With regard to essential hypertension, we agree that this is a multifactorial condition. Obviously, all variables, including blood pressure levels itself, cannot show clear cutoff differences between normotensive and hypertensive patients, and there is no possibility of identifying a marker of hypertension in the whole population. As a consequence, neither an elevated $V_{\text{max}}$ of red blood cell SLC nor any other variable can represent a marker of essential hypertension. In contrast, this assumption is not true for the identification of hypertensive patient subsets or hypertension sequelae, which could both be influenced by major genes rather than polygenes. With the use of the method by Canessa et al. (2) with appropriate modifications, Redgrave et al. (4) and our group (5) have clearly demonstrated the elevation of SLC activity in a subset of patients with essential hypertension known as “nonmodulators.” An elevated $V_{\text{max}}$ of red blood cell SLC predicted the blood pressure responses to changes in sodium intake in salt-sensitive but not salt-resistant subsets of patients with essential hypertension (6,7). Nosadini et al. (8) clearly linked SLC hyperactivity to the not salt-resistant subsets of patients with essential hypertension pressure responses to changes in sodium intake in salt-sensitive but

Angina Pectoris, Myocardial Infarction and Verapamil

The excellent review of unstable angina (UA) and non–Q-wave myocardial infarction by Zaacks et al. (1) contained a statement that may mislead the reader: “The Multicenter Diltiazem Post Infarct Trial found a significant reduction of adverse cardiac events in patients receiving diltiazem who did not have pulmonary edema on presentation. Similar favorable findings cannot be extrapolated to include other calcium channel blockers such as verapamil . . .” Zaacks et al. do not include the results from the Danish Verapamil Infarction Trial (DAVIT) II (2) in their review. The DAVIT II, a double-blind, randomized, placebo-controlled postinfarct trial of verapamil (120 mg t.i.d.), which included 1,775 patients, demonstrated a significant reduction in major events (i.e., first reinfarction or death in verapamil-treated [18.0%] compared with placebo-treated patients [21.6%]; hazard ratio [HR] 0.80, 95% confidence intervals [CI] 0.64 to 0.99). In an an priori–determined subgroup analysis, in relation to treatment for congestive heart failure (CHF) before randomization, in patients without CHF verapamil significantly prevented death (7.7%) as compared with placebo (11.8%) [HR 0.64, 95% CI 0.44 to 0.94]. Also, the reinfarction rate was significantly lower in the verapamil group (9.2% vs. 12.7%) [HR 0.67, 95% CI 0.46 to 0.97]. No harm was found in patients with CHF.

In a recent, small, double-blind postinfarct study of patients with CHF being treated with the angiotensin-converting enzyme inhibitortrandolapril, verapamil significantly prevented death (7.7%) as compared with placebo (11.8%) [HR 0.64, 95% CI 0.44 to 0.94]. Also, the reinfarction rate was significantly lower in the verapamil group (9.2% vs. 12.7%) [HR 0.67, 95% CI 0.46 to 0.97]. No harm was found in patients with CHF.

REFERENCES

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Sulfonylurea Drugs and Cardiovascular Mortality

The study by Garratt et al. (1) emphasizes an important concept that is emerging from the cumulative published data: sulfonylurea agents worsen cardiovascular risks in type 2 diabetes. This study documented a higher mortality among diabetic patients treated by direct angioplasty who received sulfonylurea drugs as compared with those who did not.

In a recent study from our institution published in the *European Heart Journal* (2), we documented similar adverse effects of sulfonylurea therapy after elective coronary angioplasty. This comprehensive risk-adjusted study involved ~16,000 patients and showed that sulfonylurea therapy exerted an independent adverse outcome after angioplasty and accounted for much of the long-term survival advantage for bypass surgery over angioplasty in diabetic patients.

For three decades, data have been accumulating suggesting potential adverse effects of sulfonylurea therapy on large-vessel atherosclerotic vascular disease (3). These agents improve glucose control by increasing insulin levels. Increased insulin levels have independent adverse effects in both diabetic and nondiabetic patients, possibly by increasing atherogenesis and cardiovascular events. Furthermore, sulfonylurea agents cause vasoconstriction and block the adenosine triphosphate-sensitive potassium (K_{ATP}) channels not only in the pancreas but also in the cardiac cells and coronary vasculature. This impairs ischemic preconditioning and may predispose to larger infarctions and dangerous arrhythmias.

The recently published United Kingdom Perspective Diabetes Study (UKPDS) (4) documented improved survival with metformin as compared with sulfonylurea agents in overweight type 2 diabetic patients. These cumulative data should caution us against the use of sulfonylurea agents as first-line therapy for diabetic patients with coronary artery disease. The use of alternative oral agents is both logical and feasible with the availability of metformin, troglitazone, rosiglitazone, and orlistat, all of which improve diabetes by improving insulin sensitivity (rather than raising insulin levels).

Approximately four of five diabetic patients die of cardiovascular causes, irrespective of whether or not atherosclerotic disease is present at baseline (3). Although we often relegiate the medical management of diabetes to endocrinologists and primary care physicians, cardiologists should ensure that the therapies that have been shown to improve cardiovascular prognosis (e.g., aspirin, statins, angiotensin-converting enzyme inhibitors) are used when indicated, and agents like sulfonylureas, which may increase cardiovascular risk, are avoided when possible.

James H. O’Keefe, Jr., MD
Ben D. McCallister, MD
Eugene H. Blackstone, MD
Cardiovascular Consultants, P.C.
Kansas City, Missouri

REFERENCES