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REVIEW

A consensus statement for the clinical use of the renal sodium-glucose co-transporter-2 inhibitor dapagliflozin in patients with type 2 diabetes mellitus

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ABSTRACT

Introduction: The present review developed a clinical consensus based on a Delphi method on Dapagliflozin, a selective inhibitor of the renal sodium-glucose co-transporter-2 (SGLT2-I) in the treatment of patients with Type 2 diabetes mellitus.

Areas covered: Panel members, using a 5-point scale, were asked to rate 9 statements on pharmakodinamic, mode of action on glycaemic and extra-glycaemic effects, and safety of dapaglifozin, Members also aimed to identify the patient most susceptible to the treatment with dapagliflozin .

Expert commentary: Dapagliflozin is effective in lowering the plasma glucose concentration with a good safety profile. Dapagliflozin can be utilized in combination with all other antihyperglycaemic agents at all stages of the disease: however, a reduced GFR limits its efficacy. As for the other drugs of the class, Dapagliflozin positively modifies other risk factors for CV disease: these effects will be tested in the so far largest cardiovascular outcome trial for the SGLT2 inhibitors so far, the DECLARE trial, which will communicate whether this class of drugs will be disease-modifier in patients with type 2 diabetes also in primary prevention.

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Dapagliflozin; sodium-glucose co-transporter-2 inhibitor; diabetes type 2; cardiovascular disease; diabetic complications

1. Background

Glycemic control is crucial to reduce the risk of long-term diabetic complications. Pharmacologic intervention is required in the vast majority of patients with type 2 diabetes mellitus (T2DM); however, treatment itself needs to be intensified over the time in the attempt to ensure long-term glycemic control. Recently, a number of new glucose-lowering agents have become available: the sodium–glucose cotransporter-2 (SGLT2) inhibitors (canagliflozin, dapagliflozin, and empagliflozin) belong to the latest class of antidiabetic agents to be introduced in the diabetes pharmacopeia [1]. The SGLT2 is responsible for most of the glucose reabsorption at the level of the renal tubule. This reabsorption, which is enhanced in individuals with T2DM, contributes to maintain hyperglycemia, setting the ground for the use of specific inhibitors of SGLT2 (SGLT2-I). Because of this inhibition, tubular glucose threshold is lowered, and glucose is lost into the urine, leading to reduction of plasma glucose levels. Of note, the glucose-lowering effect occurs independently of pancreatic β-cell function or insulin sensitivity [2].

Dapagliflozin was the first SGLT2-I approved in the Europe in 2012 and therefore the one with the longest usage in the clinical practice. Yet, due to the short time in the market, there are still clinical uncertainties on its efficacy, durability, positioning, and safety. Furthermore, there is growing consensus that the populations enrolled in clinical trials may differ in significant ways from those seen in practice [3]. In the attempt to consolidate available knowledge, a group of Italian experts conveyed in order to develop a clinical consensus regarding dapagliflozin and its clinical use. Such consensus was based on the Delphi method.

2. Methods

The Delphi method is a structured communication technique which relies on a panel of experts to rank level of knowledge when the evidence-based information in a given area does not entirely capture clinical needs [4]. For the present consensus process, a two-step modified Delphi method was used. The first step consisted of one round of *online* questionnaires and the second one of a face-to-face meeting. The online questionnaire was generated by a panel of eight expert diabetologists and included nine statements for total of 40 items. The eight members of the expert panel were identified on the basis of their scientific activity (academic position, scientific publications, congress and course presentations, membership in national and/or international Scientific Societies and Committee, etc.). The eight experts identified the total of 9 statements and 40 items after a preliminary evaluation of the topics with a major need of clarification and debate in the community of Italian experts in diabetes. Such

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questionnaire was then administered to 42 expert diabetologists (i.e. the panel) via a web-based platform. The members of this panel were clinicians with strong experience in diabetes, homogeneously located in the whole country. They were asked to rate each items using a 5-point scale (1, extremely disagree; 2, disagree; 3, agree; 4, mostly agree; and 5, extremely agree). Consensus was considered reached if ≥66% of the panel strongly agree/disagree on the inclusion/exclusion of a given item. After completion of the survey, items were categorized as follows: a, negative consensus: ≥66% with a score of 1 and 2; b, positive consensus: ≥66% with a score of 3, 4, and 5; and c, no consensus: ≤66% for 1 + 2 or 3 + 4 + 5. In the occasion of the face-to-face meeting, evidences from the literature were thoroughly examined for those items not achieving agreement. As a result of the discussion, items that were considered clear-cut were only briefly discussed, and some of the discussion on the items went off-track. This obviously resulted in some off-track discussion in this report as well. One item was judged futile and dropped while three underwent rewriting. The final document then consists of 9 statements and 39 items (see Table 1): 4 items related to mechanism of action (statement 1); 3 items related to glucose-lowering efficacy (statement 2); 8 items related to clinical use (statement 3); 3 items related to the effect on blood pressure (BP) (statement 4); 4 items related to effect on body weight (statement 5); 4 items related to tolerability (statement 6); 4 items related to special patient populations (statement 7); 6 items related to cardiovascular (CV) and renal aspect (statement 8); and 3 items related to CV outcome studies (statement 9). In round 2, 33 of 39 items reached consensus after discussion (26 positive and 7 negative), while no consensus was reached for 6 items. The overall discussion was technically driven by an expert in the Delphi methodology, as reported in the Acknowledgments.

