

Should patients with type 2 diabetes focus on glycemic control to reduce their cardiovascular risk?

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KEY WORDS

diabetes complications, diabetes treatment, evidence-based medicine, glycemic control, randomized trials

ABSTRACT

3 very large randomized trials have recently announced their results, massively expanding the evidence base for the efficacy and safety of intensive glycemic control in patients with type 2 diabetes. Taken together, these trials indicate that tight glycemic control is potentially harmful (one of the trials was stopped earlier than planned because of an increased risk of death in patients assigned to the intensive glycemic control arm) while offering potential benefits of unclear importance to patients. In this commentary, we review these trials, their methods, results, and implications for practice. We finish by formulating a recommended approach to the contemporary evidence-based management of patients with type 2 diabetes.

Context – diabetes in the new millennium Clinicians who care for patients with type 2 diabetes have long recognized their role in reducing their patients' risk of diabetes-related complications. When focusing on glycemic control, clinicians have also recognized that their actions had to balance the need for glycemic control against the increased burden of treatment (use and side effects), self-monitoring, and hypoglycemia. These were the goals of diabetes treatment.

To guide decision making, clinicians had a large number of small randomized trials measuring, largely, surrogate outcomes (e.g., glycated hemoglobin – HbA_{1c}) that were assumed to be related to these goals of diabetes treatment. In 2003, we found that only 20% of diabetes trials measured and reported any outcome that could possibly matter to patients.¹ By this we mean outcomes that, if changed by treatment, would make the treatment desirable to patients.² These so-called patient important outcomes reflect the effect of therapy of patients' ability to live longer, feel better, and live their lives unhindered by complications of the disease or the treatment.

Short of measuring patient-important outcomes directly, diabetes trials forced evidence-based clinicians to assume and imagine

a relationship between the outcomes measured and patient-important outcomes.³ This situation seems immutable given our recent study of the diabetes pipeline.⁴ In this study of over 400 registered trials, many not yet completed, only 18% of these diabetes trials will measure patient important outcomes as their primary endpoint, and 45% will measure these as secondary endpoints. Given what we know about reporting bias preferentially affecting nonsignificant outcomes and the small size of these trials, many of these patient-important outcomes will be measured but never reported.⁵

Why call for direct measurement of patient important outcomes rather than rely on a surrogate marker as HbA_{1c}? In fact, HbA_{1c} has been strongly associated with outcomes in the Diabetes Control and Complications Trial (DCCT) in patients with type 1 diabetes receiving insulin and in the epidemiological analyses of the United Kingdom Prospective Diabetes Study (UKPDS), for instance.^{6,7} Until recently, we were making the point, with indirect evidence at best, that this surrogate marker was related with a great degree of uncertainty to patient important outcomes in the context of patients with type 2 diabetes in general and in particular to those treated with therapies other than insulin.³ To this effect,

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TABLE 1 Study characteristics

	ADVANCE	ACCORD
Patients	11,140 type 2 diabetes (mean duration 8 years; mean HbA _{1c} 7.5%), 55 or older (mean age 66), and history of one macro (32%) or microvascular complication (10%) or one additional risk factor for cardiovascular disease, and demonstrated adherence to treatment in a run in period. At end of study, 55% received acetylsalicylic acid, 46% statins, and 88% any antihypertensive.	10,521 Type 2 diabetes with HbA _{1c} ≥7.5% who had coronary artery disease and were 40–79 years old or had cardiovascular risk factors and were 55–79 years old (mean age 62, diabetes duration 10 years, HbA _{1c} 8.3%). Severely obese participants, those with history of severe hypoglycemia or kidney impairment were excluded.
Interventions	Gliclazide (90% at end of study) plus recommended protocol (dose increase in gliclazide, addition of metformin (74%), glitazone (17%), acarbose (19%), insulin (40%) with aim of HbA _{1c} ≤6.5%. After the first 5 visits in the first 3 months, these patients were seen every 3 months. This group had a lower systolic blood pressure throughout the trial compared to the control group.	Intensive glycemic management with target HbA _{1c} <6%. Any agents allowed (metformin 95%, secretagogue 87%, glitazone 91%, acarbose 23%, exenatide 12%, insulin 77%). Visits monthly in the first 4 months, then every 2 months with monthly interim phone calls.
Control	Switched off gliclazide to another sulfonylurea, HbA _{1c} goal as per local practice guidelines. After the first 3 visits in the first 6 months, these patients were seen every 6 months.	Standard therapy with target HbA _{1c} 7.0–7.9%. Any agents allowed (metformin 87%, secretagogue 74%, glitazone 58%, acarbose 5%, exenatide 4%, insulin 55%). Visits every 4 months.
Outcomes measured	Composite of macro- and microvascular complications and each of the components (death from cardiovascular causes, nonfatal myocardial infarction or stroke; new or worsening nephropathy (itself a composite of development of macroalbuminuria, doubling of creatinine, need for renal replacement therapy, or death due to renal disease), or retinopathy (development of proliferative retinopathy, macular edema, diabetes related blindness, or use of retinal photocoagulation). Other outcomes included hospitalizations, hypoglycemia.	Composite of macrovascular complications (death from cardiovascular causes, nonfatal myocardial infarction or stroke), death from any cause, microvascular complications, hypoglycemia, and quality of life.

