Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 54, No. 5, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.05.014

Aiming for the Best Control of Glycemia in Patients With Heart Failure and Type 2 Diabetes

The "Sweet Spot"*

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Glycemic control has been a key target of therapy for patients with diabetes. In addition to the control of symptoms, it has been proposed that the potential reduction of additional morbidity and mortality represented another rationale for glycemic control. It has been assumed that physiologic perturbations associated with inadequate metabolic glucose control would be improved by restoration of normalized metabolism. In patients with type 1 (insulinopenic) diabetes mellitus, studies have indeed demonstrated significant microvascular (but less macrovascular) benefit when euglycemia as measured by glycosylated hemoglobin A1c (HbA1c) is approached with multiple daily insulin injections (1,2).

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Insulin resistance resulting in impaired glucose handling (metabolic syndrome, type 2 diabetes) has become an increasing worldwide problem that has not been resolved in the 5 decades since the first sulfonylurea was developed. Early efforts in the type 2 diabetic patient to restore normal glycemia were hampered by the lack of efficacy of early oral medications. Although a heavily promoted plethora of newer and more potent agents have become available, the difference between the mortality/morbidity rates of type 2 diabetic and nondiabetic patients has not been narrowed. Some small studies have suggested that tight insulin control of glycemia benefited these patients in the short term, broadening the interest in glucose control in intensive care units after myocardial infarction (3), in critical illness, and among guideline writers (4). The anticipation that reduction of morbidity or mortality by installation of a insulin/glycemic pump or nomogram replacing the sliding scale has been countered by the reality of evidence to the contrary (5). Likewise, more intensive regimens of oral agents to improve mortality and morbidity from macrovascular disease in type 2 diabetes have shown mixed results (6–10).

Guidelines have been written recommending how best to give the diabetic patient "quality care." But these diabetes guidelines were not developed for heart failure patients who require numerous medications for that diagnosis, often have concomitantly decreased renal function, and may have a narrower therapeutic window for optimizing outcomes. The underlying hypothesis that there may be a benefit to tight glycemic control in this population requires testing.

Patients with both heart failure and diabetes are often enrolled in an intensive disease-management program. Given the cost of treating patients with the combination of heart failure and diabetes, it is imperative to delineate the impact of strategies that can be used to decrease mortality, morbidity, and overall cost. Recognizing this problem, Aguilar et al. (11) report in this issue of the *Journal* the 2-year follow-up data from a retrospective observational database of 5,815 predominantly obese males with heart failure and diabetes treated in ambulatory clinics at Veterans Affairs medical clinics. Other than sex, they represented the typical heart failure patient with a mean age of 69 years and body mass index of 31.7 kg/m^2. Approximately one-half of the patients had reasonably preserved left ventricular function (ejection fraction ≥40%). The patients were stratified into quintiles based upon their HbA1c. After adjusting for clinical characteristics, the data demonstrated a U-shaped curve, with the quintiles at the lowest and highest HbA1c levels exhibiting the highest mortality.

Patients with the lowest HbA1c levels manifested clinical characteristics that were both favorable and unfavorable. These patients seemingly had fewer complications from their diabetes with less intensive treatment required. In addition, a higher proportion had a preserved or near-normal ejection fraction, less peripheral arterial disease, and there were fewer hospitalizations for heart failure within the prior 2 years. These favorable characteristics were counterbalanced by patients in this lowest quintile (≤6.4%) being older and having a lower glomerular filtration rate (GFR), more anemia, greater prevalence of chronic obstructive pulmonary disease, a bit more cancer, and less use of statins or angiotensin-converting enzymes/angiotensin receptor blockers). Interestingly, the lowest quintile HbA1c group

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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JACC Vol. 54, No. 5, 2009
July 28, 2009:429–31

patients were more likely to be solely on a sulfonylurea to control glycemia and were less likely to receive a biguanide, thiazolidinedione, or insulin. The lowest quintile group actually had similar GFR, hemoglobin, lipid profile, ejection fraction, and prior hospitalization history to the quintile that exhibited the lowest mortality (those with glycohemoglobin ≥7.2). Thus, the most striking difference between the lowest HbA1c quintile group that was at highest risk and the mid HbA1c quintile group with the lowest mortality appeared to be the "baseline" glycohemoglobin. In the group with the lowest quintile of glycohemoglobin, we are likely seeing the "real-world" risk of unawareness of spontaneous or iatrogenic hypoglycemia in the cardiac population (12).

