EDITORIAL (SEE JOHNSON ET AL., DEC. 2002, P. 2244)

# Is Metformin Cardioprotective?

The study by Johnson et al. (1) in the December 2002 issue of *Diabetes Care* makes conclusions that in part seem to support the controversial finding of the U.K. Prospective Diabetes Study (UKPDS) that metformin usage as monotherapy was associated with a lower death rate compared with sulfonylureas or insulin (2,3). Such a claim has huge importance to practitioners and patients. Diabetes incidence and costs (the large bulk of which are attributed to type 2 diabetes) are skyrocketing around the world. The increased cardiovascular (CV) risk with diabetes is well recognized (4), and atherosclerotic heart disease, stroke, peripheral vascular disease, and heart failure account in large part for the excess death rate. The decision about what drug to use for monotherapy is currently based on many factors, such as contraindications, side effects, and cost of the available drugs; our wish to minimize weight gain; the patient's age and accompanying coillnesses; the practitioner's familiarity and comfort level with the various drugs; and perhaps most importantly, what drugs are covered by the patient's insurance. Efficacy does not play much of a role, as there is little solid evidence for any class of drugs being much different than the rest when used as monotherapy (5). However, showing clinically relevant CV benefits for any of the available drugs would move this decision point to the top of the list. It would be hard to be enthusiastic about another drug irrespective of what other advantages it might have.

In their study, Johnson et al. (1) retrospectively surveyed oral agent usage in Saskatchewan from 1 January 1991 to 31 December 1999, looking for "new users," who were determined based on not having been prescribed an oral hypoglycemic agent in the prior 12 months. The survey used the computerized outpatient prescription drug database of Saskatchewan Health, which covers 91% of the province's residents. Subjects entered the study if a prescription for sulfonylurea or metformin was given during the index period (1 January 1991 to 31 December 1996) and they had been enrolled in the plan for the previous year. The latter was required to confirm lack of usage of any diabetes therapy in the prior year. Prescription records were then tracked. To be included in the study, subjects had to take the oral agent or a combination of metformin and sulfonylurea for at least a year. Study end points were death, exit from the study, or end of the study (31 December 1999). Death certificates were surveyed by trained coders for cause of death; CV death was determined from specific coding using World Health Organization–standardized decision rules.

A total of 12,272 "new users" were identified and followed for an average 5.1 years; 8,866 were included in the data analysis, with the remainder excluded for failing to meet all required details of the protocol. The analyzed population was 34.2% sulfonylurea-users, 13.0% metformin-users, and 52.8% combination users (lumped together whether they began with sulfonylurea or metformin, because the mortality results were the same irrespective of which drug was given first). Deaths were 13.8% of the metformin-users, 13.6% of the combination-users, and 24.7% of sulfonylurea-users, with a similar trend for the number of CV-related deaths. Odds ratios for all-cause and CV-related mortality remained significantly lower in the metformin and combination users after adjusting for age, sex, nitrate use, and chronic disease score.

What do we conclude from these results? The authors are to be congratulated for having surveyed a large, general population and for having made every effort to include all eligible subjects. Further, their finding of lowered mortality in the metformin users (alone or in combination) seems irrefutable. However, the key question is "Why?" The study is weakened by the data that are not available. Prospective randomized studies eliminate bias by making certain that subjects are matched at the start of a study for all variables that could affect the outcome. In contrast, population-based retrospective studies often fail to uncover important biases. This point was emphasized by Robert Turner, the lead author of the UKPDS, in an editorial to another paper that reported increased cardiovascular risk of metformin (6). Crucial for Johnson et al.'s study is knowing that the patient populations began as equals. Unsettling is that the sulfonylurea users were mostly men, were older, and used more nitrates than the metformin users, although the differences were small. Other relevant issues are unknown: one cannot determine from the data glycemic control, lipid values, usage of tobacco or "statins" or ACE inhibitors, etc. Also, it must be known if prescribing habits of the Saskatchewan doctors were such that metformin and sulfonylureas were used interchangeably. Today's contraindications for metformin include renal dysfunction (proteinuria has a high predictive risk for CV disease), medically treated congestive heart failure, and chronic lung and hepatic disease. This means that relatively healthy patients receive that drug. In turn, the wider safety profile of sulfonylureas often makes them the only oral therapy for moderately sick patients. In the Johnson et al. study, 65–70% of the subjects received sulfonylureas alone or as the first drug before adding metformin. One must know the criteria for each drug's use to fully interpret this study.

