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Lessons Learned from Glycemia Control Studies

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Abstract Hyperglycemia occurs in patients with diabetes and in nondiabetic patients during acute illness. Epidemiologic and observational studies have demonstrated that hyperglycemia is associated with significant adverse outcomes. Nevertheless, studies evaluating the benefits of normalizing glycemia have produced inconsistent results. For instance, intensive control of hyperglycemia had been shown to provide microvascular benefit in type 1 and type 2 diabetic patients, but its macrovascular benefits had only been clearly demonstrated in type 1 diabetic patients. Moreover, although initial studies in critically ill patients showed decreased morbidity and mortality with tight glycemic control, subsequent studies yielded conflicting results. A series of recent studies provide further insight and show that intensive glycemic control in type 2 diabetic patients does provide macrovascular benefit but is associated with increased risk of hypoglycemia. In the critically ill patient, tight glycemic control could be detrimental; thus, a less aggressive glycemic target of 140 to 180 mg/dL is preferred.

Keywords Glycemic control · Hyperglycemia · Type 2 diabetes · Glucose

Clinical Trial Acronyms

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
DCCT	Diabetes Control and Complications Trial
EDIC	Epidemiology of Diabetes Interventions and Complications
NICE-SUGAR	Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial
VISEP	Volume Substitution and Insulin Therapy in Severe Sepsis

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Introduction

Diabetes is a chronic illness affecting millions of individuals in the United States and worldwide [1-3]. Both type 1 and type 2 diabetes are associated with significant morbidity and mortality. Individuals with diabetes have a two–to fourfold increased incidence of cardiovascular disease and are twice as likely to die from a myocardial infarction (MI) when compared with nondiabetic individuals [4, 5]. A hallmark of both types of diabetes is hyperglycemia; however, hyperglycemia may also occur in acute illness in individuals with previously normal glucose tolerance ("stress hyperglycemia"). Irrespective of its cause, considerable evidence exists that hyperglycemia is associated with adverse outcomes [6–9]. Earlier studies demonstrated that control of hyperglycemia is associated with improved outcomes [10–12]; however, some recent studies raised questions about the safety and benefit of blood glucose normalization [13•–16•]. This review article discusses major findings from these recent studies as it impacts inpatient and outpatient management of glycemia.

What is the Rationale for Controlling Hyperglycemia in Diabetic Patients?

Prior studies clearly established a link between hyperglycemia and poor outcomes in diabetic patients [9, 17]. The findings of the DCCT published in 1993 provided direct evidence that the risk of microvascular (retinopathy, nephropathy, and neuropathy) complications in type 1 diabetic patients can be significantly reduced by keeping blood glucose at near-normal levels [12]. An observational follow-up to DCCT (EDIC) published in 2005 later showed a reduction in macrovascular (heart attacks and strokes) risks as well [18]. These findings raised the question of whether normalization of blood glucose in type 2 diabetic patients will produce similar benefits. Some answers to this question came from the UKPDS; this study followed 5102 newly diagnosed type 2 diabetic patients in 23 centers in the United Kingdom for an average of 10 years and showed reduced microvascular complications in patients in which glycemic control was intensified (median hemoglobin A_{1c} [HbA_{1c}] of 7% compared with 7.9%) [1]. However, despite a favorable trend (MI decreased by 16%; P=0.052 for insulin and sulfonylureas vs conventional therapy), the intensive treatment arm of this study did not show a macrovascular benefit, and therefore the role of glycemic control on cardiovascular outcomes and death in type 2 diabetic patients was not clear. Nonetheless, a metformin monotherapy study in overweight patients did find a mortality and MI benefit of improved glycemia (diabetes-related death decreased by 36%, P=0.011; MI decreased by 39%, P=0.01) [19].

Are There Additional Benefits of Intensive Glycemic Control Beyond Microvascular Protection?

