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Update on long-term efficacy and safety of dapagliflozin in patients with type 2 diabetes mellitus

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***Abstract*:** Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a novel class of antihyperglycaemic agents with an insulin-independent mode of action. Dapagliflozin is a member of the SGLT2 inhibitors class that has received marketing authorization in Europe and the US for use in patients with type 2 diabetes. This review summarizes current evidence from clinical trials assessing the clinical efficacy and safety of dapagliflozin, and presents data regarding its cost-effectiveness. Treatment with dapagliflozin results in similar reduction in haemoglobin A_{1c} with other oral antihyperglycaemic drugs, which is preserved over 4 years of treatment. However, compared with most antidiabetic agents, dapagliflozin provides additional clinical benefits including body weight loss and blood pressure reduction. Moreover, treatment with dapagliflozin does not increase risk for hypoglycaemia, but is associated with increased incidence of mild to moderate urinary and genital tract infections. A pivotal outcomes trial of dapagliflozin is expected to clarify its effect on cardiovascular endpoints, whilst a causative relationship between dapagliflozin and select malignancies is unlikely. Finally, based on recent economic evaluations dapagliflozin seems to be a cost-effective option for type 2 diabetes in some settings.

Keywords: BMS512148, cost-effectiveness, dapagliflozin, Farxiga®, Forxiga®, sodium–glucose cotransporter 2 (SGLT2), type 2 diabetes mellitus, Xigduo®

Introduction

Type 2 diabetes mellitus (T2DM) has reached epidemic proportions affecting 56 million people in Europe, accounting for 8.5% of the adult population. Prevalence of T2DM is expected to increase in the following years with projections suggesting that 69 million Europeans will be affected by 2035 (10.3% of the adult population) [International Diabetes Federation, 2013]. The pathophysiology of T2DM is characterized by insulin resistance and progressive loss of β-cell function. Treatment is based on the use of therapeutic agents that address these problems. Nevertheless, available therapeutic options have also significant limitations, such as increased risk of hypoglycaemia with sulphonylureas and insulin. Moreover, management of comorbidities including obesity and hypertension poses unique challenges.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a novel class of antihyperglycaemic agents with an insulin-independent mode of action. Glucose filtered in the glomerulus is primarily reabsorbed in the S1 segment of the proximal convoluted tubule through the SGLT2. Pharmacologic inhibition of the SGLT2 results in glucosuria, thus lowering blood glucose levels. Dapagliflozin is a member of the SGLT2 inhibitors class that has received marketing authorization in Europe and the US. Dapagliflozin is indicated along with diet and exercise as monotherapy for patients with T2DM who are intolerant to metformin or for whom metformin is contraindicated. It can also be used as an adjunct to other glucose-lowering agents including insulin for patients with inadequate glycaemic control. In the US, the recommended starting dose for dapagliflozin is 5 mg once daily taken in the morning, which can be increased to 10 mg for patients requiring additional glycemic control [AstraZeneca Pharmaceuticals and Bristol-Myers

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Squibb, 2014]. Nevertheless, the approved summary of product characteristics in Europe suggests that dapagliflozin is initiated at a daily dose of 10 mg [European Medicines Agency, 2014a]. A fixed-dose combination of twice daily dapagliflozin 5 mg with metformin 850 or 1000 mg is also commercially available in Europe [European Medicines Agency, 2014b]. A similar, once daily, extended release formulation of dapagliflozin with metformin was recently approved in the US.

Glycaemic efficacy

Monotherapy

Current guidelines advocate the use of metformin as first-line treatment, while other hypoglycaemic drugs are indicated only when metformin is considered inappropriate due to intolerance [Inzucchi *et al.* 2012; Garber *et al.* 2013]. When used as monotherapy, treatment with dapagliflozin 10 mg for 12 weeks was equally effective with metformin in reducing haemoglobin A_{1c} (HbA_{1c}) (mean difference 0.12% [95% confidence interval (CI): −0.41 to 0.17]) [List *et al.* 2009]. Nevertheless, there is a paucity of head-to-head trials comparing dapagliflozin with other antidiabetic agents as first-line treatment.

