Resolving drug effects from class effects among drugs for type 2 diabetes mellitus: more support for cardiovascular outcome assessments

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Online publish-ahead-of-print 6 April 2011

This editorial refers to ‘Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study’, by T.K. Schramm et al., on page 1900

As illustrated most recently by the controversy surrounding the myocardial infarction risk associated with rosiglitazone, 1 substantial uncertainty remains regarding the effects of different glucose-lowering drug classes and, importantly, different drugs within each class on cardiovascular (CV) risk and mortality outcomes in patients with type 2 diabetes (T2DM). In the setting of the ongoing proliferation of anti-hyperglycaemic therapeutic classes and formulations with myriad therapeutic options for the treatment of T2DM presently available, 2 this uncertainty has prompted regulatory agencies in both Europe and the USA to reassess the approval process for new T2DM medications, with changes focused primarily on excluding with a specified degree of statistical certainty incremental CV risk prior to new drug approval. 3 Long-term randomized clinical outcome trials with both new and presently available medications are recommended, but not mandated. In the absence of definitive CV risk assessment from randomized trials for presently available drug classes and individual drugs within each class, critical analyses of existing databases are both imperative and informative.

In this context, Schramm et al. have now reported the results of a nationwide registry-based observational analysis of clinical outcomes associated with various insulin secretagogues each compared with metformin. 4 While this is not the first study to evaluate outcomes with these drug classes comparatively, the observations are among the most robust published based on the very large sample of patients with drug choices largely free of selection bias, sufficient numbers of events ascertained to yield substantial statistical power to analyse outcomes for each insulin secretagogue individually, with additional stratification by history of previous myocardial infarction. The overall results of the study suggest that most but not all insulin secretagogues (sulphonylureas and meglitinides) are associated with worse outcomes compared with metformin. Tolbutamide, glibenclamide (known as glyburide in the USA and Canada), glipizide, and gliclazide were all associated with significantly increased mortality and CV risk compared with metformin, but outcomes with gliclazide and repaglinide were not statistically different from those with metformin.

In interpreting these data, it is of key importance to note that the observation of less benefit with most sulphonylureas in the study compared with metformin should not be interpreted as causing harm. Given the fact that metformin has an estimated risk reduction of approximately 40% for major adverse cardiac events and death compared with placebo, 5 when comparing outcomes associated with other drugs against metformin, hazard ratios of up to 1.7 would suggest treatment effects similar to or better than placebo, especially when considered in the context of favourable effects on microvascular disease risk associated with improved glucose control. Therefore, beyond the direct comparisons with metformin of each secretagogue, the most important and novel finding of the present study is the variability of the estimates of hazard associated with individual insulin secretagogues, suggesting that some may be better than others with regard to the outcomes assessed. Of course, as noted by the investigators, such interpretations are limited by the non-randomized observational nature of the present analyses deriving from an administrative database, with some variance in the propensity to prescribe the specific secretagogues analysed that may confound associations beyond the ability to adjust completely for differences in patient mix between the secretagogue groups. The apparent paradox of superior outcomes with metformin, a drug with modest glucose-lowering properties, compared with sulphonylureas that are approximately twice as potent raises the possibility that some

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1 doi:10.1093/eurheartj/ehr077

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benefit of glucose control with sulphonylureas may be offset by adverse effects of the drugs. Sulphonylureas are the oldest non-insulin drug class presently available for the treatment of T2DM, having been used for more than half a century. In 1971, the University Group Diabetes Project (UGDP) randomized trial reported increased CV and all-cause mortality with tolbutamide, a first-generation sulphonylurea,6 prompting early termination of that arm of the trial and modification of the US product label to include a ‘special warning on increased risk of CV mortality’. Based on presumed within-class similarities with no definitive proof to the contrary, that warning has persisted in the product label of every sulphonylurea subsequently marketed in the USA, although no further signals of adversity have been observed with sulphonylureas as a drug class in larger trials.7,8 Of note, such warnings are generally not present in the labelling of these drugs in Europe.

In a recent consensus statement on the medical management of hyperglycaemia in T2DM published jointly by the American Diabetes Association and the European Association for the Study of Diabetes, sulphonylureas were recommended as ‘second step’ therapy that can be added to metformin and lifestyle modification (considered ‘first step’ therapies) if additional glycaemic control is needed.9 Importantly, the consensus statement did not treat all sulphonylureas equally. Gliclazide, glipizide, and glimepiride were deemed preferable, the use of chlorpropamide and glibenclamide (glyburide) was discouraged explicitly because of their greater risk of hypoglycaemia and prolonged pharmacodynamic effects, and the use of other sulphonylureas was discouraged implicitly by omission. However, in the absence of data on clinical trial mortality and CV disease outcomes, these specific recommendations remain grounded primarily on clinical judgement. Based on these concerns, we have previously published somewhat different recommendations for patients with T2DM who concomitantly have CV disease, with insulin secretagogues endorsed later in the algorithm.10 In accordance with the new data from Schramm et al.,4 the choice of secretagogue may be just as (or more) important.

