GLYCEMIC TARGETS IN DIABETES CARE: EMERGING CLARITY AFTER ACCORD

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ABSTRACT

Through the 1990s convincing evidence emerged from studies involving relatively recent onset diabetes that glycemic control achieving glycated hemoglobin A₁c levels of approximately 7% was associated with improved microvascular outcomes. Based on advocacy groups’ statements encouraging lower targets and recognition of cardiovascular disease as the leading cause of death in diabetes, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was funded in 1999 to explore more intensive targets and techniques in the treatment of type 2 diabetes. Most surprisingly, intensive management targeting normal levels of glycemia was associated with increased mortality and the ACCORD trial was terminated early in 2008. Post hoc analyses have allowed the emergence of some clarity around the role of glycemic management and targets in diabetes care and are the subject of this review.

INTRODUCTION

Since publication of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial in June of 2008 documenting increased mortality associated with more intensive management of hyperglycemia in diabetes, there has been considerable confusion and controversy regarding the appropriate targets for glycemic control in diabetes. Two techniques are commonly used to assess glycemic control. First, mea-
suring glucose using a hand-held device or subcutaneous sensor is the mainstay of patient self-management and allows patients to modify their treatment based on both current glucose as well as trends. These results are often recorded in logbooks or downloaded electronically to allow periodic review by health care providers. Second, hemoglobin A1c (A1C) is generally a laboratory-based measurement which is thought to reflect the time-weighted average plasma glucose over the preceding 8–12 weeks. A1C is a glycated form of hemoglobin A, the dominant hemoglobin of normal adults (1). Glycation is the non-enzymatic attachment of a sugar to amino groups in proteins sometimes referred to as “browning” and is driven by the Maillard reaction. In fact, the browning of meat when cooking at high temperature while basting with sugar-containing liquids is an accelerated form of the same process.

Here we will explore the evidence base for particular glycemic targets in diabetes care, the impact of the ACCORD trial on current thinking, and recent post hoc analyses of ACCORD and their contributions to our understanding of what may have contributed to the excess mortality in ACCORD before speculating about how best to operationalize its findings in current diabetes management.

THE DIABETES CONTROL AND COMPLICATIONS TRIAL STUDY AND TREATMENT TARGETS IN TYPE 1 DIABETES

Although preclinical models and epidemiologic studies as well as more limited interventional studies had suggested that lower average glycemia as assessed by the A1C test was associated with reduced risk of complications, definitive data in this regard was not available until the Diabetes Control and Complications Trial (DCCT) was published in 1993 (2). This landmark study involved 1,441 patients with type 1 diabetes mellitus (T1DM) — approximately half with no retinopathy at baseline (the primary prevention cohort) and half with mild retinopathy (the secondary intervention cohort). All participants were randomly assigned to intensive or conventional treatment arms with an average of 6.5 years of differential therapy between 1983 and 1993.

Intensive therapy consisted of insulin administration by an insulin pump or by three or more insulin injections a day. Insulin doses were adjusted by the participants, based on at least four self-monitoring of blood glucose (SMBG) checks daily as well as anticipated dietary intake and physical activity. The goals of intensive therapy were to achieve SMBG between 70 and 120 mg/dL before meals, SMBG < 180 mg/dL after meals, a weekly 3AM SMBG > 65 mg/dL, and an A1C
within the normal range (≤ 6.05%). Intensively treated participants visited the research clinic each month and had weekly contact with a member of the health care team to review and adjust their treatment.

Conventional therapy consisted of one or two daily injections of insulin, generally mixed neutral protamine Hagedorn (NPH) and regular insulin, daily urine glucose or SMBG, and education about diet and exercise. The goals of conventional therapy included prevention of hyperglycemic symptoms, ketonuria, weight loss, and frequent severe hypoglycemia.

Ninety-nine percent of the patients completed the study. Although only 5% of the participants in the intensive group were able to sustain the goal of a normal A1C levels, the average value in the intensive participants, ~7%, was substantially lower than in conventional treatment group participants, ~9%. Average capillary blood glucose 7-point profiles in the intensive treatment group were 155 ± 30 mg/dL, compared with 231 ± 55 mg/dL in the conventional therapy group. In both the primary prevention and secondary intervention cohorts, intensive therapy was shown to reduce the risk of development and progression of proliferative or severe non-proliferative retinopathy, the need for treatment with retinal photocoagulation, the development of microalbuminuria or proteinuria, and the appearance of neuropathy. Although some had suggested a potential adverse effect of intensive insulin treatment to exacerbate cardiovascular disease, in the DCCT there was a non-significant trend to reduce macrovascular disease (3).

