1. Introduction

Type 2 diabetes mellitus (T2DM) is an epidemic disease that affects more than 360 million people worldwide [1]. Today we have a greater choice of treatments for T2DM patients, including several oral and injectable agents. In addition to lifestyle measures, which are always necessary, these drugs have demonstrated an ability to improve glycaemic control [2,3]. In recent years, several antidiabetic drugs such as thiazolidinediones and incretins, with novel mechanisms of action, have become available, extending the number of treatment options [2]. However, some patients remain uncontrolled despite the current range of old and new drugs [4]. Indeed, for every one of these agents, there are good and poor responders [5-7]. Therefore, unmet needs persist in many patients. Many classes of antihyperglycaemic agents are directly or indirectly dependent on the level of insulin secretion, with the main exceptions being metformin, thiazolidinediones and α-glucosidase inhibitors. On the other hand, these newer antidiabetic drugs have no direct effects on pancreatic β-cell dysfunction.

A new class of oral antidiabetic drugs (OADs) – namely, the sodium-glucose cotransporter-2 inhibitors (SGLT-2-i), or “gliflozins” – promotes urinary glucose excretion by inhibiting glucose reabsorption in the kidney [8]. In T2DM, many studies have confirmed that SGLT-2-i have very significant beneficial effects on glycaemic control and induce body weight loss as well as reduce blood pressure, all without causing hypoglycaemia [8]. In short, this new antidiabetic class of drugs has shown promising results in both preclinical and clinical studies of T2DM [9]. In contrast to other antidiabetic agents, SGLT-2-i are equally effective for glycaemic control,

**Adverse effects and safety of SGLT-2 inhibitors**

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Abstract

In type 2 diabetes (T2DM), glycaemic control delays the development and slows the progression of complications. Although there are numerous glucose-lowering agents in clinical use, only approximately half of T2DM patients achieve glycaemic control, while undesirable side-effects, such as hypoglycaemia and body weight gain, often impede treatment in those taking these medications. Thus, there is a need for novel agents and treatment options. Sodium – glucose cotransporter-2 inhibitors (SGLT-2-i) have recently been developed for the treatment of T2DM. The available data suggest a good tolerability profile for the three available drugs – canagliflozin, dapagliflozin and empagliflozin – approved by the US Food and Drug Administration (FDA) for the American market as well as in other countries. The most frequently reported adverse events with SGLT-2-i are female genital mycotic infections, urinary tract infections and increased urination. The pharmacodynamic response to SGLT-2-i declines with increasing severity of renal impairment, requiring dosage adjustments or restrictions with moderate-to-severe renal dysfunction. Most patients treated with SGLT-2-i also have a modest reduction in blood pressure and modest effects on serum lipid profiles, some of which are beneficial (increased high-density lipoprotein cholesterol and decreased triglycerides) and others which are not (increased low-density lipoprotein cholesterol, LDL-C). A number of large-scale and longer-term cardiovascular trials are now ongoing. In patients treated with dapagliflozin, a non-significant excess number of breast and bladder cancers has been reported; considered as due to a bias, this is nevertheless being followed in the ongoing trials. No other significant safety issues have been reported so far. Although there is some benefit for several cardiovascular risk factors such as HbA1c, high blood pressure, obesity and increases in LDL-C, adequately powered trials are still required to determine the effects of SGLT-2-i on macrovascular outcomes.

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whatever the mechanisms causing hyperglycaemia, while being independent of insulin secretion and insulin action, the magnitude of hyperglycaemia, and initial body weight and duration of diabetes, with a consequently lower risk of hypoglycaemia. This explains why these drugs may also be considered a treatment for type 1 diabetes mellitus (T1DM) patients [10].

2. Rationale to ensure the safety and tolerability of new antidiabetic agents

Today, the safety of new drugs, and the frequency and severity of adverse events, represent an issue of major and legitimate concern as well as a source of heated controversy [11]. The US Food and Drug Administration (FDA), followed by the European Medicine Agency (EMA), have issued new guidelines to the drugs industry to assess the cardiovascular risk of new OADs and to promote studies to monitor other potentially serious adverse events, including the increased risk of various cancers [12]. Controversies regarding the effects of rosiglitazone therapy on cardiovascular complications, pioglitazone on bladder cancer, and incretins on exocrine pancreatic risk, pancreatitis and pancreatic carcinoma, and even thyroid carcinoma, have raised concerns about the use of those drugs [11,13-15]. Beyond such major risks, the tolerability of all drugs is another important issue for patients who need to take them every day for years, as in T2DM. Potential adverse events such as gastrointestinal disturbances [with metformin, α-glucosidase inhibitors and glucagon-like peptide (GLP)-1 agonists], hypoglycaemia (with insulin, sulphonylureas and meglitinides), weight gain (with insulin, sulphonylureas, meglitinides and thiazolidinediones) and risk of cardiovascular disease (with thiazolidinediones) limit their use.