In the past 2 years, we have seen the results of the largest and most comprehensive investigations on whether correcting hyperglycemia to near-normal levels produces any cardiovascular benefit in type 2 diabetic patients. The first two reports were both randomized control trials (RCTs): ACCORD and ADVANCE. Both studies were published in the same issue of the *New England Journal of Medicine* in June 2008 [14•, 15•]. The third report, the VADT, was published in the same journal about 6 months later in 2009 [13•].

The ACCORD study was a RCT that randomized 10,251 type 2 diabetic patients with a median glycated HbA_{1c} level of 8.1% to standard (target HbA_{1c} 7.0% to 7.9%) or intensive (target HbA_{1c}<6.0%) therapy. The primary outcome was a composite of nonfatal stroke, nonfatal MI, and death from cardiovascular causes. Stable HbA_{1cs} of 7.5% and 6.4% were achieved within the first year in the standard and intensive arms, respectively [14•]. The study was ended prematurely after a mean of 3.5 years of follow-up, due to 22% higher mortality noted in the intensive therapy arm of the study, primarily related to cardiovascular death. Moreover, the results did not show any significant reduction in a composite of major cardiovascular events, although a 24% decrease in nonfatal MI in the intensive therapy arm was noted compared with the standard therapy.

ADVANCE and VADT like ACCORD randomized patients to standard therapy or intensive glucose control. In the ADVANCE study, 11,140 type 2 diabetic patients were randomized, whereas 1791 were randomized in the VADT study. Patients were followed up for a median of 5 years in ADVANCE and 5.6 years in VADT. Both studies had primary end points that included development of major cardiovascular outcomes following randomization. At the conclusion of the studies, patients in the intensive arms of ADVANCE and VADT studies achieved a mean HbA_{1c} of 6.5% and 6.9%, respectively, compared with an HbA_{1c} of 7.3% and 8.4% in the standard treatment arm. Similar to ACCORD, ADVANCE and VADT showed no significant reduction in major cardiovascular events in the intensive therapy arm when compared with the standard arm of the study. However, consistent with prior findings in UKPDS, the two studies showed significant reduction of microvascular events (21% relative reduction in nephropathy in ADVANCE; decreased progression of albuminuria in VADT) in the intensive therapy arm.

The above studies were highly publicized and raised concern that intensive control of glycemia in type 2 diabetic individuals may not provide any cardiovascular benefit. However, questions have been raised about aspects of the study design that may have limited these studies' ability to detect cardiovascular benefit. For instance, the treatment may not have been of sufficient duration to detect a clinical benefit. Consistent with this hypothesis, in the UKPDS study no macrovascular benefit was noted in the intensive control arm in the first 10 years of follow-up [1]. Nevertheless, post-trial monitoring for an additional 10 years (UKPDS 80) revealed a 15% risk reduction in MI (P=0.01) and 13% reduction in all-cause mortality (P=0.007) in the intensive treatment group [20••].

Another possibility is that the sample size was insufficient to detect a difference in clinical outcomes. Some insight on the role of sample size can be revealed from a recent metal-analysis of the four RCTs described above (ACCORD, ADVANCE, VADT, and UKPDS) [21•]. This meta-analysis included a total of 27,049 participants and 2370 vascular events. Contrary to the findings in the RCTs, it showed intensive glycemic control reduced the risk of

major cardiovascular event by 9% primarily through decreased risk of MIs (15%; hazard ratio, 0.85; 95 CI, 0.76–0.94). However, intensive glycemic control had no significant effect on cardiovascular death or all-cause mortality. Similar results were also observed in two other meta-analyses that included a large number of participants [22, 23].

Therefore, taken together, these results suggest intensive glycemic control does reduce the risk of macrovascular diseases in type 2 diabetic patients but the recent RCTs (ACCORD, ADVANCE, and VADT) may not have been of sufficient duration and power to detect this clinical benefit. Another potential interpretation, given the UKPDS 80 data, is that cardiovascular benefit simply comes much later after early glycemic intervention.

Is There a Downside to Intensive Glycemic Control?

