Editorial

Glycated Hemoglobin as a Prognostic Risk Marker in Nondiabetic Patients After Acute Myocardial Infarction

What Now?

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The pandemic of insulin resistance and diabetes mellitus continues to increase and remains a tremendous threat to global health. It is estimated that ≈11% of US adults have diabetes mellitus and another 35% have prediabetes based on elevated fasting glucose or glycohemoglobin (HbA1c) levels.1 Despite improvements in the management of cardiovascular risk factors, diabetes mellitus continues to confer an ≈2-fold increased risk for the development of myriad cardiovascular complications, a finding that is independent of comorbid conditions and remains poorly understood.2

Multiple studies have expanded the relationship between dysglycemia and adverse cardiovascular outcomes by demonstrating that even milder abnormalities of glucose control (below the diagnostic threshold of diabetes mellitus) are associated with increased cardiovascular risk.3–5 In participants who did not have a history of previously diagnosed diabetes mellitus or cardiovascular disease enrolled in the Atherosclerosis Risk in Communities (ARIC) study, baseline HbA1c levels of 5.5% to <6%, 6% to <6.5%, and ≥6.5% were associated with a 23%, 78%, and 95% greater risk for the development of coronary heart disease, respectively, compared with those with an HbA1c of 5.0% to 5.5%.3 Although this graded, continuous relationship between HbA1c and adverse cardiovascular outcomes has been demonstrated in patients with and without known diabetes mellitus, HbA1c appears to be a stronger cardiovascular risk marker in patients without previously diagnosed diabetes mellitus.3,6

Dysglycemia in Nondiabetic Patients With Acute Myocardial Infarction

It well recognized that hyperglycemia is commonly present in patients presenting with an acute myocardial infarction (MI) and is associated with a graded increased risk of death or cardiovascular complications in patients both with and without previous recognized diabetes mellitus.7 Despite the breadth of studies that have examined the prognostic significance of hyperglycemia during an acute coronary syndrome, it remains unclear whether elevated glucose levels are merely a marker of increased illness severity or a mediator in the adverse outcomes. Similarly, despite the common occurrence of hyperglycemia in acute coronary syndrome, optimal glycemic treatment strategies and optimal levels of glucose control in the acute coronary syndrome setting have not been well studied, and future work in this area remains a critically important need.7

In the current issue of Circulation, Timmer et al8 expand current knowledge of dysglycemia in the setting of acute MI by examining the prognostic value of HbA1c, in addition to admission glucose levels, in patients without previously recognized diabetes mellitus. Using observational data from a contemporary cohort of >4000 consecutive patients admitted with an acute MI and treated with primary percutaneous coronary interventions, the authors demonstrate that, despite significant correlation between the 2 measures of dysglycemia, increasing quartiles of admission glucose levels and quartiles of HbA1c levels identify patient subgroups with different baseline clinical characteristics. As the levels of HbA1c increased, patients were more likely to have prior cardiovascular disease and a more unfavorable baseline cardiovascular risk profile. Consistent with other studies,7 increasing levels of admission glucose were associated with greater infarct size and more evidence of acute hemodynamic derangement. The authors confirm the well-described relationship between admission hyperglycemia in the setting of acute MI and increased acute and subacute mortality.

Additionally, the authors demonstrate that increasing quartiles of HbA1c (even below the diagnostic threshold for diabetes mellitus) were associated with increased mortality rates over an average 3.3 years of follow-up. The relationship between HbA1c and long-term mortality persisted in multivariable models adjusted for other independent predictors of mortality, and the hazard was independent of admission glucose levels. Conversely, admission glucose was not predictive of long-term mortality in models that adjusted for HbA1c levels. As the authors conclude, these data suggest that admission glucose levels represent a marker for increased risk in the acute and subacute setting after acute MI, and that HbA1c, as a surrogate for more chronic dysglycemia, is a more useful marker of patients with greater long-term risk of death.

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.5,10 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.5

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,8 ~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.11 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.12

Despite these limitations of the study,8 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 antiplatelet 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.13 It is possible that intensive glycemic control instituted earlier in the disease process, such as 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.14 Whether these results of more intensive, early glycemic therapy in the relatively low-cardiovascular-risk patients of UKPDS (only 2% had macrovascular diseases)13 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.15 Data from the UKPDS demonstrating a reduction in macrovascular events with metformin provide strong support for this recommendation in patients with cardiovascular disease.14 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,16 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.17

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%)10 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).18 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.19,20 In addition, potential adverse effects of these glycemic therapies may alter the long-term cardiovascular risk-to-benefit ratio in patients with prediabetes.
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 al 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

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