Second-line treatment

For patients already treated with background metformin use of dapagliflozin, reduced HbA_{1c} compared with glipizide (mean difference −0.30%; 95% CI −0.51 to −0.09) over 4 years of treatment [Langkilde *et al.* 2013]. Similarly, as add-on to pioglitazone, dapagliflozin provided sustained glycaemic control compared with placebo over 48 weeks of treatment (difference *versus* placebo in HbA_{1c} −0.67%; 95% CI −0.88 to −0.46) [Rosenstock *et al.* 2012].

Unfortunately, there are no head-to-head trials directly comparing dapagliflozin with dipeptidyl peptidase-4 (DPP4) inhibitors or glucagon-like peptide-1 (GLP1) analogues as add-on therapy. Nevertheless, some indirect inferences can be drawn based on findings from Bayesian network meta-analyses. As an adjunct to metformin, mean difference in HbA_{1c} for dapagliflozin *versus* DPP4 inhibitors was −0.08% [95% credible interval (CrI) −0.25 to 0.10] [Goring *et al.* 2014], while in patients treated with sulphonylurea monotherapy, addition of dapagliflozin provided similar glycaemic efficacy to GLP1 analogues (mean difference in HbA_{1c} 0.11%; 95% CrI −0.18 to 0.40) [Orme *et al.* 2014].

Third-line treatment

When dapagliflozin was used on top of metformin plus sitagliptin, a sustained reduction in HbA_{1c} of 0.6% (95% CI −0.8 to −0.4) was noted compared with placebo after 48 weeks of treatment [Jabbour *et al.* 2014]. Moreover, in patients treated with basal insulin at a dose of at least 30 international unit (IU)/day and up to two other antidiabetic agents, addition of dapagliflozin 10 mg effectively reduced HbA_{1c} compared with placebo over 2 years of treatment (−0.35%; 95% CI −0.55 to −0.15) [Wilding *et al.* 2013].

Body weight reduction

As monotherapy, dapagliflozin was equally effective with metformin in reducing body weight (−1.00%; 95% CI −2.04 to 0.04) [List *et al.* 2009]. In patients already treated with metformin, use of dapagliflozin was associated with a significant weight loss of −5.07 kg (95% CI −6.21 to −3.93) compared with glipizide [Langkilde *et al.* 2013]. Similar results were observed for use of dapagliflozin as add-on to pioglitazone for 48 weeks (−2.30 kg; 95% CI −3.37 to −1.23 compared with placebo) [Rosenstock *et al.* 2012]. Of note, based on the results of a network meta-analysis, treatment with dapagliflozin in patients inadequately controlled on sulfonylurea alone resulted in significant body weight reduction compared with placebo (−1.54 kg; 95% CrI −2.16 to −0.92), in contrast to GLP1 analogues (−0.65 kg; 95% CrI −1.37 to 0.07) and DPP4 inhibitors (0.57 kg; 95% CrI 0.09 to 1.06) [Orme *et al.* 2014]. Finally, when used as third-line therapy as adjunct to metformin and sitagliptin, dapagliflozin resulted in significant weight loss compared with placebo (−2.1 kg; 95% CI −3.2 to −1.0) [Jabbour *et al.* 2014].

In a study utilizing dual-energy X-ray absorptiometry, Bolinder and colleagues explored whether weight loss is accounted for by changes in fat or fluid components. Almost two-thirds of the observed body weight reduction with dapagliflozin was attributed to loss of fat mass, which is probably related to the caloric loss induced by glucosuria [Bolinder *et al.* 2012].