Intensified glycemic control, although beneficial, may be associated with adverse effects. A recent meta-analysis of studies (33,040 participants) looking at the effect of intensive glycemic control on cardiovascular outcomes and death in patients with type 2 diabetic patients showed participants in the intensive treatment group of the studies were, on average, 2.5 kg heavier than those in the standard treatment at study end. Furthermore, almost twice as many patients in the intensive treatment arm developed severe hypoglycemia when compared to those with standard treatment (2.3% vs 1.2%) [22]. This is of concern because increased incidence of severe hypoglycemia appears to correlate with increased mortality [14•, 23]. Nevertheless, one can speculate that the intensive arm of these studies may have shown mortality benefit if achieved without increased incidence of severe hypoglycemia. Therefore, intensive glycemic control should be approached with caution to avoid hypoglycemia. Antiglycemic regimens that can achieve glycemic control similar to those in the recent RCTs (ACCORD, ADVANCE, UKPDS) without weight gain or increasing the risk of hypoglycemia may help achieve the clinical benefits associated with intensive control without the associated adverse effects.

Should Glycemic Control in Type 2 Diabetic Patients Be Individualized?

Although intensive glycemic control is beneficial, it also comes with potential adverse effects. Therefore, achieving maximal clinical benefits while minimizing adverse effects would be ideal. It is possible that certain patient characteristics will predict whether a patient is more or less likely to benefit from a treatment strategy. For instance, it may be possible to identify patients who are more or less likely to develop severe hypoglycemia if treated with intensive glycemic regimen. Moreover, there may be underlying characteristics of patients that make them more or less likely to benefit from intensive treatment. A profile is beginning to emerge from recent studies suggesting that certain characteristics of individuals (eg, body mass index, duration of diabetes, and prior history of atherosclerosis or severity of atherosclerosis) may influence whether they benefit from intensive glycemic treatment.

Reaven et al. [24••] investigated whether baseline coronary atherosclerosis, assessed by coronary artery calcium (CAC), influenced cardiovascular outcome following intensive glycemic treatment in the VADT study participants. Their results showed that among patients treated intensively, event rates were lower (4/1000 person-years) in those with CAC $\leq$ 100 when compared to those with CAC greater than 100 (39/1000 person-years). Similarly, subgroup analysis in the meta-analysis by Turnbull et al. [21•] showed patients with no history of macrovascular disease prior to randomization were more likely to benefit from intensive glycemic treatment, whereas those with a prior history of macrovascular disease yielded no benefit (test of homogeneity, P=0.04). This suggests that presence and extent of coronary artery disease in patients with type 2 diabetes may determine benefit from aggressive glycemic control. Moreover, other factors (eg, body mass index and duration of diabetes, which may relate to atherosclerotic burden) have also been implicated as factors likely to predict benefit from intensive glycemic control [23].

Consequently, a better understanding of which patients will benefit from intensive glycemic therapy may afford the clinician an opportunity to provide individualized care and should be the focus of further studies.

What is New in the Management of Hyperglycemia in the Acutely Ill Patient?

Hyperglycemia in the inpatient setting is typically a consequence of stress-induced hyperglycemia and diagnosed or undiagnosed diabetes. Similar to chronic hyperglycemia in the outpatient setting, hyperglycemia in hospitalized patients is associated with poor outcomes [25, 26]. Prior studies of glycemic control in hospitalized patients suggested correcting hyperglycemia improved outcomes [11, 27, 28]. The landmark study by Van den Berghe et al. [11] was among the first large RCT to evaluate the benefits of normalizing blood glucose in critically ill patients. Patients in this study were randomized to tight

control (fasting blood glucose goal, 80–110 mg/dL) or usual care (treatment only when blood glucose exceeded 215 mg/dL). Tight glycemic control in this study was associated with a 34% reduction in mortality. It was in the setting of these results and similar findings in other studies [28, 29] that the American College of Endocrinology, the American Association of Clinical Endocrinology (AACE), and the American Diabetes Association (ADA) developed treatment recommendations for inpatient hyperglycemia that favored tight glycemic control [30].