Do the results suggest a lowered mortality in the metformin users or increased mortality in the sulfonylurea users? The data are not analyzed in that fashion, but inferences can be made. Data from several studies show all-cause mortality in middle-aged Caucasian males with diabetes of ~5% per year (7). In a Finnish study, CV mortality of patients with diabetes who were not previously known to have CV disease was ~3% per year (4). Thus, the 13% all-cause mortality and 7% CV mortality in metformin users vs. 24% all-cause mortality and 11% CV mortality in the sulfonylurea users over the 5 years of the study suggest a lower than expected mortality rate with metformin. Why? One could speculate it reflects the known CV benefits of metformin over sulfonylureas, less weight gain and lowered triglyceride levels (8,9), and the resulting effects on potential CV pathogenic mechanisms such as plasminogen activator inhibitor-1 (10). To be valid, it needs to be shown that CV-related mortality was in fact low-

ered. The Johnson et al. (1) study is to be commended for being as precise as possible in determining the cause of death of the study patients. The data are not supportive. Deaths in the metformin-users (alone) were 159, with 80 identified as CV-related (50%); deaths in the combination users were 635, with 299 CV-related (47%); and deaths in the sulfonylurea users were 750, with 351 CV-related (47%). These data seemingly eliminate a protective effect of metformin on the CV system. What was the protective effect? In the absence of knowing another death-protective mechanism of metformin, it seems reasonable to conclude that the results stem from an unrecognized difference in the treatment populations.

Have other published studies determined that any class of oral hypoglycemic agents has protective or detrimental effects in terms of CV morbidity or mortality? Definitive findings with metformin are lacking. The UKPDS reported *improved* CV-related end points, including myocardial infarction and stroke, in obese patients who received it as monotherapy and *worsened* CV-mortality in patients who received combination metformin and sulfonylurea (2). After much discussion and analysis, these provocative findings have been dismissed by most experts as a statistical aberration (6,11). A subsequent small study reported increased CV mortality with metformin over sulfonylureas in patients with known ischemic heart disease after a 5-year follow-up (12), but not after a 7.7-year follow-up (13). One is not confident that the final answer is in on this subject. What about sulfonylureas? Many years ago, the University Group Diabetes Program raised concerns of increased CV risks with sulfonylureas because of an observed higher incidence of sudden death with tolbutamide (14). However, it is now generally accepted that the UKPDS put that issue to rest by finding no increased rate of myocardial infarction or mortality with sulfonylurea usage (3,6). Moreover, a potential causative mechanism of CV jeopardy with sulfonylureas, impaired ischemic preconditioning, is seemingly not evident with newer sulfonylureas, such as glimepiride compared with glyburide (15,16). Perhaps of most interest in terms of CV protection is the thiazolidinedione ("glitazone") class of drugs. Multiple studies have shown impressive protective effects against many of our current concepts regarding the heightened CV risk with diabetes: inflammation, altered thrombolysis, endothelial dysfunction, etc. (17–19). Outcome studies are underway to determine if, and how much, CV disease is impacted by these drugs and in whom. We anxiously await these results. However, until outcome results are available, a case cannot be made for CV risk profiles being an important factor in determining what drug to prescribe as monotherapy or combination therapy for type 2 diabetes.

**AFSHIN SASALI, MD**
**JACK L. LEAHY, MD**

From the University of Vermont College of Medicine, Division of Endocrinology, Diabetes and Metabolism, Burlington, Vermont.

Address correspondence and reprint requests to Dr. Jack L. Leahy, University of Vermont College of Medicine, Division of Endocrinology, Diabetes and Metabolism, Given C-331, Burlington, Vermont 05405. E-mail: jleahy@zoo.uvm.edu .

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