Utility of Glycated Hemoglobin as Prognostic Marker in Nondiabetic Patients After Myocardial Infarction

To interpret the utility of HbA1c as a long-term prognostic risk factor after acute MI, it is important to note several
potential limitations of this study and current challenges in the treatment and prevention of cardiovascular disease in patients with prediabetes and newly diagnosed diabetes mellitus.

Although the authors adjust for potential confounders that may influence long-term risk, it is possible that residual confounding by medication use and/or other HbA1c-associated cardiometabolic risk factors (such as low high-density lipoprotein cholesterol, central adiposity, more severe hypertension, increased inflammatory markers) may persist. Additionally, although HbA1c has a strong correlation with average blood glucose concentrations over the previous 2 to 3 months, factors other than glycemic control may influence HbA1c levels. These potential confounding factors include disorders of red blood cell turnover, renal disease, ethnic differences, and potentially genetic factors. Finally, the use of quartiles for risk assessment may limit the ability to detect possible increased mortality at very low HbA1c levels, as reported in the Atherosclerosis Risk in Communities (ARIC) cohort.

For many patients, the acute MI hospitalization represents a period in which previously unrecognized diabetes mellitus may be initially diagnosed. Given improvements in laboratory standardization, the American Diabetes Association has recently endorsed the use of HbA1c as a diagnostic test for diabetes mellitus (HbA1c level of ≥6.5%) in addition to the traditional criteria based on fasting plasma glucose or oral glucose tolerance testing. Hemoglobin A1c has several advantages, including greater convenience, because fasting is not required, and as a long-term marker of glycemic control, it is less influenced than plasma glucose by acute stress and illness. Indeed, in the study by Timmer et al., ~5% of patients met the HbA1c criteria for newly diagnosed diabetes mellitus, and this group may represent a particularly high-risk population that has not been recognized or treated. One important caveat to note is that, although HbA1c is a specific marker for the presence of diabetes mellitus, it appears to have lower sensitivity for the diagnosis of diabetes mellitus than criteria based on oral glucose tolerance testing. Thus, sole reliance on HbA1c to diagnose diabetes mellitus may lead to an underestimate of the true burden of disease and reduced subsequent treatment. In a prior study of patients without previously recognized diabetes mellitus who underwent oral glucose tolerance testing early after MI, 31% met the diagnostic criteria for diabetes mellitus, a proportion that remained relatively constant when the glucose tolerance test was repeated at 3 months.

Despite these limitations of the study, the authors are successful at establishing HbA1c as a robust marker of increased risk after acute MI in patients without a history of diabetes mellitus. The quandary that faces clinicians is, what now? How can the increased risk be mitigated? What additional therapeutic strategies should be implemented after MI? Clearly, it is imperative that aggressive measures of secondary prevention (such as antplatelet therapy, aggressive lipid control, blood pressure control, lifestyle modification, and cardiac rehabilitation) be implemented in all survivors of acute MI, but the best therapeutic strategy to specifically lower the HbA1c-associated residual mortality risk remains uncertain.

Recent clinical trials targeting more intensive HbA1c levels in patients with established type 2 diabetes mellitus at high cardiovascular risk have demonstrated that intensive glycemic strategies, although effective at reducing HbA1c levels and possibly reducing the rates of nonfatal MI, have not reduced cardiovascular mortality or total mortality. It is possible that intensive glycemic control instituted earlier in the disease process, such as those with newly diagnosed diabetes mellitus, may result in improved outcomes. The long-term follow-up of the UK Prospective Diabetes Study (UKPDS), a trial that initiated more intensive glycemic treatment in patients with newly diagnosed diabetes mellitus (either sulfonylurea or insulin or, in overweight patients, metformin), provides some support that early, more intensive intervention may reduce microvascular disease, MI, and death. Whether these results of more intensive, early glycemic therapy in the relatively low-cardiovascular-risk patients of UKPDS (only 2% had macrovascular diseases) extend to the higher-risk population of post-MI survivors with newly diagnosed diabetes mellitus is not known and warrants further study.

Most patients with newly diagnosed type 2 diabetes mellitus will be started on oral glycemic therapy, in addition to lifestyle modification. Metformin has been recommended as the initial pharmacological therapy in the absence of specific contraindications. Data from the UKPDS demonstrating a reduction in macrovascular events with metformin provide strong support for this recommendation in patients with cardiovascular disease. Beyond metformin, decisions about additional glycemic medications become more difficult in the post-MI patient. Sulfonylurea and insulin therapy are associated with hypoglycemia and weight gain. Thiazolidinediones are associated with volume retention and increased rates of heart failure, a complication particularly relevant after MI. Incretin-based therapies (glucagon-like peptide-1 agonists and dipeptidyl peptidase-IV inhibitors) have less risk of hypoglycemia and less weight gain, but outcome data on cardiovascular safety and efficacy are yet to be completed.

What about the ~30% to 40% of patients with prediabetes (defined by the American Diabetes Association as a HbA1c of 5.7% to 6.4%) who presented with an acute MI in this study? How can their risk of future cardiovascular complications be reduced? It is clear from the 10-year follow-up of the Diabetes Prevention Program (DPP) that lifestyle modification and, to a lesser degree, metformin, substantially reduce the development of diabetes mellitus compared with placebo (10-year diabetes mellitus incidence reductions of 34% and 18%, respectively). Ideally, these reductions will translate into reductions in both microvascular and macrovascular events, but further follow-up of the DPP is necessary to confirm potential long-term benefits. Other studies in prediabetic patients have demonstrated that certain glycemic agents may also reduce the incidence of diabetes mellitus, but these studies have had limited power to detect differences in cardiovascular outcomes. In addition, potential adverse effects of these glycemic therapies may alter the long-term cardiovascular risk-to-benefit ratio in patients with prediabe-
tes who have sustained an MI. For example, in patients with impaired glucose tolerance, pioglitazone reduced incident diabetes mellitus by 72% compared with placebo, but was also associated with more weight gain and edema.19

In conclusion, the study by Timmer et al8 adds to the growing body of literature that HbA1c is an important risk marker in the absence of a history of diabetes mellitus in survivors of acute MI. There remain many unanswered questions and challenges concerning the pathophysiological mechanisms contributing to these adverse outcomes and therapeutic strategies to lower the risk of this population. Ongoing and future clinical trials should shed much-needed light on this clinical quandary.

Disclosures
Dr Aguilar has received consulting fees from Amylin and Sanofi-Aventis. Dr Aguilar is a research investigator in the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial and Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL) trial and is supported by a National Heart, Lung, and Blood Institute Mentored Career Development award (5K01-HL092585-03).

References
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