Blood pressure reduction

A recent meta-analysis investigated the effects of SGLT2 inhibitors on blood pressure [Baker *et al.* 2014]. Dapagliflozin was associated with a reduction in systolic blood pressure of 3.78 mm

Hg (95% CI −4.49 to −3.07). Similarly, diastolic blood pressure was also reduced by 1.41 mm Hg (95% CI −1.80 to −0.96). These effects are attributed to osmotic diuresis associated with use of dapagliflozin and were corroborated in 2 trials using 24-hour ambulatory blood pressure monitoring [Iqbal *et al.* 2014]. Changes in blood pressure were observed as early as 12 weeks after initiation of treatment with dapagliflozin and were similar to those induced by hydrochlorothiazide [Lambers Heerspink *et al.* 2013].

Hypoglycaemia

Based on pooled results from 3 studies, dapagliflozin did not increase incidence of hypoglycaemia compared with other antidiabetic agents [odds ratio (OR) 0.49; 95% CI 0.18 to 1.39] [Vasilakou *et al.* 2013]. Incidence of hypoglycaemia was approximately 10-fold less with dapagliflozin relative to glipizide [Langkilde *et al.* 2013]. Of note, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when these are used in combination with dapagliflozin [European Medicines Agency, 2014a].

Urinary and genital tract infections

Treatment with dapagliflozin 10 mg was associated with an increased incidence of urinary tract infections (UTIs) (OR 1.43; 95% CI 1.05 to 1.94) based on pooled data from 12 placebo-controlled trials [Vasilakou *et al.* 2013]. These events were mild to moderate in intensity and were more common in females than males, while pyelonephritis was uncommon and with a similar incidence rate (0.1%) as in placebo-treated patients [US Food and Drug Administration, 2011]. Discontinuation rates due to UTIs were generally low (0.3% for dapagliflozin-treated and 0.1% for placebo-treated subjects). Events suggestive of UTI were evaluated by means of a urine culture in 39–50% of patients allocated to dapagliflozin and in 50% of patients treated with placebo. Approximately two-thirds of these urine cultures turned out positive for common pathogens identified in patients with T2DM and UTI [Johnsson *et al.* 2013].

Moreover, treatment with dapagliflozin was associated with a marked increase of genital tract infections (OR *versus* placebo 3.48; 95% CI 2.33 to 5.20) [Vasilakou *et al.* 2013]. The most commonly reported events were vulvovaginal mycotic infections in females and balanitis in males; however none of them was classified as serious [European Medicines Agency, 2012].

Cardiovascular safety

A meta-analysis of cardiovascular events submitted by the sponsor to the European Medicines Agency included safety data collected in the dapagliflozin clinical development programme through to 15 July 2011. Based on a total of 145 events, dapagliflozin did not increase the hazard ratio (0.82; 95% CI 0.58 to 1.15) for the composite cardiovascular endpoint (defined as time to first event of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina) compared with control arms [European Medicines Agency, 2012]. Similar findings were reported in a meta-analysis of 14 trials (OR 0.73; 95% CI 0.46 to 1.16) [Vasilakou *et al.* 2013]. Nevertheless, the long-term effect of dapagliflozin on cardiovascular outcomes will be elucidated after completion of an ongoing placebo-controlled trial that is expected to enroll more than 17,000 patients with T2DM at high risk for cardiovascular events. The primary outcome of this pivotal trial is a composite cardiovascular endpoint including cardiovascular death, myocardial infarction or ischemic stroke. Hospitalization for unstable angina or heart failure, as well as all-cause mortality, will also be investigated. The trial is expected to be completed by 2019 [ClinicalTrials.gov identifier: NCT01730534].

Neoplasms

A higher incidence of breast cancer was noted in patients treated with dapagliflozin (nine women, n = 5501 as opposed to one patient in the control group, n = 3148). However, study day of diagnosis ranged from day 6 to day 334 [European Medicines Agency, 2012]. Thus this relatively short interval between exposure to study drug and diagnosis of breast cancer mitigates against a causative relationship.