3. Consensus process

3.1. Mechanism of action

Dapagliflozin is a highly specific SGLT2-I causing urinary glucose excretion through reduced tubular glucose threshold: this represents the main mechanism of the glucose-lowering action of the drug. Following its administration, daily urinary glucose excretion averages 50–80 g/24 h, which remains constant over time [5]. Such an effect is immediate and allows a swift glucose-lowering action. Dapagliflozin does not have a direct effect on beta cell function and on insulin action in peripheral insulin-sensitive tissues (skeletal muscle, adipose tissue, and liver). However, due to the improvement in glycemic control and the consequent relief of glucose toxicity, both beta cell function and insulin sensitivity can be improved [6,7]. Due to its rapid effects on kidney, dapagliflozin rapidly reduces also glucose toxicity. Several registrative trials confirmed that the insulin-independent fast glucose-lowering effect of dapagliflozin does not generate specific metabolic or apparent CV harm [8]. A possible direct effect on the alpha cell leading to increase glucagon secretion has been claimed [9]. Whether or not this mechanism has relevant clinical implications will require further evidence. One possible consequence, however, is the limitation of the risk of hypoglycemia. Due to the renal mechanism of action, the ability of dapagliflozin (as well as all other SGLT2-I) to lower plasma glucose levels is directly proportional to the glomerular filtration rate (GFR): the glucose-lowering efficacy decreases progressively with GFR reduction. As GFR approaches 45 ml/min/1.73 m^2, all gliflozins become largely ineffective in lowering plasma glucose levels [10–12].

The panel agrees that: 1. The glycosuric effect is the main mechanism of action of dapagliflozin; 2. It may reduce the glucose-toxicity; 3. The glucose-lowering efficacy decreases with reduction of glomerular filtration rate.

3.2. Antihyperglycemic action

Administration of dapagliflozin to T2DM patients lowers fasting plasma glucose by ≈17 mg/dl and postprandial glucose levels by ≈38 mg/dl. These effects are associated with an average 0.5–0.6%, up to 1.4%, HbA1c reduction. Such a reduction occurs both as monotherapy and in association with other glucose-lowering agents including insulin [13–24].

Dapagliflozin can be used at any stage of T2DM, and it is effective independently of baseline HbA1c and duration of the disease, unlike other antidiabetic agents (e.g. glinides or sulfonylureas) that show progressive loss of glucose-lowering efficacy mainly because of β-cell function loss. Unlike sulfonylureas, dapagliflozin does not increase the risk of hypoglycemia.

Though the majority of dapagliflozin studies has short duration, few long-term studies showed that dapagliflozin is associated with significant durability and remains well tolerated over time [14,25–27].

Dapagliflozin administration can be associated with increased glucagon secretion and endogenous glucose production, an effect that may hamper some of the glucose-lowering efficacy [6]. Therefore, the association with metformin- or incretin-based therapies might result in a more persistent efficacy due to the inhibitory effect of the former on hepatic glucose production and the glucagon suppression exerted by the latter.

Besides the glycemic effect, dapagliflozin, through osmotic diuresis and loss of glucose in the urine, exerts a lowering effect on BP and body weight that may be of clinical significance, as well as other SGLT2-I (vide infra).

The panel concurs that dapagliflozin: 1. Acts on both fasting and post-prandial glucose; 2. It is effective regardless of the duration of the disease; 3. Its glucose-lowering efficacy persists over the time.

4. Use in clinical practice

4.1. Plasma glucose and HbA1c

According to the European Medicines Agency recommendations, SGLT-I can be used as first-line mono-therapy in metformin-intolerant patients and as add-on in those with inadequate glycemic control with metformin as well as other glucose-lowering agents, including insulin. Because of its specific mechanism of action, which is independent of effects on β cell function and insulin action, a significant reduction in HbA1c is obtained in monotherapy as well as in combination with all other therapeutic options. Dapagliflozin efficacy has been demonstrated in patients with a broad spectrum of HbA1c (7.0–12%), with an HbA1c reduction more pronounced in subjects with higher baseline HbA1c levels [10].