This is why today the tolerability and safety of new drugs are major concerns, and why all new antidiabetic agents are under the surveillance of regulatory agencies based on their data before marketing, from phase-II and -III studies, and post-marketing adverse drug reactions (AEs). Also, although the drug regulatory process is designed to detect adverse drug reactions before the drug receives marketing authorization, for obvious reasons the premarking detection of all potential adverse reactions associated with a drug may not be possible. In such cases, the regulatory authorities must also react to and manage adverse reactions identified at the post-marketing stage [12].

The present report includes an analysis of the data for this new class of drugs, the SGLT-2-i, with the knowledge that some medium- and long-term adverse effects cannot be discussed because this family of drugs has only been recently introduced into the market and then in only a few countries. This review focuses on the first three representatives of this class already on the market: canagliflozin, dapagliflozin and empagliflozin. These three compounds have all reached phase-III clinical trials: two of them (canagliflozin and dapagliflozin) have previously been approved for use in T2DM by both the EMA and FDA [16-18], while the third one, empagliflozin, has only just been approved for use in T2DM by the EMA in May and FDA in August of this year [19].

3. Is familial renal glycosuria a model?

There is a natural experimental condition known as “familial renal glycosuria”. This disorder, also called “renal diabetes”, represents a benign autosomal-dominant syndrome, the result of a decrease in the number and activity of SGLT-2 transporters. It is an asymptomatic condition that does not lead to renal failure or other complications [20]. However, although individuals with familial renal glycosuria do not have diabetes (hyperglycaemia), this does not preclude the need for long-term safety data of OADs in T2DM patients. Indeed, during the therapeutic use of OADs, massive glycosuria may be drug-induced in hyperglycaemic patients at high cardiovascular risk and with an increased risk of other pathological states as infections and cancer.

4. Hypoglycaemia

This adverse event is seen with some glucose-lowering therapies and is occasionally a limitation factor in achieving good glycaemic control. Hypoglycaemia is also associated with negative effects such as undesirable symptoms like weight gain (through increased appetite), poor adherence to therapy, uncontrolled glycaemia because of the fear of new hypoglycaemic episodes, poor quality of life and, in some patients, accidents such as falls and cognitive disorders, mainly in elderly and frail patients [21-23]. A link between severe hypoglycaemia and increased cardiovascular risk and total mortality has recently been described [21,22]. Because of their mechanism of action – which is not dependent on insulin secretion and includes lowering the renal threshold for glucose from 200mg/dl to around 100mg/dl while maintaining glucose levels above the hypoglycaemic range – the SGLT-2-i are less likely to cause hypoglycaemia by themselves. This means that as a monotherapy add-on to metformin (Met), there is no real (or only marginal) increase in hypoglycaemia compared with a placebo or when added to other drugs that can cause hypoglycaemia, such as sulphonylurea (SU), Met + SU, pioglitazone (Pio) with or without SU and especially insulin [17-19,24-28]. Thus, the incidence of hypoglycaemia is low except in patients taking SUs or insulin as either their allocated treatment or in addition. This represents a major strength of the SGLT-2-i, as it allows the use of new drug combinations without increasing hypoglycaemia.

5. Genital infection

By their very nature, the most common major safety concern of SGLT-2 inhibition is that the drugs cause glucose levels to rise in urine, which can lead to urinary tract and genital infections, increased urinary frequency and electrolyte imbalances. An increase in urinary glucose excretion caused by SGLT-2-i treatment also has the potential to increase...
fungal growth in the perineum and genitourinary tract. Non-sexually transmitted perineal and genitourinary tract mycotic infections are considered adverse events of particular interest. In fact, use of the three drugs (canagliflozin, dapagliflozin and empagliflozin) is accompanied by an increase in genital infections compared with a placebo and affects more women than men (by four to five times), mostly as vulvitis [16-19,24-30]. However, the vast majority of cases are diagnosed with typical symptoms and require only a single standard antibiotic treatment [29,30]. In women, the diagnosis is mostly mycotic vulvovaginitis and, in men, mycotic balanitis. Rates of genital infection in men are several-fold lower than rates of vulvovaginitis in women. Genital infections are more frequent in premenopausal women and much more common in those with a history of genital infection and/or obesity, and not influenced by baseline HbA1c levels. In clinical trials, the incidence of genital infections with the maximum drug dosage is between 5% and 15% [24,25,27,28], and is not proportional to the amount of glycosuria and, thus, not related to SGLT-2 inhibitors [24,25,28]. The time interval before the first genital mycotic infection is the same for men and women: rates are highest in the first few months of treatment followed by an attenuation in frequency.

