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Possible risk of sulphonylureas in the treatment of non-insulin-dependent diabetes mellitus and coronary artery disease

Dear Sir,

We are grateful for the possibility to expand further on our above referenced hypothesis [1] in response to the letter by Dr. Fasching.

Even though the relevance of the results of the UGDP – as devastating for sulphonylureas and biguanides as they were – may have been debatable [2], there has never been a study to rule out any cardiotoxic effect of sulphonylurea therapy. Recent findings in animals and humans have provided a pathophysiological plausibility for our hypothesis, as sulphonylureas appear to aggravate the hypoxaemic damage to the myocardium in the case of coronary occlusion or artery disease [1, 3, 4, 5]. In fact, such a pathophysiological scenario fits well with the observation that the alleged cardiotoxic effect of sulphonylureas appears to exert itself in an increased lethality of myocardial (re-) infarctions or cardiac death rates, rather than by increasing cardiac events or the incidence of cardiovascular morbidity [1, 7]. In this situation, appropriate studies directed at efficacy and safety of sulphonylurea drugs have been demanded recently [5, 6, 8].

The UKPDS is certainly not going to be helpful in this context, as patients with clinically relevant coronary artery disease have been excluded during the recruitment process: the entire cohort included only 3% patients with a history of angina pectoris (excluding those with present angina), 2% with a history of myocardial infarction (prior to 1 year before recruitment) and patients with heart failure were excluded [9]. Furthermore, the study does not have the statistical power to rule out clinically relevant differences concerning cardiovascular morbidity and mortality between the four treatment arms represented under *Intensive Therapy* [9, 10].

Finally, we agree with Dr. Fasching that sulphonylureas must not be judged as a drug class; rather more every sulphonylurea drug needs to be studied individually for its effectivity and safety vis-à-vis the relevant endpoints for Type II diabetes mellitus, i.e. cardiovascular morbidity and mortality – rather than being limited to surrogate markers [11]. The fact that any such positive evidence has never been demonstrated for this (and any other) oral antidiabetic drug is most disturbing and, indeed, should alarm the “doctors and frighten their patients”.

In our opinion, the – albeit incomplete – evidence implementing a cardiotoxic effect of sulphonylurea drugs has be-

come substantial enough to shift the burden of proof on to those who are still using sulphonylurea drugs in Type II diabetic patients with coronary heart disease to document that this is actually safe.

Yours sincerely,

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