Ninety-three percent of DCCT participants were rolled over into the Epidemiology of Diabetes Interventions and Complications (EDIC) study for which they continue to be monitored today. Glycemic control in both groups drifted toward an A1C of ~8% within 1–2 years. With 17 years of follow-up after randomization, despite similar glycemic control in both groups for 10 years, cardiovascular disease (defined as nonfatal myocardial infarction, stroke, death from cardiovascular disease, confirmed angina, or the need for coronary-artery revascularization) was reduced by 42% and nonfatal myocardial infarction, stroke, and cardiovascular deaths were reduced by 57% (4). After a mean of 27 years’ follow-up, intensive diabetes treatment for 6.5 years was also associated with 33% reduction in all-cause mortality (absolute risk difference, 109 deaths per 100,000 patient-years) when compared to conventional therapy (5).

There were adverse events associated with the intensive treatment regimen in the DCCT, specifically a three times higher rate of severe hypoglycemia requiring assistance (6) and a 33% increase in risk of becoming overweight (>120% of “ideal”), approximately 5 kg for the average participant, and associated with features of metabolic syndrome (7).
The authors of the DCCT study recommended that most patients with T1DM be treated with an intensive treatment regimen under the close supervision of a health care team consisting of a physician, nurses, nutritionist, and behavioral and exercise specialists as needed. The process of community translation has been challenging. Recent epidemiological analysis of patients with type 1 diabetes who were followed from diabetes-onset in specialized centers document that for those who achieve the 25-year average A1C < 7.6%, the risk of developing retinopathy requiring laser photocoagulation or persistent macroalbuminuria is exceptionally low (8). Prudence has been encouraged regarding intensive glycemic therapy in populations such as children younger than 13 years of age, elderly people, and patients with advanced complications such as end-stage renal disease and cardiovascular or cerebrovascular disease (9). Further, people with T1DM who do not experience warning adrenergic symptoms of hypoglycemia, often termed “hypoglycemic unawareness,” are at significantly greater risk for severe recurrent hypoglycemia with grave risk for injury or death. The development of continuous glucose monitoring may provide an additional level of safety in such individuals (10).

The American Diabetes Association (ADA) suggests that the A1C treatment goals in T1DM should be <7.5% for younger people (<18 years), <7.0% in adults, <7.5% in older adults who are healthy, <8.0% in older adults with complicating factors and intermediate health, and <8.5% in older adults with very complex medical problems and poor health (11). Furthermore, they suggest that a lower A1C target may be pursued in individual patients (e.g., those with recent onset disease, long life expectancy, or no significant cardiovascular disease), but only if it can be achieved without significant hypoglycemia or other adverse effects of treatment. Conversely, they recommend that less-stringent A1C goals “may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, and extensive comorbid conditions and those with longstanding 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” (12).

TREATMENT TARGET STUDIES IN TYPE 2 DIABETES BEFORE ACCORD

Very similar results to those described for the DCCT study were reported for an unusual population, at least by American standards, of
Japanese patients with type 2 diabetes mellitus (T2DM). In the Kumamoto study (13), 110 T2DM patients were enrolled. They were younger than 70 years of age, treated with 1–2 injections a day of intermediate-acting insulin, exhibited no or minimal complications of diabetes, and did not have hypertension, hypercholesterolemia or other “severe medical conditions.” They had an average body mass index of approximately 20 kg/m². Participants were randomly assigned to standard treatment or an intensive program of insulin therapy designed to achieve normal glycemia. The design and execution of the trial was very similar to the DCCT trial discussed above. The control group maintained A1C values at approximately 9% whereas A1C in the intensive treatment group was reduced to approximately 7%. The separation of A1C was maintained for 6 years. The intensive participants had a reduction in microvascular complications and a non-statistically significant trend toward reduced rates of vascular endpoints. Intensive treatment was associated with a modestly increased risk of hypoglycemia and weight gain.