Based on the latest data submitted by the drug sponsors to the US Food and Drug Administration, 10 cases (0.17%) of bladder cancer were identified in dapagliflozin-treated subjects (n = 6045) compared with 1 case (0.03%) in comparator groups (n = 3512). Diagnosis of bladder cancer was mainly driven by haematuria. Moreover, risk factors that might contribute to the development of bladder cancer were balanced between

treatment arms [US Food and Drug Administration, 2013]. Although a causal relationship cannot be definitively excluded, this imbalance may well be attributed to detection bias due to frequent urinalyses in dapagliflozin-treated patients experiencing urinary tract infections. As a precautionary measure, co-administration of dapagliflozin with pioglitazone is not currently recommended in Europe [European Medicines Agency, 2014a].

Dapagliflozin in special populations

Renal impairment

Dapagliflozin is not recommended for use in patients with moderate to severe renal impairment [estimated glomerular filtration rate (eGFR) $<$ 60 ml/min/1.73 m^2]. A dedicated randomized, placebo-controlled trial of dapagliflozin in patients with chronic kidney disease (mainly stage 3, with an eGFR $\geqslant$30 and $<$60 ml/min/1.73 m^2) showed lack of glycaemic efficacy (placebo-corrected difference in HbA_{1c} −0.11%, $p = 0.435$ for dapagliflozin 10 mg) and an imbalance in incidence of bone fractures among the two groups (13 patients treated with dapagliflozin, n = 168 *versus* zero events in the placebo group, n = 84) after two years of treatment [Kohan *et al.* 2014].

Elderly patients

Glycemic efficacy of dapagliflozin in elderly subjects has been explored in a pooled analysis of 12 phase IIb/III studies. The effect of dapagliflozin on HbA_{1c} was slightly attenuated in patients $\geqslant$65 years of age compared with those $<$65 years-old. After controlling for eGFR, no conclusive evidence was found that age affects efficacy as an independent factor ($p = 0.29$) [Fioretto *et al.* 2013]. Nevertheless, hypoglycaemia, volume depletion and renal adverse events occurred more often in subjects aged $\geqslant$65 years.

Patients at risk for volume depletion

Adverse events related to volume depletion (most commonly hypotension) were observed in 0.8% of patients treated with dapagliflozin 10 mg as opposed to 0.4% in placebo-treated subjects. Hypotension due to dapagliflozin-induced osmotic diuresis was more common amongst elderly subjects, patients with moderate renal impairment or subjects treated with loop diuretics [European Medicines Agency, 2012]. Discontinuation of treatment with dapagliflozin is recommended for patients who develop volume depletion.

Are the benefits worth the costs?

T2DM is a chronic and costly disease with an increasing prevalence in both developed and developing countries. Therapeutic interventions that delay or prevent the development of its long-term complications could confer substantial cost savings to health systems worldwide, which are forced to allocate limited healthcare resources efficiently and evenly among the population [Oliver *et al.* 2004]. As a consequence, many countries have adopted the implementation of Health Technology Assessments (HTAs) and economic evaluations in the decision-making process for reimbursement of new health technologies [Oliver *et al.* 2004; Brennan *et al.* 2006].

In the UK, an HTA assessing the cost-effectiveness of dapagliflozin was commissioned by the National Institute for Health and Care Excellence (NICE) [National Institute for Health and Care Excellence, 2013]. It was based on a simulation economic model submitted by the manufacturer that evaluated the cost-effectiveness of dapagliflozin as dual therapy in combination with metformin, as add-on to insulin, or as triple therapy. For the add-on to metformin analysis, the comparators considered were sulphonylureas, DPP4 inhibitors and pioglitazone. Baseline patient characteristics, clinical effectiveness and adverse event data were taken from relevant randomized controlled trials and a network meta-analysis conducted by the manufacturer. The results of the originally submitted analysis suggested that, as add-on to metformin, dapagliflozin dominated DPP4 inhibitors and pioglitazone both in terms of costs and quality-adjusted Life Years (QALYs) gained, while compared with sulphonylureas it was associated with an incremental cost-effectiveness ratio (ICER) of £2671 per QALY gained. Nevertheless, the NICE Evidence Review Group and the Decision Support Unit identified several flaws in the original analysis. Thus a revised economic model was submitted and additional changes were applied, resulting in ICER per QALY values of £12,405 and £13,338 for the comparisons of dapagliflozin *versus* sulphonylureas and pioglitazone, respectively. Interestingly, DPP4 inhibitors were associated with higher costs and QALYs than dapagliflozin, but these differences were small (£16847 per QALY gained). Regarding add-on treatment to insulin, the NICE