To summarize, genital mycoses are the main side-effects of this new OAD class, affecting 5-10% of users, especially premenopausal women. However, the infections are mostly symptomatic and respond well to standard therapy [16-19,24-37].

6. Urinary tract infections

Urinary tract infections (UTIs) are common in patients with T2DM. Johnsson et al. [31] pooled the safety data of 12 randomized placebo-controlled trials with dapagliflozin to evaluate the relationship between glycosuria and UTIs in patients with inadequately controlled diabetes (HbA1c > 6.5-12%). Patients were treated with dapagliflozin (2.5mg, 5mg or 10mg) or placebo once daily either as monotherapy or as an add-on to Met, insulin, SU or thiazolidinedione for 12-24 weeks. The incidences of UTIs, which were either clinically diagnosed or suggested by events, were quantified in 3,152 patients, who received once-daily dapagliflozin at 2.5mg (n = 814), 5mg (n = 1,145) or 10mg (n = 1,193) as monotherapy or as add-on treatment, and 1,393 placebo-treated patients. For dapagliflozin at 2.5mg, 5mg, 10mg and placebo, the reported rates of diagnosed infections were 3.6%, 5.7%, 4.3% and 3.7%, respectively. Although urinary glucose levels increased progressively in relation to dapagliflozin dosages, the incidence of UTIs remained stable. Most of the identified infections were considered typical for patients with diabetes. Two-thirds of the UTIs were diagnosed from the usual symptoms, and most of the diagnosed infections were mild to moderate and responded to standard treatment, the vast majority resolved by a single course of antibiotics. Drug discontinuation due to UTIs was extremely rare, reported in eight (0.3%) dapagliflozin-treated patients and one (0.1%) placebo-treated patient [30]. Having an age > 65 years, female gender and a history of recurrent UTIs, but not the baseline level of HbA1c, were predictors of UTIs. This analysis also failed to demonstrate a definitive dose relationship between glycosuria and UTI.

Comparable data have been reported for empagliflozin [19,28] and canagliflozin [16,34-35]. In FDA briefing data for the latter drug, the reported incidence of UTIs was similar in subjects receiving 100mg or 300mg or a placebo – about 3-6% – with the majority of cases in women (87%). This incidence of UTIs was slightly higher in patients with moderate renal impairment: 6.2% with canagliflozin 100mg and 7.4% with canagliflozin 300mg vs 6% in the placebo group [29]. This incidence was increased in patients who were slightly older and with a longer mean duration of diabetes (12 years). Severe and upper UTIs were extremely rare. Again, the time lag before the first UTI was highest during the first 18 weeks and then declined: for canagliflozin, the median duration was 44 and 80 days (100mg and 300mg, respectively) compared with a placebo at 120 days [16]. Other commonly reported adverse events were increased urination, vulvovaginal pruritus, thirst, constipation and nausea.

7. Blood pressure

Chronic osmotic diuresis caused by glycosuria would be anticipated to reduce blood pressure, and dose-related increases in 24-h urinary volumes of between 100ml and 470ml have been reported [16-19,32-36]. Reductions in systolic blood pressure (SBP) of up to 5mmHg have been described in trials of dapagliflozin, whether used as an add-on therapy or on its own. Canagliflozin has similarly been shown to significantly reduce SBP. It is well known that SGLT-2 inhibitors have diuretic-like effects, lowering SBP by 3-5mmHg, which could benefit the majority of patients with T2DM. The precise mechanism behind the BP-lowering action of SGLT-2 inhibitors, however, is still unclear and does not appear to be based on natriuretic effects. Indeed, although these agents have mildly natriuretic effects, they are nothing like diuretics. Part of their BP-lowering effect is presumed to be due to osmotic diuresis [38]. However, they might also reduce BP too much in some patients, with consequences including hypotension (mainly postural), dizziness and dehydration [16-19]. In the FDA briefing data for canagliflozin, these symptoms were two to three times more frequent in the treated vs placebo groups, depending on the dose, and also much greater in older patients aged ≥ 75 years [34,35]. These symptoms were also more frequent in patients using loop diuretics and those with a glomerular filtration rate (GFR) < 60ml/min.