Abbreviations: ACCORD – Action to Control Cardiovascular Risk in Diabetes, ADVANCE – Action in Diabetes and Vascular Disease, HbA_{1c} – glycated hemoglobin

we were citing the apparent negative effects of glitazones and glitazars despite their satisfactory effects on HbA_{1c}.^{8,9} In the last few weeks our concerns have been largely confirmed by the publication of the largest body of evidence for patients with type 2 diabetes.

The largest body of evidence for type 2 diabetes care Epidemiological studies, some borne out of large randomized trials, e.g., UKPDS trial, had found a linear relationship between HbA_{1c}, a measure of glycemic control, and cardiovascular risk.⁷ This relationship extended well below the usual targets of glycemic control into the normal range. But large randomized trials in patients with diabetes (University Diabetes Group, UKPDS) had largely failed to show an effect of glycemic control on cardiovascular complications (metformin in overweight patients seemed to reduce cardiovascular risk in a manner independent of HbA_{1c}, a finding that has not been tested in other studies).^{10,11} Furthermore the Steno trial had shown that comprehensive diabetes care had very positive impact on patient outcomes.^{12,13}

This led to the launch of at least three very large randomized trials to assess whether tight glycemic control reduced cardiovascular complications: the Veterans Affairs Diabetes Trial (VADT), the Action in Diabetes and Vascular Disease (ADVANCE) trial, and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. With different designs and different populations,

each of these trials sought to determine if glycemic control to a level of HbA_{1c} of 6.0–6.5% reduced cardiovascular risk while actively managing traditional cardiovascular risk factors such as dyslipidemia and hypertension in patients with type 2 diabetes.

Recently, the findings of all three trials have been reported, but only one in full. The VADT was presented at the Scientific Meeting of the American Diabetes Association, as were the other trials, but the results have not been published in print. The ACCORD trial was stopped earlier than planned because of harm and the results of the glycemic arm and its effect on mortality were published in the New England Journal of Medicine.¹⁴ In the same issue, the ADVANCE trial published in full the results of its glycemic control trial.¹⁵ A complete account of these three studies would be necessary to draw definitive conclusions as to what to do in practice, but some inferences can be drawn at this point from this very large body of new evidence linking glycemic control, HbA_{1c}, and patient-important outcomes.

Evidence – an explosion of randomized trials measuring patient important outcomes TABLE 1 describes who was enrolled in these trials, what were the treatment and comparisons, and what the outcomes measured. TABLE 2 describes the design limitations of each of these studies, and their results to the extent that these studies have been published to date. In addition to these trials, and