HTA reported that the ICER for dapagliflozin compared with DPP4 inhibitors was below £20,000 per QALY in the base case and all sensitivity analyses. Overall, the HTA concluded that dapagliflozin is recommended as add-on to metformin, or in combination with insulin with or without other antidiabetic drugs [National Institute for Health and Care Excellence, 2013].

Additional cost-effectiveness analyses have been recently published for Nordic countries [Sabale *et al.* 2014] and the Netherlands [van Haalen *et al.* 2014]. A simulation economic model applying the United Kingdom Prospective Diabetes Study 68 equations [Clarke *et al.* 2004] to predict the incidence of seven diabetes-related long-term complications was utilized to estimate the cost-effectiveness of dapagliflozin compared with sulphonylurea as add-on to metformin in four Nordic countries [Sabale *et al.* 2014]. The ICER per QALY gained with dapagliflozin was €7944, €5424, €4769 and €6093 in Denmark, Finland, Norway and Sweden, respectively, suggesting that in these countries dapagliflozin seems a cost-effective alternative to sulphonylurea in patients inadequately controlled with metformin alone [Sabale *et al.* 2014]. In addition, an analysis based on a similar simulation model in the Netherlands suggested that dapagliflozin is a cost-effective treatment option for patients on insulin therapy that have inadequate glycaemic control [van Haalen *et al.* 2014]. Of note, both analyses were based on short-term data derived from a single trial (a sulphonylurea-controlled [Sabale *et al.* 2014] and a placebo-controlled trial [van Haalen *et al.* 2014], respectively), while specific limitations regarding estimation of costs [Sabale *et al.* 2014] can further reduce their applicability. Moreover, it is questionable whether these results are generalizable to other countries due to country-specific variations in clinical practice and differences in costs of drugs and diabetes-related events. More specifically, an assessment estimating the benefit of dapagliflozin conducted by the Institute for Quality and Efficiency in Health Care in Germany concluded that it does not confer any additional benefit neither as monotherapy nor as add-on treatment, mainly due to lack of clinically relevant trials comparing dapagliflozin with appropriate comparator therapy [Institute for Quality and Efficiency in Health Care, 2013].

In Australia, the Pharmaceutical Benefits Advisory Committee initially rejected the manufacturer's submission for reimbursement of dapagliflozin on the basis of uncertain comparative clinical effectiveness [Pharmaceutical Benefits Advisory Committee, 2012a, 2012b]. Nevertheless, a resubmission including data from more clinical trials and a cost minimization analysis comparing dapagliflozin with sitagliptin resulted in approval of dapagliflozin for listing for the treatment of patients with T2DM as dual combination therapy with metformin or a sulphonylurea [Pharmaceutical Benefits Advisory Committee, 2013]. Finally, recent economic analyses have been presented at the International Society for Pharmacoeconomics and Outcomes Research 19th Annual International Meeting. Based on these analyses, in the US, dapagliflozin is dominated both in terms of costs and QALYs by the newer SGLT2 inhibitor canagliflozin [Neslusan *et al.* 2014], whilst it appears to be a cost effective option compared to sulphonylurea as add-on to metformin in Argentina, Chile and Colombia [Elgart *et al.* 2014a, 2014b].

Conclusion

In conclusion, dapagliflozin is a new addition in the antidiabetic armamentarium with similar glycaemic efficacy to other oral antihyperglycaemic agents and low risk for hypoglycaemia. Dapagliflozin offers additional clinical benefits including body weight loss and blood pressure reduction. The main safety concern is related to an increased incidence of urinary and genital tract infections. A pivotal outcomes trial of dapagliflozin is expected to clarify its effect on cardiovascular endpoints.

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Conflict of interest statement

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