8. Renal effects

Chronic kidney disease (CKD) is a major health problem in patients with T2DM. Stage 3-5 CKD (GFR < 60ml/min) affects around 25% of such patients and represents an under-recognized problem in clinical practice. Most OADs have limitations in cases of renal impairment because they require
dose adjustments or are contraindicated for safety reasons. In fact, the activity of SGLT-2-i depends on the number of nephrons, which means that the first consequence of renal impairment on SGLT-2-i action is reduced efficacy. For this reason, the use of SGLT-2-i is neither recommended nor allowed in those with an estimated GFR (eGFR) < 40ml/min because of the lack of effectiveness rather than risks. In patients with reduced baseline eGFR (40-60ml/min), mild transient changes in eGFR (~4 to 6ml/min), albumin-to-creatinine ratio and blood urea nitrogen were observed in the early phase of a study in stage-3 CKD patients. However, 26-week SGLT-2-i treatment resulted in a return of these parameters to baseline levels, along with an increase in serum potassium and magnesium in such patients [18-19]. In canagliflozin-treated patients, the 24-h glucosuric effect decreased progressively in those with moderate-to-severe renal impairment [16,39]. In diabetic patients with glomerular hyperfiltration, SGLT-2-i may improve GFR and might possibly protect long-term renal function [40-41].

9. Lipoproteins

The cardiovascular (CV) safety of antidiabetic agents represents a major issue because of the well-established high CV risk in T2DM subjects. The FDA has imposed strict rules for the potentially increased CV risk of every new antidiabetic agent based on premarketing, phase-II and phase-III trials, and post-marketing study data [12]. Yet, all SGLT-2-i raise low-density lipoprotein cholesterol (LDL-C), thereby raising doubt concerning the CV risk induced by such increases. Thus, in T2DM patients with a baseline LDL-C between 90 and 110mg/dl, the increase is about 5% with dapagliflozin 10mg, and 2.4% and 3.1% with empagliflozin 10mg and 25mg, respectively [18]. The magnitude of the increase seems slightly higher with canagliflozin, with mean increases in LDL-C of 4.5% with 100mg/day [16,42].

On the other hand, a small increase in high-density lipoprotein cholesterol (HDL-C) is consistently reported with all SGLT-2-i [16-19]. With canagliflozin monotherapy, HDL-C was increased by 6.8% and 6.1% in the 100mg/day and 300mg/day treatment groups, respectively, compared with a placebo (p < 0.001 and p < 0.01, respectively) [42]. With dapagliflozin 10mg, a mean 6.3% HDL-C increase has been reported [43]. It has sometimes been postulated that the detrimental effects of the LDL-C increase induced by SGLT-2-i might be counterbalanced by the parallel HDL-C increase, leading to little or no change in the LDL-C/HDL-C ratio in most clinical trials. However, these findings have to be viewed with caution, as HDL-C particles are dysfunctional in T2DM patients – there is a marked reduction in their antiatherogenic effects – and it is still not clear whether the slight HDL-C increase observed with SGLT-2-i is truly cardioprotective.

Serum triglyceride levels have been mildly reduced in several studies with SGLT-2-i [16–19]. A mean 5.2% decrease in plasma triglycerides was reported with dapagliflozin 10mg [43]. With canagliflozin 300mg, mean plasma triglyceride levels decreased by 7.5% to 16% [18,35]. Thus far, however, the long-term effects of SGLT-2-i-induced lipid changes remain unknown, although the results of the ongoing CV outcome trials are expected to clarify this point.

