Diabetes Technol Ther 2008;10:467–477
48. Lenters-Westra E, Slingerland RJ. Six of eight hemoglobin A1c point-of-care instruments do not meet the general accepted analytical performance criteria. Clin Chem 2010;56:44–52