Should the algorithm for the treatment of type 2 diabetes be evidence-based?

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Abbreviations

ADOPT	A Diabetes Outcome Progression Trial
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation
UKPDS	UK Prospective Diabetes Study

To the Editor: In a recent issue of *Diabetologia*, Schernthaner and colleagues [1] state that the last consensus statement from the ADA and EASD released in October 2008 [2] was not based strongly enough on clinical evidence, and raise some concerns about the role of sulfonylureas in treating type 2 diabetes.

Trials evaluating drugs for the treatment of type 2 diabetes with the highest degree of evidence are sparse, and to the best of my knowledge include only the UK Prospective Diabetes Study (UKPDS) [3, 4], A Diabetes Outcome Progression Trial (ADOPT) [5], Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) [6] and PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) [7]. The first

three of these studies in which sulfonylureas were used found in favour of their beneficial effect in the long-term, either on glycaemic control, beta cell function or cardiovascular events.

Concerning beta cell function, Schernthaner et al. advocate the positive results with rosiglitazone in ADOPT [5]. However, it is worth considering that after 5 years, beta cell function was identical between the rosiglitazone- and glibenclamide (known as glyburide in the USA and Canada)-treated groups, and higher than in the metformin-treated group. UKPDS data also demonstrated a similar effect on beta cell function after 6 years, comparing metformin vs sulfonylureas [8].

Concerning cardiovascular events, in the most recent trial, namely ADVANCE [6], based on modified-release gliclazide (gliclazide MR) with normalisation of HbA_{1c} (down to 6.5%) and low risk of hypoglycaemia, a significant 10% decrease in the composite macro- and microvascular endpoint associated with a 12% (non-significant trend) decrease in cardiovascular mortality was observed, in spite of the limited follow-up time (5 years). Moreover, the significant 21% risk reduction for new or worsening nephropathy must be considered for its preventive value on cardiovascular events [9]. In the UKPDS and ADOPT, the effect of sulfonylureas on cardiovascular endpoints was favourable too, even in comparison with metformin, as in ADOPT [5]. More surprisingly, Schernthaner et al. report the results of observational studies analysing cardiovascular events, such as that of Tzoulaki et al. [10], published in the *BMJ* in 2009. This study represents the paradigm of a non-evidence-based study due to a retrospective design and multiplicity of flaws.

Finally, as reported in the same issue of *Diabetologia* by Nolan [11], even if new compounds look promising on the

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basis of preliminary studies on efficacy, the compelling endpoints still remain long-term efficacy, vascular protection and safety.

Even though international guidelines do not cover all the various different clinical profiles due to the extraordinary complexity of diabetes pathogenesis, a global consensus is still valuable in helping clinicians negotiate the difficulty and heterogeneity of daily practice.

Duality of interest The author has received fees for lectures and consultations from Astra-Zeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Novartis, Roche, Servier and Takeda.

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