10. Cardiovascular safety

Currently, the available information on outcomes such as stroke, heart attack and other CV complications is limited. The data for dapagliflozin submitted to the US FDA are the most comprehensive so far, and include a hazard ratio of 0.67 [95% confidence interval (CI): 0.42-1.08] for a composite endpoint comprising CV-related death, non-fatal stroke, non-fatal myocardial infarction and hospitalized angina [18]. Yet, a short-term (24-week) study in T2DM patients with preexisting CV disease treated with dapagliflozin failed to find any excess CV risk [42]. For this reason, several large and longer-term CV outcomes studies with SGLT-2-i are currently ongoing [44-47]. However, looking at the preliminary data from phase-II/-III studies of dapagliflozin, and the phase-II/-III studies [18] and intermediate data from CANVAS (Canagliflozin Cardiovascular Assessment Study), there were no signs of CV harm during the first 18 months [45]. In all phase-II/-III studies, only one specific indicator was found for fatal and non-fatal stroke with canagliflozin, but it was not significant [relative risk (RR): 1.47 (95% CI: 0.83-2.59)]. Is the transient hypotension observed with the drug a possible explanation for this? This was not confirmed by the time course of the events. Some data suggest an early increase (within the first 30 days) for CV events, while MACE-plus analysis in CANVAS vs controls revealed 13 vs one events (two-to-one randomization, n = 2 886/1 441 patients).

These data represent a very small and non-significant number of patients and, at this time, CV risk is not considered a serious hazard with these drugs [45]. Nevertheless, only long-term trials specifically designed to answer the question will give clear information in future. Thus, larger studies with CV endpoints are currently ongoing and expected to provide data from 2017 onwards. So far, CANVAS I (NCT01032629) has recruiting >4 000 T2DM patients who are at increased CVD risk [45], while the Empagliflozin Cardiovascular Outcome Event Trial (EMPA-REG-OUTCOMES, NCT01131676) has recruited an estimated 7 000 patients to date [46] and the Dapagliflozin Effect on Cardiovascular Events trial (DECLARE, NCT01730534) has only just begun recruiting participants [47].

11. Drug interactions

UDP-glucuronosyltransferase (UGT) inducers (such as rifampin, phenytoin, phenobarbital and ritonavir) increase the metabolism of canagliflozin, thereby decreasing active canagliflozin levels in the blood. Thus, doses of canagliflozin need to be increased from 100mg to 300mg in such patients. On the other hand, canagliflozin increases the area under the curve (AUC) for digoxin and, thus, patients receiving digoxin treatment should be monitored [16]. On the other hand, there were no clinically meaningful drug – drug interactions
for dapagliflozin observed with several medications used concomitantly by T2DM patients, including Met, sitagliptin, digoxin, simvastatin and warfarin [48,49].

12. Uric acid levels

SGLT-2-i have been reported to lower serum uric acid (SUA) levels [50]. This is related to the subsequent increased urinary excretion of SUA most probably due to glycosuria.

13. Liver effects

Mean exposure to dapagliflozin in patients with moderate and severe hepatic impairment was 36% and 67% higher, respectively, compared with healthy subjects with no liver issues. However, no pharmacokinetic interactions were found between dapagliflozin and simvastatin, valsartan, warfarin or digoxin [48,49]. The possible hepatic adverse effects of canagliflozin, described in a report submitted to the FDA at the end of 2012 [51], have not been confirmed so far.

14. SGLT-2 inhibitors and malignancy

The potential relationship between SGLT-2-i and cancer is also under investigation. Cancers are more frequently seen in diabetic patients, and some anti-diabetic agents, such as Pio, and GLP-1 drugs for pancreatitis have been suspected of increasing their incidence, although this has not been confirmed by either studies [13-15] or regulatory agencies [52]. The overall proportion of patients with cancers or undetermined tumours is similar in TD2M patients treated with dapagliflozin compared with a placebo or comparator agent (1.43% vs 1.30%, respectively). However, breast and bladder cancers are somewhat more commonly seen with dapagliflozin. The FDA submission file reported nine breast cancers in 4 287 patients receiving dapagliflozin vs no cases in 1 941 patients taking a placebo or comparator, and seven bladder cancers in 4 310 patients taking dapagliflozin compared with no cases in 1 962 patients taking a placebo or comparator [53]. However, it should be noted that haematuria was documented before exposure to dapagliflozin in four of the seven patients later found to have bladder cancer, and the women with breast cancer had been taking dapagliflozin for <1 year (two of the nine cases were diagnosed within 6 weeks of starting dapagliflozin treatment).

The incidence of breast or bladder tumour events was low for canagliflozin and had a similar rate vs non-canagliflozin-treated patients [16]. A pooled analysis of nine trials with approximately 8 000 person-years of exposure showed no differences in the incidence of bladder cancer between the canagliflozin (five out of 6 648 patients) and control (four out of 3 640 patients) groups [34]. No data for cancer cases with other SGLT-2-i studies are currently available. The US FDA in its review of dapagliflozin noted a non-significant excess number of breast and bladder cancers, with the latter potentially due to ascertainment bias related to the treatment of drug-related urinary symptoms [54].