TABLE 2 Design features and results

	ADVANCE	ACCORD
Design limitations	Investigators, patients, and clinicians were aware of treatment assignment. Outcome adjudicators were blind to assignment.	Investigators, patients, and clinicians were aware of treatment assignment. Outcome adjudicators were blind to assignment.
Other considerations	While for many of the events of interest there were more than 300 events, the effect on patient important outcomes lacked precision (i.e., confidence interval was too wide).	Trial was stopped early because of an increase in all cause mortality. Most outcomes were imprecisely measured but death and myocardial infarction.
Results reported in print	Follow up 5 years (loss 0.1%). HbA _{1c} throughout study was 6.5 vs. 7.3%. Death from any cause: 8.9 vs. 9.6%, HR 0.93 (0.83–1.06), major macrovascular events: 10 vs. 10.6%, HR 0.94 (0.84–1.06), development of macroalbuminuria HR 0.70 (0.57–0.85), doubling of creatinine RR 1.15 (0.82–1.63), renal replacement therapy or death from renal causes RR 0.64 (0.38–1.08). Also hospitalizations HR 1.07 (1.01–1.13), severe hypoglycemia HR 1.86 (1.42–2.40). There were no significant treatment subgroup interactions.	Follow up 3.5 years (loss 0.5%). HbA _{1c} throughout study was 6.4 vs. 7.5%. Death from any cause: 5 vs. 4%, HR 1.22 (1.01–1.46), major macrovascular events: 6.9 vs. 7.2%, HR 0.90 (0.78–1.04). Death from cardiovascular causes 2.6 vs. 1.8%, HR 1.35 (1.04–1.76), nonfatal myocardial infarction 3.6 vs. 4.6%, HR 0.76 (0.62–0.92), nonfatal stroke 1.3 vs. 1.2, HR 1.06 (0.75–1.50). Severe hypoglycemia 16.2% vs. 5.1% (<i>p</i> < 0.001). There were some borderline subgroup interactions suggesting benefit in patients with lower HbA _{1c} at baseline and no history of cardiovascular events at baseline (mostly from the prevention of nonfatal myocardial infarction; no interactions for all cause mortality were significant). Other outcomes were not reported at the time of writing this report.

Abbreviations: HR – hazard ratio, RR – relative risk, others – see [TABLE 1](#)

drawing mostly from press accounts, the VADT enrolled 1791 patients (mean age 60, mean HbA_{1c} 9.5%) followed for 6 years. Patients in the intensive arm had HbA_{1c} of 6.9% vs. 8.4% in the less intense arm. Insulin was used in 90% of patients in the intensive arm vs. 74% of patients in the less intense arm. Reportedly there were no significant differences in macrovascular events between the groups; the results for microvascular events were not presented at the meeting.

As these tables describe, these trials represent the largest body of evidence linking tight glycemic control as practiced today and the associated risks and benefits. In summary, these very well conducted trials indicate that the impact of intensive or tight glycemic control in the average patients with type 2 diabetes is largely harmful: increased risk of hypoglycemia and severe hypoglycemia, increased risk of hospitalizations, and in one study, stopped early for this finding, increased risk of death. These downsides could be justified if they were associated with important benefits: yet benefits appear limited to the control of other surrogates, such as macroalbuminuria, a surrogate of renal outcomes. Meta-analyses of these three trials, when fully reported, may allow for the identification of other important treatment effects that, because of their limited occurrence in these trials, remain imprecisely defined.

The implications The spin has already begun, with headlines emphasizing the effect of therapy on the composite endpoints (all diabetes related complications), indicating that perhaps the patients enrolled had too much cardiovascular burden at the outset of the trial to benefit, that treatments were too aggressive too fast, and ignoring

the potential harmful effects – including mortality – attributing these to either a single agent (rosiglitazone), to weight gain, or to chance.

Composite endpoints that include components of varying importance to patients are difficult to interpret and can be misleading.¹⁶ The ADVANCE trial clearly illustrates this danger ([TABLE 2](#)). While the key effect appears to have been on macroalbuminuria, the composite suggests an effect on “new or worsening renal outcomes”, which in turn affects the composite “microvascular complications” which in turn affects the composite endpoint “macrovascular and microvascular complications”. This means that the effect on macroalbuminuria, which constitutes 1.2 of the 1.9% risk difference reported for major macro and microvascular endpoints, gets sold as “prevention of all diabetes related complications by 10%”.¹⁶ We have published a users’ guide to the interpretation of composite endpoints that readers could use to learn how to interpret these findings without being misled.¹⁷

Every study result can be true or erroneous, the latter either due to chance or bias. To date, and with the exception of the Kumamoto trial in Japanese patients treated a-la-DCCT,¹⁸ there has not been any large diabetes trial measuring patient important outcomes in patients with type 2 diabetes that has convincingly shown that these patients benefit from tight glycemic control. This contrasts with the stronger data linking blood pressure control and statin use in these patients. The mortality data in the ACCORD trial could represent a chance finding exacerbated by the decision of the Data Monitoring Committee and the NIH (the government sponsor of the trial) to stop the trial early; we have previously reported that stopping trials early could overestimate the impact of treatment on the monitored outcome, in this case, all-cause

mortality.¹⁹ Given the apparent high quality of the reported trials, bias against the treatments remains an unlikely possibility.

