Journal of Diabetes

doi: 10.1111/1753-0407.12668 Journal of Diabetes •• (2018), ••–••

EDITORIAL

# American College of Physicians diabetes guidelines attempt to turn back the clock, conflating good HbA1c with hypoglycemia

The Clinical Guidelines Committee of the American College of Physicians (ACP) recently released the following guidance statements:[1]

> Clinicians should aim to achieve an HbA1c level between 7% and 8% in most patients with type 2 diabetes

and

> Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA1c levels less than 6.5%.

These guidelines are not only regressive, going back to the care of patients with diabetes that was current 10–15 years ago, but also misleading. The authors term the guidelines "evidence-based", yet limit their evidence to older studies, choosing to ignore the newer studies and therapeutics of the past decade. They also ignore widely available and accepted data proving that the lower the **HbA1c**, the fewer complications people have.

## Why do we consider this to be erroneous, and how should recommendations to improve glycemic control be explained in light of up-to-date approaches?

The ACP group misinterprets a group of cardiovascular outcome studies performed and reported a decade ago in which approaches to glucose lowering caused excess hypoglycemia and led to equivocal evidence of glycemic benefit. The ACP highlights the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial, in which 257 deaths occurred over 3.5 years with an achieved **HbA1c** of 6.4% among 5128 intensively treated high cardiovascular risk patients, compared with 203 deaths with an achieved **HbA1c** of 7.5% among 5123 patients having "standard treatment".[2] Most importantly, the ACP confuses the benefits of a lower **HbA1c** goal with the adverse effect of treatments that cause hypoglycemia.

Hypoglycemia emerged as a much stronger predictor of adverse outcome in ACCORD, associated with more than doubling of mortality in the intensively treated group and with more than tripling in the standard treatment group.[3] Furthermore, it was not the lower HbA1c target that predicted a worse outcome. Rather, those intensively treated people whose on-trial HbA1c levels were lower actually had a reduction in mortality compared with the standard control group, whereas those with higher on-trial HbA1c had a higher mortality rate. In fact, at the time the study was stopped due to the excess mortality in the intensively managed group, there was already a 10.5% reduction in non-fatal myocardial infarction (MI).[4] The increase in mortality was only seen in the subset of people with higher HbA1c levels at baseline.[5] The approach taken to intensive treatment in that trial involved more use of bolus insulin, thiazolidinediones, and repaglinide, with more than triple the likelihood of use of three, four, or five classes of glucose-lowering medicines with insulin,[6] an approach now recognized to be particularly likely to increase hypoglycemia rates.

An important caveat is that HbA1c only partially reflects mean glucose levels.[7] A recent study using continuous glucose monitoring suggested that approximately half the variance in HbA1c is not explained by mean glucose.[8] Chronic kidney disease and other states associated with anemia are conditions in which low HbA1c often is discordant with glucose levels.[9] The important implication: rather than being a marker of hypoglycemia risk, low HbA1c may track with a variety of illnesses in which adverse cardiovascular outcome and mortality occur at such increased frequency as to obscure the beneficial effect of better glycemic control.

Progression of diabetic retinopathy, surely a significant complication, was reduced by more than half among participants in ACCORD undergoing intensive rather than standard glycemic treatment,[10] and allocation to intensive rather than standard glycemic treatment in ACCORD significantly reduced MI, coronary

revascularization, and unstable angina, an effect explained by the reduction in HbA1c.[11] In the UK Prospective Diabetes Study, the mean HbA1c of 7.9% in the control group (a level that would surely be typical if the ACP guidelines were accepted) led to a 46% rate of diabetes-related endpoints over the course of the study, 12% higher than the 41% rate among those randomized to the intensive intervention with mean HbA1c of 7.0%, with 25%–30% reductions in vision loss and need for laser photocoagulation, a 33% reduction in the development of microalbuminuria, and a 16% reduction in MI,[12] with subsequent 10-year follow-up revealing the same reduction.[13] In the Action in Diabetes and Vascular disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, every 1% increase in HbA1c levels above 7.0% for macrovascular events and death, and above 6.5% for microvascular events, was associated with a 38% higher risk of a macrovascular event, a 40% higher risk of a microvascular event, and a 38% higher risk of death, with all effects highly significant.[14]

We have argued elsewhere that avoiding hypoglycemia is critical[15] and reducing treatment certainly is appropriate in people with diabetes experiencing significant low glucose levels. However, conflating low HbA1c with hypoglycemia constitutes a conceptual and logical error. We presume that the notions espoused by the ACP group are based on this misunderstanding, but would urge that such be avoided. The use of therapies such as the thiazolidinediones, sodium–glucose cotransporter 2 inhibitors, and glucagon-like peptide-1 receptor agonists associated with cardiovascular benefit over and above that due to glycemic control, and not intrinsically causing hypoglycemia, represents important and growing understanding of correct approaches to the treatment of type 2 diabetes (T2D). We look forward to helping the ACP to recognize such approaches in their ongoing efforts to improve outcomes of treatment of people with T2D, and we would emphasize that there is potential for harm from establishing goals well above glycemic levels that have been shown to reduce diabetes complications.

## Should we "de-intensify" treatment for those with HbA1c below 6.5%?

This is a particularly bizarre suggestion in a set of "evidence-based recommendations" because there is no evidence, no controlled study, and no "real-life big data" that "de-intensified" treatment improves outcome. The only time that de-intensification improves the patient's condition is when drugs are stopped for hypoglycemia and/or other adverse effects. Why would deliberate measures be taken to worsen the level of glycemia of a person with T2D showing excellent glycemic control?

Collaboration of all groups working to improve diabetes outcomes should be our goal, and we should endeavor to optimally individualize care in a manner not exposing people with diabetes to under-treatment, developing globally acceptable guidelines that will address specific situations and deficiencies of care a variety of populations, including those of both developed and developing countries.

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Zachary Bloomgarden
*Editor-in-Chief*
*Icahn School of Medicine at Mount Sinai*
*zbloom@gmail.com*



 