Both sulphonylureas and meglitinides lower blood glucose primarily by binding to pancreatic β-cell sulphonylurea receptors (SURs; Figure 1), which are subunits of the plasma membrane ATP-sensitive K⁺ (KATP) channels. Drug binding leads to inhibition of K⁺ efflux, triggering a cascade of events leading to glucose-independent insulin release from pancreatic β-cells, but also to impaired ischaemic pre-conditioning in cardiac myocytes. KATP channel inhibition in other cells and tissue types may also contribute to the overall effects of individual sulphonylureas. The figure was produced using Servier Medical Art, http://www.servier.com/Smart/ImageBank.aspx?id=729.

Figure 1  Schematic representation of the effect of sulphonylurea medications on pancreatic β-cells and cardiac myocytes. Sulphonylureas bind to sulphonylurea receptor proteins (SURs), subunits of the hetero-octameric ATP-sensitive K⁺ (KATP) channels. Drug binding inhibits KATP channel-mediated K⁺ efflux, triggering a cascade of events leading to glucose-independent insulin release from pancreatic β-cells, but also to impaired ischaemic pre-conditioning in cardiac myocytes. KATP channel inhibition in other cells and tissue types may also contribute to the overall effects of individual sulphonylureas. The figure was produced using Servier Medical Art, http://www.servier.com/Smart/ImageBank.aspx?id=729.
efflux and triggers a cascade of intracellular events resulting in increased insulin release, independent of circulating glucose concentrations. Various members of these drug classes have different pharmacokinetic and pharmacodynamic properties, including variable half-lives, clearance pathways, binding affinities, and specificities for the different SURs expressed in different tissues, and variable inhibitory potencies for the $K_{ATP}$ channel. For example, in addition to inhibiting $K_{ATP}$ channels in pancreatic $\beta$-cells via the SUR1 receptor, some sulphonylureas also have significant inhibitory effects on the sarcolemmal and mitochondrial $K_{ATP}$ channels of cardiac myocytes (Figure 1) via the SUR2A receptor, as well as on vascular smooth muscle cell $K_{ATP}$ channels via the SUR2B receptor. Studies in vitro and in vivo in animals have shown that sulphonylurea-mediated inhibition of $K_{ATP}$ channels in cardiac myocytes may impair the cardioprotective process of ischaemic pre-conditioning, and studies using surrogate measures in humans have supported this notion, but whether interference with ischaemic pre-conditioning affects CV and mortality outcomes is still unclear. Impaired ischaemic pre-conditioning is a potential explanation for the increased myocardial infarction case-fatality rate in patients treated with sulphonylureas in some studies, however, this remains highly speculative and has not been supported by other analyses. Of course, apparently conflicting data from clinical studies could be attributable to the use of different sulphonylureas, further underscoring the importance of considering individual drugs rather than the entire drug class in future analyses. For example, the increased mortality signal observed in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial associated with more intensive glucose control leading to early termination of the study was not observed in the similarly designed Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, with glyburide as the most prevalent sulphonylurea used in ACCORD and glarglucide prescribed by study protocol in ADVANCE. Although completely speculative, the possibility remains that differential effects of these two sulphonylureas, as suggested by data and commentary from Schramm et al., may underpin the different outcomes observed in these two recent trials.

Aside from interference with the process of ischaemic pre-conditioning, other potential mechanisms by which sulphonylureas may be associated with lower clinical benefit compared with metformin are increased risk of hypoglycaemia which, in the context of T2DM, may have particularly pernicious effects on patient survival, weight gain, with its associated adverse effects on global CV risk profiles, and possibly the inhibition of $K_{ATP}$ channels in other tissues (Figure 1).

With the global prevalence of T2DM increasing rapidly, it has never been more critical to understand the CV efficacy and safety of individual glucose-lowering medications. The study by Schramm et al. once again highlights the high degree of clinical uncertainty that exists regarding the CV effects of presently available drugs, underscoring the importance of the recent shift in regulation towards requiring CV assessment of emerging glucose-lowering therapies. Ideally, all drugs used to treat T2DM should undergo CV efficacy and safety evaluation, but for drugs that are already approved, and especially for those that are generic, it remains to be determined where the responsibility will fall to support such large and expensive clinical trial evaluations.

**Conflict of interest:** none declared.

**References**