News and Views from the Literature

Diabetes Mellitus

The Sulfonylurea Controversy: Friend or Foe?

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It is not uncommon for the first clinical presentation of diabetes or the metabolic syndrome to be a cardiovascular event, such as an acute coronary syndrome, stroke, or heart failure. Cardiologists are thus in a unique position both to identify patients with these disorders and to initiate treatment. Cardiologists take an aggressive role in treating conditions for which we do not have a unique "disease ownership," such as hypertension and dyslipidemia; so should we consider taking a role in treating patients with diabetes. The need for involvement by the cardiologist in the treatment of glucose disorders is compounded by the fact that some treatments are cardioprotective (thiazolidinediones, metformin, and acarbose), whereas there is evidence that others, such as the sulfonylurea drugs (SUDs), might actually be cardiotoxic under ischemic circumstances.

Sulfonylureas Attenuate Electrocardiographic ST-Segment Elevation During an Acute Myocardial Infarction in Diabetics

Huizar JF, Gonzalez LA, Alderman J, Smith HS
J Am Coll Cardiol. 2003;42:1017–1021.

The mechanism of action of the SUDs involves the blockade of adenosine triphosphate-sensitive potassium channels (K_{ATP}) within the pancreatic ß cells. These channels are also found in the heart and smooth muscles cells and are closed under steady state conditions by the presence of ATP. During conditions of myocardial ischemia, the ratio of adenosine triphosphate to adenosine diphosphate falls, thus opening the potassium channels. It is the opening of these channels that results in the ST-segment elevation observed on the electrocardiogram (ECG) with acute myocardial infarction (AMI). The K_{ATP} channels also play a role in myocardial resistance to metabolic stresses. In their article, Huizar and colleagues cite animal studies demonstrating that the ST-segment elevation during AMI is attenuated in animals pretreated with the sulfonylurea glyburide.

It has been demonstrated in isolated human myocardium and in patients undergoing balloon angioplasty that sulfonylurea treatment abolishes the cardioprotective efficacy of ischemic preconditioning.

Experimentally, SUDs increase infarct size and accelerate the death of hypoxic cardiomyocytes through blockade of K_{ATP} channels that mediate ischemic preconditioning in myocardium. This increases the vulnerability of the myocardium to ischemic insults in the presence of SUDs. Indeed, it has been demonstrated in isolated human myocardium and in patients undergoing balloon angioplasty that SUD treatment abolishes the cardioprotective efficacy of ischemic preconditioning. Garratt and collegues[1] observed a 2.77-fold increase in mortality among diabetics with AMI and treated with primary coronary angioplasty who were being treated with SUDs compared with diabetics not treated with SUDs (Figure 1).

Other mechanisms by which SUDs might increase mortality in patients with MI include inhibition of the

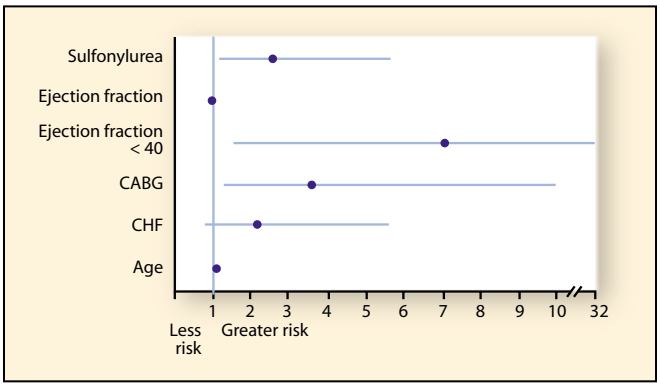

Figure 1. *Multivariate correlates of in-hospital mortality. CABG, coronary artery bypass graft; CHF, congestive heart failure. Adapted with permission from Garratt et al.*

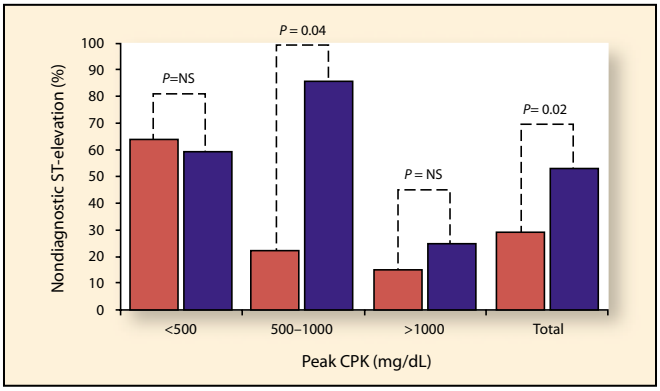

Figure 2. *Nondiagnostic ST-segment elevation during acute myocardial infarction, subdivided by infarct size (total of 88 patients). Red bars = control; purple bars = sulfonylureas. NS, nonsignificant; CPK, creatinine phosphokinase. Adapted with permission from Huizar et al.*

endogenous fibrinolytic system through enhanced production of proinsulin, which is known to stimulate endothelial production of plasminogen activator inhibitor-1.

The study by Huizar and colleagues was a retrospective review of diabetic patients who presented to the Metro West Medical Center with a diagnosis of AMI from October 1996 through August 2000 who met diagnostic criteria for thrombolytic therapy. They were divided into those who were taking SUDs and those who were not. Patients with a left or right bundle-branch block, paced rhythms, and left ventricular hypertrophy were excluded. The first ECG on presentation to the emergency department was evaluated for the presence of ST-elevation. Eighty-eight diabetic patients met the criteria for inclusion. A significantly greater number of nondiagnostic ST-segment elevations was observed in the SUD group than in the non-SUD group (53% vs 29%, $P = .02$) (Figure 2).

The implication of these results, despite the limitations of the trial (outlined in an accompanying editorial by Brady and Jovanovic[2]), is that diabetic patients treated with SUDs who present with an AMI will be less likely to have an ECG meeting criteria for thrombolysis and therefore might not be treated at presentation with either thrombolytic agents or primary percutaneous transluminal coronary angioplasty. This could result in a delay in the patient receiving maximal therapy and thus in worse outcomes. The authors conclude that until the question of whether SUDs have a cardiotoxic effect is resolved their use in patients with cardiovascular disease should "remain a cause for concern to cardiologists…."

Certainly with the variety of agents now available to treat diabetic patients, particularly the thiazolidinediones (Avandia [GlaxoSmithKline, Research Triangle Park, NC] and Actos [Takeda Pharmaceuticals, Lincolnshire, IL]), the biguanide metformin, and the combination agent Avandamet (GlaxoSmithKline), with their positive metabolic effects on lipids and coagulation, we now have first- and second-line options available other than the SUDs for treating diabetic patients, most of whom have occult or clinically significant cardiovascular disease. As we have learned from the treatment of hypertension, it is not only getting to our treatment goal that matters, but also how we get there. ■

References

1. Garratt K, Brady P, Hassinger N, et al. Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. *J Am Coll Cardiol.* 1999;33:119–124.
2. Brady P, Jovanovic A. The sulfonylurea controversy: much ado about nothing or cause for concern? *J Am Coll Cardiol.* 2003;42:1022–1025.

Thrombolysis

Long-Term Management of Venous Thromboembolism

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Recently, several important studies have been completed and published that have evaluated the intensity of long-term anticoagulation in patients at risk for recurrent thromboembolism. Two studies specifically looked at the intensity of warfarin therapy to