15. Bone effects and fractures

Owing to its mechanism of action, SGLT-2-i could potentially affect renal tubular transport of bone minerals [55]. For this reason, bone turnover has been studied for several SGLT-2-i. Dapagliflozin had no effect on markers of bone formation and resorption or on bone mineral density (BMD) after 50 weeks of treatment in both male and postmenopausal female T2DM patients, who were inadequately controlled by Met alone [55]. Bone formation was measured by procollagen type 1 N-terminal propeptide (P1NP) and resorption by C-terminal cross-linking telopeptides of type 1 collagen (CTX), while BMD was assessed by standardized dual-energy X-ray absorptiometry (DXA) measurements. In a study where BMD was followed by DXA in older T2DM patients receiving canagliflozin treatment for 52 weeks (DIA3010), a very small, non-clinically relevant BMD decrease was measured and was probably due to weight loss [55].

As for fractures, the number seen with dapagliflozin was extremely small and similar to that reported for placebo. When large sets of data were pooled for patients receiving canagliflozin (n = 6177), there was a small increase in adjudicated fractures, with an incidence rate/1 000 person-years of exposure of 12.28 ± 1.24 for canagliflozin vs 9.44 ± 1.55 in the non-canagliflozin group (FDA Broad Dataset, July 2012). This discrepancy between normal formation/resorption markers and BMD evolution, and the fact that fractures were recorded early after the initiation of treatment has yet to be clarified, which means that, so far, no definitive conclusions can be drawn [55,56]. The potential excess number of fractures was mostly limited to the upper extremities, making it highly unusual for a bone-fragility issue and suggesting that falls may be a factor, although again the information submitted so far is not sufficient for drawing any conclusions [56]. Further data on BMD and fractures are forthcoming and are needed to confirm whether there is a safety issue related to fractures and a putative link with falls.

16. In summary

Based on the currently available data, the overall safety of the three SGLT-2-i discussed in this review is relatively good. Monami et al. [57] recently published a meta-analysis of 31 trials (22 trials vs placebo, five vs metformin, one vs glipizide and three vs sitagliptin), involving a total of 7 524 patients taking SGLT-2-i and 3 628 taking a placebo or comparator agent, for efficacy and adverse events (AEs). In their review as in our present study, these new anti-diabetic agents were mostly found to induce a significant increase in genital mycotic infections [Mantel-Haenszel odds ratio (MH-OR): 3.34-6.04] that was more frequent in women and especially those who were premenopausal, with only a slight increase in men. The risk of UTIs was consistent but very small; found in all trials vs comparators or a placebo, it was only statistically significant in the single study vs glipizide (p < 0.025). Predictors of these two infectious syndromes
are a history of such recurrent infections, female gender and age > 65 years, but not baseline HbA1c levels, amount of glycosuria or SGLT-2-i dose. For all serious AEs, the MH-OR was 0.74-1.07 (no risk) and, for total hypoglycaemia, the MH-OR was 0.74 vs Met (not significant, NS), 0.73 vs sitagliptin (NS) and 0.05 vs glipizide (p < 0.01). For hypoglycaemia vs placebo, the MH-OR was 1.34 (p < 0.01), which is usually found with a placebo (as with Met and sitagliptin) and not clinically meaningful.

17. Conclusion

Apart from genital mycotic infections and urinary infections that are somewhat frequent, but usually mild and rarely leading to drug discontinuation, SGLT-2-i appear to be well tolerated. However, at this time, they are not recommended for patients with a history of recurrent urinary and/or genital infections. The long-term CV tolerability is being monitored in several ongoing trials, as justified by the LDL-C elevation, transient hypotension and volume depletion seen with all SGLT-2-i. On the other hand, potentially beneficial effects are expected with favourable effects on BP, body weight, triglycerides and HDL-C. As for malignancies, the only risk found was with dapagliflozin for bladder cancer, which merits follow-up, although it appears unlikely because of its early appearance after starting the drug. The need for adequate renal function is well documented, although the mode of action in SGLT-2 transporters in the proximal tubule should not aggravate any existing damage in the glomerulus, and may even offer benefits through less glucotoxicity, lower SBP and reduced proteinuria. Indeed, SGLT-2-i at all doses have shown no association with serious major AEs and, so far, appear to be a safe new class of OADs for treating T2DM, particularly because of significant improvements in HbA1c, body weight and BP without hypoglycaemia, thus contributing to the management of T2DM patients by offering new oral drug combinations.

Disclosure of interests

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