The United Kingdom Prospective Diabetes Study (UKPDS) has been widely conceived of as a trial of treatment targets, although as you will see, it is not (14,15). Nevertheless, it is essentially the nidus for treatment recommendations today for the more than 300 million people in the world with T2DM. In the UKPDS, patients in the United Kingdom with newly discovered T2DM were enrolled and treated with a lifestyle intervention for 3 months, exhibiting an average reduction in A1C from approximately 9% to 7%. Those patients with a fasting plasma glucose (FPG) level greater than 108 mg/dL after the diet run-in were randomized to one of two treatment policies. In standard treatment, participants continued the lifestyle intervention: pharmacologic treatment was only initiated if the FPG level reached 270 mg/dL or the patient became symptomatic. In the intensive treatment program, all patients were randomly assigned to treatment with either a sulfonylurea, insulin, or metformin (the latter, only in a subpopulation of overweight patients) in addition to lifestyle management, with doses of the randomized treatment increased as needed to try to achieve and maintain an FPG level of less than 108 mg/dL. However, in the intensive treatment program, additional agents were only used if the patient became symptomatic or the FPG level increased to greater than 270 mg/dL. Thus, UKPDS effectively is a comparative effectiveness trial of pharmacological therapy initiated immediately for patients with an FPG level >108 mg/dL after a diet run-in versus delayed therapy until patients become symptomatic or have an FPG level >270 mg/dL with a sub-randomization to three classes of anti-
hyperglycemic therapy. Fundamentally, it is not a trial of treatment targets.

As a consequence of the design of the UKPDS, although A1C was reduced in the first year to approximately 6% in the intensive treatment group, over the average 10 years of randomized follow-up it increased to approximately 8% despite additional therapies being provided to many participants. The average A1C in the standard treatment group was approximately 1% higher throughout the trial. Associated with this 1% difference in A1C, there was a reduction in the risk of clinical microvascular complications (retinopathy, nephropathy, and neuropathy) in the group receiving intensive treatment. Although there was a trend toward reduced rates of macrovascular events in the more intensively treated group, it did not reach statistical significance. The risk of severe hypoglycemia was small (on the order of 1% to 5% per year in the insulin-treated group) and weight gain was modest; both were higher in patients randomly assigned to insulin and lower in those receiving metformin.

The UKPDS cohort was followed for an additional 10-year period. As in the DCCT, during this non-interventional phase of the study, the A1C difference between groups essentially disappeared after the first year. During the 10-year follow-up, the relative benefit of more intensive treatment of hyperglycemia documented at the end of the randomized portion of the trial was maintained for all complications, resulting in the emergence of statistically significant benefits on cardiovascular end points and total mortality (16).

Other trials of T2DM treatment were similarly not assessments of glycemic treatment targets and their relative effects on diabetes complications and are not reviewed here, although mentioned for completeness (17). These include including the University Group Diabetes Program, the Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes Mellitus, the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction trial, and the Steno-2 study.

THE ACCORD AND TEMPORALLY ASSOCIATED STUDIES

In 1999 the ACCORD study was funded based primarily on uncertainty about the effect of glycemic control on the major cause of mortality in diabetes, namely cardiovascular disorders. Although no trial at that point in time had achieved and sustained glycemic control at an A1C level of < 7%, most international bodies recommended an A1C target of ≤ 6.5% (18). Furthermore, it was recognized that the avail-
ability of multiple classes of antihyperglycemic therapies that were not associated with hypoglycemia made it possible to at least consider targeting normal levels of glycemia, namely an A1C of \(<6\%\). Two other studies of glycemic targets in T2DM were planned and executed in a similar timeframe — Action in Diabetes and Vascular Disease — Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) (19) and the Veterans Affairs Diabetes Trial (VADT) (20). Each study randomized middle-aged and older individuals who were at high risk for cardiovascular events based on the presence of clinical cardiovascular disease or multiple risk factors. ACCORD and VADT aimed for an A1C target of \(<6\%\) using complex combinations of oral agents and insulin. ADVANCE aimed for an A1C \(\leq 6.5\%\) using a somewhat less intensive approach based on the addition of the sulfonylurea gliclazide in patients earlier in the natural history of disease. Although all of the studies showed at least a suggestion of benefit on microvascular endpoints, none of the trials showed a statistically significant benefit on combined vascular end points. ACCORD showed a 22\% increase in total mortality, whereas VADT had numerically more deaths in the intensively treated group (hazard ratio, 1.07). In the three studies, there were suggestions that people who at baseline were without clinical cardiovascular disease and who had shorter duration of disease or lower baseline A1C showed greater benefits from more intensive glucose-lowering strategies (21,22).