Since the initial studies by Van den Berghe et al. [11], other studies investigating the effect of tight glycemic control in hospitalized patients yielded conflicting results [16•, 31–33]. Two of these studies were recent RCTs designed to assess the effect of intensive insulin therapy in critically ill patients with mortality as a primary end point [16•, 32]. The first study, VISEP [32], was a multicenter trial with 537 participants designed to evaluate the effect of intensive insulin therapy as well as two choices of fluid resuscitations. The target blood glucose level in the intensive arm was 79 to 110 mg/dL and 180 to 200 mg/dL in the standard treatment arm. The study was stopped prematurely in part due to a high rate of hypoglycemia in those randomized to intensive control (12.1%) compared with standard treatment (2.1%, $P<0.001$).

The second study, NICE-SUGAR [16•], was a large multicenter RCT in which 6104 patients underwent randomization to intensive control (3054) or conventional therapy (3050). The target blood glucose level in the intensive arm of the study was 81 to 108 mg/dL, whereas that of the conventional therapy was 180 mg/dL or less. Control of hyperglycemia was achieved in both groups by intravenous infusion of insulin. In the conventional group, insulin infusion was initiated once the blood glucose level passed 180 mg/dL and was discontinued once it dropped below 144 mg/dL. The primary end point was death from any cause within 90 days following randomization. Contrary to expectations, the result showed mortality increased from 24.9% in conventional arm to 27.5% ($P=0.02$) in the intensive arm of the study, although not at 28 days. Furthermore, patients in the intensive arm were 13-fold more likely to have severe hypoglycemia when compared with the conventional arm (6.8% vs 0.5%; $P<0.001$), but this was not directly linked to death.

Further complicating the picture, a recent meta-analysis of published RCTs investigating the benefit of intensive glycemic control (including NICE-SUGAR) suggest intensive treatment does provide a mortality benefit to patients in the surgical, but not in the medical, intensive care unit [34, 35•].

Taken together, these results suggest that although treating hyperglycemia in the critically ill patient does provide mortality benefit, a less stringent glycemic target similar to that of patients in the conventional arm of the NICE-SUGAR trial may be more appropriate.

Taking into account the findings of these and other studies, the ADA and AACE updated their consensus statement on impatient glycemic management [36••]. Their guideline suggested initiation of insulin infusion in the critically ill patients at a blood glucose level no higher than 180 mg/dL, with a goal of maintaining levels between 140 to 180 mg/dL. One can certainly ask whether it is the target goal of glycemia that is the issue in such studies, or might it alternatively be the insulin adjustment algorithm to achieve targeted glycemic control.

Unlike the situation in critically ill patients, no RCTs exist to guide recommendations on glucose targets in hospitalized patients who are not critically ill and thus represent an area requiring future investigation. Nevertheless, the current ADA/AACE recommendations for non-critically ill hospitalized patients is to target a premeal blood glucose level of less than 140 mg/dL and random blood glucose levels of less than 180 mg/dL.

Conclusions

Most clinicians would agree that hyperglycemia needs to be treated; however, the glycemic target continues to be a subject of debate. I believe that the newly recommended glycemic targets of near 140 mg/dL in hospitalized patients [36••] will likely yield improved outcomes, and should be the subject of future studies. Work on improved algorithms to decrease variability and hypoglycemia risk may more safely permit targeted glucose control.

In type 2 diabetic patients, antiglycemic strategies that can achieve normal or near-normal glycemia without increased risk of hypoglycemia should be preferred, especially early in the course of the disease. Such strategies may include drug regimens that combine well-established medications such as metformin with the newer agents (eg, dipeptidyl peptidase-4 inhibitor and glucagon-like peptide 1 agonist). Moreover, clinicians need to move toward individualized care that will tailor glycemic targets and antiglycemic agents based on the individual characteristics of the patients.

As we continue to seek a better understanding of the things we do not fully understand, we must not fail to execute those treatments that we already know reduce morbidity and mortality in chronic and acute hyperglycemic states, including aggressive blood pressure and lipid control. The role of lifestyle modification, controlling hypertension, and correcting unfavorable lipid profiles cannot be overstated.

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