Author's response to reviews

Title: Hypoglycaemia incidence and the risk of vascular events - an analysis of the prospective DiaRegis registry

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Submission: Tschöpe et al. Hypoglycaemia incidence and the risk of vascular events – an analysis of the prospective DiaRegis registry

Dear Dr. Shipley,

attached you will find a manuscript on the incidence rates and predictors of hypoglycaemia in inadequately controlled type-2 diabetic patients, who underwent treatment intensification. The primary objective was to determine the proportion of patients with at least 1 episode of severe hypoglycemia (requiring medical help or hospitalization) within one year. Hypoglycaemia related secondary objectives were to evaluate the number of patients with at least 1 episode of severe, moderate or mild hypoglycemia, and to evaluate the number of hypoglycaemic events per patient, respectively. We originally submitted this manuscript to BMC Medicine, the editor of which felt that it would be better suitable for BMC Endocrine Disorders.

The results suggest that there is a high risk (14.1%) for hypoglycaemia in patients whose treatment is intensified after failure of oral mono or oral dual combination therapy. This risk is particularly high for episodes of hypoglycaemia that are symptomatic but where patients require no help (9.7%) and these episodes are experienced for a mean of 3.4±3.7 times per year. Predictors of hypoglycaemia were prior anamnestic hypoglycaemia (OR 4.05; 95%CI 3.04-5.39), microvascular disease such as retinopathy (3.27; 1.07-30.02), clinically relevant depression (1.81; 1.14-2.88) and, with respect to pharmacotherapy insulin use (2.99; 2.27-3.95). On the contrary, glitazones (0.55; 0.35-0.86), DPP-4 inhibitors (0.57; 0.43-0.76) and GLP-1 analogues (0.48; 0.28-0.81) were associated with a reduced risk. Although sulfonylureas were clearly linked with anamnestic hypoglycaemic events, there was no significant association between SU use and the risk of hypoglycaemia during the 12 months FU. Incident hypoglycaemia was associated with an increased risk for stroke / TIA, amputation, autonomous neuropathy, non-proliferative retinopathy and depression during follow-up.
Diethelm Tschöpe (DT), Peter Bramlage (PB), Christiane Binz (CB), Michael Krekler (MK), Evelin Deeg (ED) and Anselm Gitt (AG) are named authors on this manuscript. DT, PB, CB, MK and AKG designed the study; ED analysed the data, DT and PB drafted the article. All authors revised the manuscript for important intellectual content and approved the final manuscript.

The manuscript is not under consideration elsewhere, none of the paper’s contents have been previously published, all authors have read and approved the manuscript; and all authors have disclosed any potential relationship with industry as follows: CB and MK declare to be employees of Bristol-Myers Squibb. DT, PB and AKG received consultancy fees, attended advisory boards and have held lectures for a number of pharmaceutical companies including Bristol-Myers Squibb and Astra Zeneca.

We look forward to a favourable review of our manuscript.

Yours sincerely,

Peter Bramlage, MD