**POST HOC ANALYSES FROM ACCORD**

Two post hoc analyses from the ACCORD study have added important insights into the risk of mortality associated with intensive management in that trial. Based on the top level observation that excess mortality with intensive glycemia control was most evident in ACCORD, which lowered the A1C fastest of the three studies and to a lower end of trial A1C than the VADT, some hypothesized that it was the initial rate of reduction of glucose or the absolute level of A1C achieved that led to increased mortality with intensive treatment. Riddle et al (23) showed quite conclusively in an epidemiological analysis from ACCORD that a higher average on-treatment A1C was a stronger predictor of mortality than the A1C for the last interval of follow-up or the decrease of A1C in the first year. In fact, those with little or no A1C reduction in the first year in ACCORD experienced the highest mortality. Furthermore, in the intensive treatment strategy group in ACCORD, the risk of death increased linearly from an A1C of 6\% to an A1C of 9\%. Additionally, mortality was only increased in the
intensive treatment group as compared to standard treatment when the average on-treatment A1C was >7%. Or put another way, in the intensive treatment group, aiming for an A1C of <6% was not associated with increased mortality as long as the achieved A1C was <7%.

The authors speculated that unmeasured confounders may account for the excess mortality in those treated using the intensive strategy who failed to achieve an A1C of <7% such as poor adherence perhaps driven by psychosocial issues or the emergence of other serious medical problems, each of which could independently contribute to poor control and to mortality. They recognized that hypoglycemia, weight gain, and specific drugs could have also contributed, although no convincing signal for these possibilities have emerged despite multiple analyses. Finally, it should be recognized that the dominant treatments used in ACCORD were metformin, thiazolidinediones, and insulin, all aimed at treating or overwhelming insulin resistance; thus, it is possible that those that did not respond to intensive management in ACCORD were those with the most severe insulin resistance, a condition known to be associated with increased cardiovascular risk (24).

Hempe, McCarter and colleagues for more than a decade have been trying to understand the implications of the observation that some people with diabetes have persistently higher than expected A1C levels and some have lower A1C levels when compared to other individuals with similar blood glucose levels. They have posited that the existence of inter-individual differences in the quantitative relationship between blood glucose concentration and A1C could complicate the clinical use of A1C for diabetes management. The hemoglobin glycation index (HGI) was developed to measure biological variation in A1C in a population due to factors other than blood glucose. In the DCCT trial, they showed that participants with high HGI have greater risk for microvascular complications (25). Specifically with respect to ACCORD, they hypothesized that intensive treatment to an A1C target of <6% may have inadvertently produced harms related to hypoglycemia in a subgroup of ACCORD diabetes patients with A1C levels that were higher than their blood glucose levels would suggest. In ACCORD, HGI = observed A1C - predicted A1C, where predicted A1C was calculated for each participant based on a linear regression equation of baseline fasting glucose and baseline A1C (26). As shown in Table 1, participants with low or high HGI have respectively lower or higher than average A1C levels based on their FPG levels. As shown in Table 2, intensively treated ACCORD participants in the high tertile of HGI (i.e., a higher A1C than would be predicted based on their fasting glucose at baseline) had a 41%
increase in total mortality and no benefit on the primary endpoint (the first occurrence of myocardial infarction, stroke, or cardiovascular death). On the other hand, those in the lower and middle tertiles of HGI had no increased mortality and an approximately 24% benefit on the primary endpoint. Thus, for the first time, Hempe et al were able to identify a marker, HGI, which at baseline identifies a subpopulation in ACCORD who experienced only harms and a subpopulation in ACCORD who experienced only benefits from intensive glycemic control. As suggested for some time in other settings, A1C is perhaps not a one-size-fits-all indicator of overall blood glucose control. Unfortunately, the linear regression equation from ACCORD is not generalizable to other populations, so it is not possible to a priori identify people for intervention with differential intensity. Furthermore, confirmation of the findings in other populations is required before adoption would be prudent.

### BLOOD GLUCOSE TREATMENT TARGETS IN T2DM

Until 2008, the ADA treatment target of an A1C < 7% for T2DM was largely informed by the DCCT study of patients with T1DM. The UKPDS study, although fundamentally not a study of treatment targets did result in an average A1C of 7% and better outcomes in the more intensively treated arm over 10 years of follow-up and was used to support the target of < 7%. The benefits from the DCCT,
<table>
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<tr>
<th>HGI Subgroup</th>
<th>Intensive Treatment (i)</th>
<th>Standard Treatment (S)</th>
<th>Adjusted Hazard Ratio (I/S)</th>
<th>Interaction Between Treatment and HGI (P Value)</th>
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<td>At risk</td>
<td>Events</td>
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<td>Overall</td>
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<td>446</td>
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<td>Low</td>
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<td><strong>Total mortality</strong></td>
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<td>151</td>
<td>9.9</td>
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Abbreviations: HGI, hemoglobin glycation index; CI, confidence interval.
*First occurrence of non-fatal myocardial infarction, non-fatal stroke or cardiovascular mortality.
†Bonferroni correction for multiple comparisons.