Patients in the highest HbA1c quintile (glycohemoglobin >9.0) were younger with more aggressive (complicated) diabetes, peripheral vascular disease, higher lipids and insulin, as well as biguanide use. The higher mortality in this group is thus not unexpected.

There are some limitations of the study that deserve restating. As this is a Veterans Affairs study, women are underrepresented. In most such studies, women are a bit older than men, have lower GFR, more preserved ejection fraction heart failure, and more anemia. In this they would seem to represent the lowest HbA1c quintile and be more at risk for cardiovascular events. None of the studies of which we are aware suggests that tight control of glycemia benefits women more than men. Interpretation of the relationship between glycohemoglobin and mortality is limited by a lack of information on the underlying causes of the death. It would reasonable to suspect, however, that the contribution of hypoglycemia to morbidity and mortality may have been higher in the quintile with the lowest glycohemoglobin, especially because a higher percentage of patients was taking medications known to cause such events (12). Among the unstated limitations in most such studies is that during the 2-year follow-up, new drugs will have become available and changed the profile of current patient care. Indeed, the pharmaceutical marketplace has seen the addition of many more agents aimed at the control of diabetes mellitus since 2002. Unfortunately, none of these agents (incretins or inhibitors of inappropriate glucagon secretion) has been tested in the crucible of a health outcome trial. Until they are, we must understand that our attempts at "normalization" of impaired glucose metabolism as manifested by a marker such as HbA1c fall far short of the goal of eliminating the excess of cardiovascular risk suffered by the diabetic population.

Several reasonable explanations exist for the findings of this study. Unmeasured factors associated with low HbA1c may exist that increase the risk of mortality in these patients. The therapies used varied in the different groups, and the excess risk may be a reflection of these variations. Moreover, concomitant kidney disease in patients using sulfonylureas could increase risk for patients receiving this single agent. Other comorbid illnesses, including subclinical right ventricular dysfunction with hepatic or renal impairment may alter the safety of some of these agents, promoting episodic hypoglycemia and increased catechol states. Symptoms of hypoglycemia in these patients may be masked by the customary use of beta-blockers and by symptoms of heart failure such as fatigue and dizziness. Certainly it would be important to distinguish whether it was the level of HbA1c or the response of the patient to the medications administered that relates most closely to the outcomes observed. This deserves some discussion, as it is the higher mortality when glucose is "controlled better" and with less medicine that is the unexpected finding.

We have always assumed that restoration of euglycemia would eliminate some of the excess morbidity and mortality of diabetes. The current findings that this is not so are concordant with other studies, including the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, which demonstrated that very tight control of glucose in patients with diabetes (with or without episodes of hypoglycemia) may not improve mortality, and may, in fact, increase it (13). This observational data adds support to the growing concern that we may need to redefine the optimal HbA1c level in various patient populations, including heart failure. As we move forward in optimizing care for patients with heart failure and diabetes, we need a shift in the targets of therapy. Clearly the outcomes of cardiovascular morbidity and mortality should be standard measures of efficacy for novel diabetes therapies. Glycemic control as measured by glycohemoglobin or nonspecific advanced glycated end products may not adequately reflect the elements of diabetes that lead to an excess in mortality or decreased microvascular blood flow. Neither may specific glycated end products such as carboxymethyl and carboxyethyl lysine, which are currently under investigation for discrimination of protective/injurious properties in the genesis of diabetic complications (14). Recognizing the fallibility of current markers and study subsets, these targets may require modification. We must question in such patients whether current concepts of metabolic control do more harm than good. In the 70-year-old heart failure patient with diabetes, this study suggests that there is little benefit to a glycohemoglobin level below 7.1%.

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Key Words: diabetes ■ heart failure ■ glycosylated hemoglobin ■ HbA1c ■ prognosis.