Some are speculating that these trials enrolled patients with too much cardiovascular burden at baseline who may not benefit given that the intervention arrived too late. These calls for even earlier treatment resemble the arguments presented to insist on estrogen administration in postmenopausal women after the publication of HERS and WHI. As in that case, these calls create an important risk: that patients will be exposed even for longer periods to treatments that today appear harmful with the expectation of benefit without proof. Even if this were to be proven true, earlier aggressive treatment does not make sense as a practice today outside of clinical trials and should be considered experimental.

The findings of these trials could be attributed to the way in which we try to lower blood glucose: perhaps current agents, through unintended effects, favorably affect certain mechanisms while unfavorably affecting others that link diabetes with an adverse prognosis. Or, perhaps, we have not understood well the pathway linking glycemia with diabetes complications. Or, perhaps, current pathways are poorly addressed by existing medications. Or perhaps, hyperglycemia in patients with type 2 diabetes is not the proper target of therapy. More research in the basic and integrated physiology laboratories and in clinical trials measuring patient-important outcomes seems necessary to move forward.

What should we do now with patients with type 2 diabetes? In a recent study, Huang et al. suggested that for some patients with type 2 diabetes, the antihyperglycemic agents imposed a greater burden on their quality of life than the complications of diabetes.²⁰ The recently published trials confirm patients' impressions of net harm associated with treatment use with the goal of tight glycemic control. What to do? Should clinicians and patients follow existing clinical practice guidelines or standards of medical care in diabetes? What to do?

This is a very difficult question that involves considering what we know, the individual circumstances of each patient with type 2 diabetes, and their values and preferences for life and health-care. To maximize patients' longevity and quality of life, my treatment approach starts by first focusing on cardiovascular risk reduction, then on self-care and well-being, and lastly on glycemic control. I recognize this approach will deviate from current guidelines and quality-of-care measures in some environments, and my hope is that some of the proposed approaches will make both guidelines and quality-of-care measures more consistent with the evidence base and with the values and preferences of our patients with type 2 diabetes. Recent developments in guideline methodology may enable this shift.²¹

I start by considering patients' cardiovascular risk estimated through one of several available estimators. For example, we have published a pen-and-paper form that can be used in the office and is based on the UKPDS trial data.^{22,23} This calculator can categorize patients by coronary risk. Then, I would suggest to patients a graded approach, such that high-risk patients get exposed to more aggressive cardiovascular risk factor control while low risk patients get less aggressive treatment. For higher risk patients, statins at a fixed dose (that used in clinical trials) and not seeking a low-density lipoprotein cholesterol goal²⁴ is often a good start, along with low-dose aspirin. If these patients also have hypertension, a regimen based on thiazides, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers appears beneficial (with tighter control in patients at highest risk of renal and cerebrovascular adverse outcomes) and represent often a cost-saving intervention.²⁵ Lower risk patients would receive some of these at a lower intensity, if necessary.

Then, I would focus my efforts in making sure these patients are not overwhelmed by their condition. I also reduce the need for self-monitoring of glucose^{26–28} and instead emphasize self-care with particular attention to adherence to healthy lifestyle (including smoking cessation), and adequate preventive care (eye and foot care, vaccinations, age-appropriate screening). I also assess for psychological wellbeing, and monitor the burden of the pharmacological approach prescribed. In all, my attitude is to reduce the "healthcare footprint" the patient endures given the benefits expected from these maneuvers.

What about glycemic control? My views here are of an endocrinologist working in secondary care; thus this approach may not apply to primary care. I offer my patients to control their glycemia to a level that best balances the burden of medication, including the risk of hypoglycemia, with their benefit in reducing hyperglycemia symptoms. Some of these symptoms may appear with glycemia greater than 10 mmol/l. Thus, keeping HbA_{1c} levels in the 7%–7.5% range appears reasonable and practicable enough for most of my patients. This level can be adjusted upwards when the burden of treatment, side effects, or the patient context suggest.

How to best achieve this level of glycemic control? Our team has been working on a series of diabetes cards that share with patients the effect of treatment on HbA_{1c} while also indicating the burden of treatment in terms of weight change, need for self-monitoring, medication intake, hypoglycemia, and side effects (readers can see these cards at http://kerunit.e-bm.org/upload/Diabets_Choice_Cards_v2.pdf; a clinical trial to evaluate their impact is underway). To the extent that these cards or other strategies to enable patient-centered conversations with patients are effective, these should result in treatment regimens that are consistent with both the evidence and the values and preferences of the informed patient.

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