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Kumamoto, and UKPDS studies were exclusively for microvascular endpoints. Although the DCCT and UKPDS were able to show benefits on cardiovascular events and mortality with long-term follow-up, it was only observed after a decade or more of less intensive follow-up treatment. The excess mortality in ACCORD rocked the diabetes world in 2008. Taking all the above into account, but largely based on the results of ACCORD, the ADA, the American Heart Association, and the American College of Cardiology suggested that the general treatment goal for T2DM should remain an A1C level of $< 7\%$ based on microvascular benefits and the potential for long-term cardiovascular benefits (21). The emphasis changed to one based on treatment individualization. The ADA (12) currently recommends that lower A1C targets may be pursued based on characteristics that suggest the potential for enhanced benefit such as in those with recent-onset disease and long life expectancy, and for enhanced safety based on an absence of significant cardiovascular disease, a nod to the ACCORD result. Furthermore, they suggest that the treatment response should be considered and more stringent targets should only be embraced as long as treatment is not complicated by significant hypoglycemia or other adverse effects of treatment. In a similar vein, the ADA recommends less stringent A1C targets in those with a history of severe hypoglycemia, limited life expectancy, or advanced complications and comorbidities. Based on the Riddle analysis of ACCORD (23), the ADA recommends less stringent A1C targets in those who do not achieve an A1C $< 7\%$ in the face of ongoing diabetes self-management education and effective doses of insulin in combination therapy with, for instance, metformin. The American College of Endocrinology continues to recommend an A1C goal $\leq 6.5\%$, but with similar language regarding individualization of targets (27). As the HGI analysis in ACCORD (26) is so new, there is no guidance as to how to incorporate those learnings. As was mentioned earlier, confirmation of the HGI findings in another population and developing generalizable techniques for assessing HGI will be necessary before guidelines are likely to embrace its findings. All active clinicians see patients with A1C levels that remain high despite SMBG evidence of good control. At least for now, caution in trying to further decrease glucose levels in those patients is prudent. Despite our medical societies' attempts to provide specific guidance appropriate to all patients under treatment for T2DM, clinical judgement and individualization both on baseline factors and treatment response remains paramount in pursuing glycemic control.
ACKNOWLEDGMENTS

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REFERENCES


DISCUSSION

Gotto, New York: I chaired the latest data safety monitoring board. We wrestled and wrestled with this data that came in, but ultimately death trumps everything else. Also, shortly after ACCORD there is a VA study and a study in Australia/New Zealand which didn’t show increased mortality, but it also failed to see benefit in intensive treatment. And recently in the last 2 weeks, there is a paper published in the *Annals of Internal Medicine*, a British study, in which they followed a large group of individuals and found there was no relationship between glycemia as they defined it, mortality. And two *New England Journal of Medicine* papers looking at two of the new DPP4 inhibitors and found no relationship between cardiovascular events and glycosylated hemoglobin.

There are a number of differences in these studies; some show one thing and some show another. What is your hypothesis about why the increase in mortality?

Buse, Chapel Hill: So there are a couple of studies that you didn’t mention. The DCCT and UKPDS involved 10 years, more or less, of more intensive management and then 10 to 15 years of follow-up. Over that period of time, statistically significant benefits were demonstrated in cardiovascular events and mortality. So one of the notions from those trials is that glycemic control today really determines what your risk of complications are for a decade or more or later. Maybe differences in glycemic control just take a lot longer than some of these short studies to demonstrate benefits on cardiovascular endpoints. The second thing is when you look at meta-analyses across trials, there is about 15% reduction in cardiovascular events for every 1% reduction in A1C. I think the question that we are raising is that maybe hemoglobin A1C isn’t the ideal marker. What the ideal marker is is completely unclear. But I think from a sort of guideline perspective, what we would suggest, at least for now, is try to achieve the A1C level that is relatively easy to achieve — generally around 7%; try to do that particularly early in the course of the disease; and recognize that glucose monitoring is an important point and avoiding hypoglycemia is absolutely critical. I think the excess mortality in ACCORD came from the fact that we were targeting hemoglobin A1C. People who had higher A1Cs than you would expect based on fasting glucose just had their glucose lowered too far in a futile effort to lower their A1C, and that we had adverse consequences from this insulin based therapy. But you know we don’t really know what the answer is.