Table 1. The online questionnaire to rate each items using a 5-point scale (1, extremely disagree; 2, disagree; 3, agree; 4, mostly agree; and 5, extremely agree). Full color available online.

	1	2	3	4	5	TOT
Statement 1: dapagliflozin mechanism of action, 5-point scale for agreement						
1.1 The glycosuric effect of dapagliflozin is the main relevant mechanism of action from the clinical point of view	0	3	9	20	10	42
	7%		93%			100%
1.2 The efficacy on glycemia decreases progressively with reduced glomerular filtration rate	0	1	4	14	23	42
	2%		98%			100%
1.3 Correcting hyperglycemia with insulin-independent mechanism can be harmful in some patients with type 2 diabetes	18	15	7	2	0	42
	79%		21%			100%
1.4 Dapagliflozin is able to contrast the glucotoxicity rapidly	1	0	4	20	17	42
	2%		98%			100%
Statement 2: antihyperglycemic action of dapagliflozin, 5-point scale for agreement	1	2	3	4	5	TOT
2.1 It acts on both postprandial and fasting glucose	0	0	9	20	13	42
	0%		100%			100%
2.2 Dapagliflozin is effective regardless of the duration of the disease	0	1	8	15	18	42
	2%		98%			100%
2.3 The glucose-lowering efficacy of dapagliflozin persists over time	0	0	18	20	4	42
	0%		100%			100%
Statement 3: dapagliflozin use in clinical practice, 5-point scale for agreement	1	2	3	4	5	TOT
3.1 It is the drug of first choice in patients failing on metformin	11	22	6	2	1	42
	79%		21%			100%
3.2 It is indicated in any combination therapy	1	6	19	9	7	42
	17%		83%			100%
3.3 It is limited in its use by the current reimbursement system	3	3	17	10	9	42
	14%		86%			100%
3.4 It has to be used preferentially in combination with insulin	5	28	7	2	0	42
	79%		21%			100%
3.5 It is effective in reducing hyperglycemia in all patients with filtrate ≥60 ml/min/1.73 m^2	1	2	15	14	10	42
	7%		93%			100%
3.6 It can be used regardless of baseline glycated hemoglobin level	0	12	9	8	13	42
	29%		71%			100%
Statement 4: Blood pressure, 5-point scale for agreement	1	2	3	4	5	TOT
4.1 The blood pressure reduction of dapagliflozin in a hypertensive patient is quantitatively significant and represents a clinical advantage	0	0	16	14	12	42
	0%		100%			100%
4.2 Dapagliflozin can be used in patients on antihypertensive therapy, with normal blood pressure	0	8	15	17	2	42
	19%		81%			100%
4.3 Dapagliflozin can be used without risks of hypotension in normotensive patients	0	2	25	10	5	42
	5%		95%			100%
4.4 It should not be used in patients treated with loop diuretics	0	13	12	8	9	42
	31%		69%			100%
4.5 It should not be used in patients on any diuretic therapy	7	26	7	0	2	42
	79%		21%			100%
Statement 5: body weight, 5-point scale for agreement	1	2	3	4	5	TOT
5.1 Weight loss with dapagliflozin is clinically relevant	0	1	18	13	10	42
	2%		98%			100%
5.2 Weight loss and reduction in glycated hemoglobin with dapagliflozin are strongly correlated	1	21	9	9	2	42
	52%		48%			100%
5.3 The condition of overweight/obesity in patients with type 2 diabetes is a preferential parameter for dapagliflozin choice	0	7	21	9	5	42
	17%		83%			100%
5.4 Dapagliflozin is appropriate in a normal-weight patient	0	4	28	6	4	42
	10%		90%			100%
Statement 6: dapagliflozin tolerability, 5-point scale for agreement	1	2	3	4	5	TOT
6.1 The increase in urinary tract infections with dapagliflozin is clinically relevant	10	22	8	1	1	42
	76%		24%			100%
6.2 The increase in genital infections with dapagliflozin is clinically relevant	0	17	14	6	5	42
	40%		60%			100%
6.3 The presence of a history of recurrent genital infections precludes from the decision to prescribe dapagliflozin	0	20	16	4	2	42
	48%		52%			100%
6.4 In case of genital infection, dapagliflozin should be permanently suspended	7	31	3	1	0	42
	90%		10%			100%
Statement 7: dapagliflozin use in special populations, 5-point scale for agreement	1	2	3	4	5	TOT
7.1 Dapagliflozin is not to be used in patient with more than 75 years	1	25	8	7	1	42
	62%		38%			100%
7.2 Dapagliflozin is to be preferred in case there was a need to avoid hypoglycemia	0	7	16	12	7	42
	17%		83%			100%
7.3 The effect of dapagliflozin on long-term renal function is not negative	0	2	14	12	14	42
	5%		95%			100%
7.4 The risk of ketoacidosis with dapagliflozin is limited to the use in patients with type 1 diabetes	11	24	5	0	2	42
	83%		17%			100%

(*Continued*)

Table 1. (Continued).

