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EXPERT OPINION

Comment and response to: dapagliflozin – do we need it registered for type 2 diabetes?

Serge Jabbour
Jefferson Medical College of Thomas Jefferson University, Department of Medicine, Division of Endocrinology, Diabetes, and Metabolic Diseases, Philadelphia, PA, USA

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Dear Editor:

Sheila Doggrell and Rinku Tuli recently reviewed one of the > 50 clinical trials conducted for dapagliflozin and drew conclusions about the approval of dapagliflozin in the United States [1]. Here, I respond to this commentary by underscoring some points supporting the design features and validity of the clinical trial and provide arguments for the approval of dapagliflozin.

It is well known that initially effective therapies for type 2 diabetes mellitus (T2DM) require dose escalation and the addition of a second or third agent is typically needed to maintain glycemic control. Metformin is recommended as first-line therapy for T2DM 'if not contraindicated and if tolerated' in the evidence-based American Diabetes Association and American Association of Clinical Endocrinologists guidelines [2,3]. In clinical practice, some type 2 diabetics cannot take metformin because of gastrointestinal intolerance and/or contraindications. Dipeptidyl peptidase-4 inhibitors, including sitagliptin, are recommended for patients who cannot tolerate metformin, and also in combination with metformin [3]. Accordingly, the study design [4] used was in accordance with current guidelines, and relevant to real-world clinical practice. Sodium-glucose co-transporter-2 inhibitors are also indicated as add-on therapy to other glucose-lowering agents as treatment intensifies [5]. In our experience, the authors' choice of prescribing insulin after metformin does not represent current practice. Physicians and patients are often reluctant to use insulin because of associated weight gain, hypoglycemia, and the potential for lifelong injections and blood glucose monitoring. As physicians, we rarely initiate insulin as second-line therapy unless the patient has severe hyperglycemia and/or is in a catabolic state.

Not all therapies, alone or in combination, have the same level of efficacy and safety in all patients; small differences among in-class drugs can make an important impact in outcomes to individual patients. This presents a need for new diabetes medications, even within classes of existing agents. A robust within-class treatment armamentarium allows individualization of therapy and is in the best interest of the patient [2,3].

Lastly, cardiovascular outcomes data typically require evaluation over several years. Unless overt risk is noted at an early stage, most drugs, including diabetes drugs, do not have available cardiovascular data when initially approved. Cardiovascular safety requirements as defined by the FDA for regulatory approval of diabetes medicines were clearly met with dapagliflozin. Further, the long-term effects of dapagliflozin on cardiovascular events are being studied in the ongoing DECLARE study (NCT01730534).

As the first of the SGLT2 inhibitors to enter the global market in 2012, extensive patient experience with dapagliflozin has amassed and demonstrates its importance in the diabetes treatment armamentarium.

Declaration of interest

The author is a paid consultant for AstraZeneca, Janssen and Eli Lilly and Company.

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Affiliation

Serge Jabbour MD
Jefferson Medical College of Thomas Jefferson University, Department of Medicine, Division of Endocrinology, Diabetes, and Metabolic Diseases, Philadelphia, PA 19107, USA
Tel: +1 215 955 1925;
Fax: +1 215 928 3160;
E-mail: serge.jabbour@jefferson.edu

Author's response

We found the placebo-controlled clinical trial by Jabbour *et al.* [1] of dapagliflozin as an add-on therapy to sitagliptin with or without metformin in subjects with type 2 diabetes to be appropriately designed and to be very interesting. This is why we used it in our Key Paper Evaluation (KPE) entitled "Dapagliflozin – do we need it registered for type 2 diabetes? [2]". In his letter, Dr Jabbour has raised 3 issues relating to our expert opinion in this evaluation.

The first issue relates to metformin being poorly tolerated or contraindicated in some subjects with type 2 diabetes, and not suitable for use in these subjects, and we concur with this in our evaluation: "Thus, it would seem preferential to us, to use the clinical proven metformin, prior to adding of dapagliflozin, and that dapagliflozin should only be considered in subjects with type 2 diabetes who are unable to take or tolerate metformin [2]". However, only a small number of subjects with type 2 diabetes are initially unable to take metformin or unable to tolerate any dose of metformin. Thus, a dose of 500 mg metformin is associated with a reduction in HbA1c without any gastrointestinal side effects [3] and a dose of 2000 mg metformin XR has no gastrointestinal side effects in 77% of subjects [4]. Our point was that the reason that half the subjects in the study of Jabbour *et al.* [1] were not taking metformin was not stated, and thus we are querying why so many were not using any metformin.

The second issue was with the approach of add-on insulin to metformin described in EASIE (Evaluation of insulin glargine versus insulin-naïve patients) trial, where the authors suggested that the achievement of better glycaemic control with insulin glargine than sitagliptin may lead to better outcomes [5]. However, despite these findings, we accept Dr Jabbour's contention that insulin is rarely used as second-line treatment in practice, and that sitagliptin is preferred.

The third issue raised by Dr Jabbour was that it is not a requirement of the US FDA that cardiovascular outcomes data be available when a new medicine is registered. We accept this, but the point we are making is that we do not agree with the FDA on this. We consider that new medicines should be shown to have beneficial effects on clinical outcomes in the disease they are being used to treat before they are registered. In type 2 diabetes, there is a good precedent for this, as the thiazolidinediones (glitazones) were registered prior to clinical outcome studies for their ability to lower HbA1c, and then troglitazone was shown to cause liver morbidity and mortality, and rosiglitazone was shown to have no benefit or may increase cardiovascular outcomes [6].

In addition to the lack of beneficial effects on cardiovascular outcomes, we argue against registration of dapagliflozin in the USA "As no clear benefits have been identified for dapagliflozin over canagliflozin, which was the first gliflozin registered by the FDA, we do not fully understand why it was necessary to register dapagliflozin". This important point was not challenged by Dr Jabbour in his letter.

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Affiliation

Sheila Doggrell PhD DSc
LSB384 Unit Co-Ordinator and Senior Lecturer in Pharmacology, Queensland University of Technology, School of Biomedical Sciences, Faculty of Health, GPO Box 2434, QLD4001, Australia