Schuster, New York: I was attending on medicine a couple weeks ago and we had a difficult diabetic patient, and one of the house staff said to me, “Okay we have hemoglobin A1C which tells me about mean hemoglobin. But I think this patient’s hypoglycemic episodes are the real problem and I’d like a test that tells me a mean hypoglycemic index, and I can’t probably use catechols because the patient has diabetic neuropathy, so what am I supposed to do?” And my question to you is, are there any thoughts about that sort of an index?

Buse, Chapel Hill: So there isn’t a blood test that you can measure once every three months to give you the total hypoglycemic burden. There are some different tests that can show you subtleties in glycemic variation over time, something called 1,5-anhydroglucitol that has been available in Japan for 30 years and in the United States for about 5 years. It hasn’t really taken off. I am not sure that it is that valuable. But most importantly, we now have these continuous glucose monitors that are quite accurate. They are now used in the Holter monitor fashion where they are put on for 7 days and the results downloaded and analyzed. For patients who are treated with insulin with an A1C of about 7%; about 50% of those people will spend hours of the day at glucose levels under 50. So there is a lot of hypoglycemia out there that goes unrecognized.

Fagin, New York: Would you like to comment on the biological underpinning of this discrepancy in terms of the ability of hemoglobin A1C to be a sensor? There is some
evidence that the association between integrated blood glucose levels and hemoglobin A1C can be an inherited phenomenon that is seen in twins; issues to do with transport of glucose into erythrocytes, erythrocyte half-life, and so on. Whether other such as fructosamine could be surrogates and what are your thoughts on that?

**Buse, Chapel Hill:** So there is a lot of work that is being done. We have a GWAS study that we are doing on this subset. There are a couple of interesting hits that have been reported before in these kinds of analysis. You touched on most of the theories. One of the other theories is differences in the rate of phosphorylation inside the red cell. Instead of measuring this HGI the way that I described, some measure it by using a ratio of hemoglobin A1C and fructosamine. Fructosamine has other issues as far as a marker for general use in diabetes. Most people in the diabetes community believe these notions to be sort of crackpot ideas. It will be a while before we get to a new paradigm. But we do need better markers or at least more understanding around this.

**Skeff, Palo Alto:** I want to reiterate what Jerry Reaven taught me when I was a resident and I found extremely useful. He said, “if you want to identify the diabetic where the physician is being too aggressive in his or her treatment, find the person who is gaining weight.” And I found that when doing rounds and somebody would say, “when did you start gaining the 50, 60, or 70 pounds,” and the reply was “when my doctor started treating me.” So they are overeating to try to, I think, buffer the hypoglycemia that sometimes we’re causing. Is this the message you relay that in the patients who are more labile in their sugar, that the aggressiveness which we should try to control them should be buffered?

**Buse, Chapel Hill:** Absolutely yes. Hypoglycemia will kill someone today or tomorrow. Hyperglycemia takes 10, 20, 30 years to catch up. So it is something that we preach all the time in our clinic. With regard to weight gain, that is another one of the hypothesis around why the intensively treated patients had excess mortality. I think the number is 25% of patients gained 5% of their body weight or more during the trial. We have tried to sort all of this out in ACCORD, and despite all the data that we have, we have not been able to pin excess mortality to hypoglycemia or pin it on weight gain, or anything in particular. The good news in 2014 is that we have a number of treatments now that are very effective glucose lowering therapies that are associated with weight loss and no hypoglycemia. So the insulin era may be evolving to an era of better care.

**Schrier, Colorado:** There is data that controlling blood pressure is more important than controlling glucose. You want to comment as far as cardiovascular complications and death?

**Buse, Chapel Hill:** My personal belief is that you should do what you can to get blood pressure, LDL cholesterol, and glucose well controlled. The glycemic control is critical for the microvascular complications. Amputations and blindness are basically going away in America as common complications of diabetes management. Blood pressure control is critical. For some reason this sort of ultimate evidenced-based application on to the blood pressure data in diabetes has resulted in the backing off on blood pressure targets from a normal target of 130 systolic, to now many recommending 140, which I think is probably a mistake.