

Coronary and cardiovascular mortality in type 2 diabetic patients treated with the sulfonylurea-metformin combination: the type of sulfonylurea is pivotal

The UKPDS results published in 1998 discarded the notion of any cardiovascular deleterious effect of sulfonylureas (SUs) as a drug class,¹ showing a trend in favor of a reduction (P=0.052) of the incidence of myocardial infarction in patients in the intensive glucose control group treated with insulin or SUs (chlorpropamide or glibenclamide) in primary prevention. However, an unexpected excess of mortality was observed in patients in the intensive group treated with the SU-metformin combination.²

In a recent meta-analysis, Rao et al³ included data from 9 observational studies published between 1999 and 2007 aimed at examining the association between combination therapy with SUs and metformin and cardiovascular risk and mortality. The pooled relative risk (95% confidence interval [CI]) for the SU-metformin combination compared with diet, monotherapy with SUs, or metformin was 1.19 (CI 0.88-1.62) for all-cause mortality, 1.29 (CI 0.73-2.27) for cardiovascular mortality, and 1.43 (CI 1.10-1.85) for composite criteria including fatal and nonfatal cardiovascular events (cardiovascular death and hospitalizations for cardiovascular disease). However, it is difficult to raise any definite conclusion in practical terms, as the approach was meta-analytic with the well-known limitations of this approach, and the specific effect of every SU was not investigated.

In fact, there are several indications favoring a specific cardiovascular effect for each SU derivative rather than a common drug class effect. Some observational studies, for instance, have shown that the "new" SUs, among them gliclazide, are associated with lower mortality and a better prognosis in type 2 diabetic patients after myocardial infarction.⁴

Recent prospective studies aimed at investigating the effects of intensive glycemic control on cardiovascular events and death have shed new light in this field. In Steno 2, an optimal and progressive antidiabetic therapeutic strategy was compared with a classic strategy in patients at high cardiovascular risk.⁵ In this study with highly positive results (53% reduction in cardiovascular mortality and morbidity with the optimal strategy), the SU used was Diamicon; this was in combination with metformin in the majority of cases. It is difficult to isolate the specific effect of Diamicon in these results, as optimal correction of blood pressure and low-density lipoprotein cholesterol was undertaken too, but Steno 2 does give at least indirect evidence of a favorable cardiovascular effect of Diamicon. In the intensive glycemic control group of ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation), a progressive strategy based upon Diamicon 30 MR was tested.⁶ In this study, 74% of patients from the intensive glycemic control arm treated with Diamicon 30 MR received metformin in combination. A trend toward a reduction in cardiovascular mortality (12% less, P=0.12) was observed in the intensive group compared with the standard group. These results are in contrast with the excess cardiovascular mortality (relative risk 1.35, P=0.02) in the ACCORD study (Action to Control Cardiovascular Risk in Diabetes), which prompted investigators to prematurely stop the study. In ACCORD, patients from

the intensive group received one or several insulin secreting agents (glimepiride 78.2%, repaglinide 50.2%), combined with metformin in 94.7% of cases.⁷ Also, in the Veterans Affairs Diabetes Trial (VADT), in which glimepiride was the SU used,⁸ a nonsignificant trend toward excess cardiovascular mortality was observed (relative risk 1.32, CI 0.81-2.14; P=0.26). The absence of statistical significance for the latter result was probably explained by the underestimation of the size of the groups.

In conclusion, there are many arguments in favor of differences between each SU derivative in terms of their preventive coronary and cardiovascular effects. Results of major recent intervention studies, ACCORD, VADT, and ADVANCE, illustrate this point. It is difficult not to draw parallels between the results of ADVANCE and the specific anti-oxidative properties of Diamicon 30 MR and its specific binding to b -cell receptors.

P. J. GUILLAUSSEAU

References:

1. UK Prospective Diabetes Study Group. Lancet. 1998;352:837-853.
2. UK Prospective Diabetes Study Group (UKPDS) Group. Lancet. 1998;352:854-865.
3. Rao AD, Reynolds K, Kuhadiya N, et al. Diabetes Care. 2008;31:1672-1678.
4. Bell DS. CMAJ. 2006;174:185-186.
5. Gaede P, Vedel P, Larsen N, et al. N Engl J Med. 2003;348:383-393.
6. The ADVANCE Collaborative Group. N Engl J Med. 2008;358:2560-2572.
7. The Action to Control Cardiovascular Risk in Diabetes Study Group. N Engl J Med. 2008;358:2545-2559.
8. Duckworth W, Abraira C, Moritz T, et al; VADT Investigators. N Engl J Med. 2009;360:129-139.