	1	2	3	4	5	TOT
Statement 8: in reference to the cardiovascular profile, 5- point scale for agreement	1	2	3	4	5	TOT
8.1 The reduction in cardiovascular events, in secondary prevention, can influence my choice of using an SGLT2 inhibitor in patients with high cardiovascular risk with a previous event	0	3	9	12	18	42
	7%			93%		100%
8.2 The reduction in cardiovascular events, in secondary prevention, can influence my choice of treatment to use an SGLT2 inhibitor in patients with cardiovascular risk factors without a previous event	0	4	17	13	8	42
	10%			90%		100%
8.3 Using dapagliflozin for the impact on cardiovascular risk factors	0	1	15	18	8	42
	3%			97%		100%
8.4 The lipid effects of dapagliflozin can positively influence my choice of treatment	3	12	19	8	0	42
	36%			64%		100%
8.5 With dapagliflozin, the reduction of uric acid plasma levels is clinically relevant	1	7	23	9	2	42
	19%			81%		100%
8.6 The reduction of albuminuria with dapagliflozin is clinically relevant	1	9	24	5	3	42
	24%			76%		100%
Statement 9: The significance of the Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58), 5-point scale for agreement	1	2	3	4	5	TOT
9.1 The DECLARE study will provide information on the use of dapagliflozin in patients with type 2 diabetes in primary prevention	0	1	10	12	19	42
	2%			98%		100%
9.2 The DECLARE study is similar in its design and recruited people to other cardiovascular outcome studies with SGLT2 inhibitors	2	18	12	6	4	42
	48%			52%		100%
9.3 The DECLARE study will be able to give more evidence, being the study with a much larger population than other cardiovascular outcome studies with SGLT2 inhibitors	0	3	16	16	7	42
	7%			93%		100%

Consensus was considered reached if ≥66% of the panel strongly agree/disagree on the inclusion/exclusion of a given item. Items were categorized as follows: a, negative consensus: ≥66% with a score of 1 and 2; b, positive consensus: ≥66% with a score of 3, 4, and 5; and c, no consensus: ≤66% for 1 + 2 or 3 + 4 + 5.
SGLT2: sodium–glucose cotransporter-2.
Green: Consensus; Red: No consensus; Brown: Mixed.

Dapagliflozin has been assessed as add-on to metformin, metformin slow/extended release, glimepiride, pioglitazone, sitagliptin, and insulin [13–15,17–24]. More recently, DURATION-8 study has shown that dapagliflozin administered in combination with exenatide once-weekly improves glycemic measures and CV risk factors in T2DM patients inadequately controlled with metformin with no significant adverse effects [28]. In patients inadequately controlled, despite high doses of insulin, addition of dapagliflozin improves glycemic control without insulin dose escalation [29]. In contrast, patients receiving placebo required a progressive increase in insulin dose to maintain glycemic control [30]. On a practical ground, the information leaflet recommends to reduce the dose of insulin or insulin secretagogues when adding an SGLT2-I to minimize the risk hypoglycemia.

In spite of this broad indication, in Italy the use of dapagliflozin, as well as all other SGLT2-I, remains low manly due to reimbursement policy and its prescription being limited to the specialist.

The panel agrees that dapagliflozin 1. Is as valid option in patients with metformin failure; 2. It can be used in combination with all other therapeutic options; 3. In spite of this, its use in Italy remains low mainly due to reimbursement restrictions and the prescription being limited to the specialist; 4. Its combination with insulin is a valid therapeutic option; 5. It is particularly effective in patients with preserved kidney function.

4.2. Blood pressure

The osmotic diuresis associated with the use of dapagliflozin is the most likely explanation for a significant and sustained reduction in BP [31] as the natriuretic effect is limited and transient. Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) are decreased to a greater extent in hypertensive than in non-hypertensive subjects [32,33]. At SBP ≤120 mm Hg, dapagliflozin caused only a marginal reduction in BP, with no substantial increase of orthostatic hypotension. In hypertensive T2DM subjects, dapagliflozin 10 mg significantly improved BP and HbA1c with no difference in tolerability compared to placebo. Its BP-lowering properties were particularly favorable in patients already receiving a β blocker or calcium-channel blocker [34]. Also, even when used in patients receiving angiotensin receptor blockers/angiotensin converting enzyme inhibitors or potassium-sparing diuretics or in those with moderate renal impairment, no increased risk for hyperkalemia has been detected [35]. Of interest, the reduction in BP is not associated with significant changes in heart rate. Because of the osmotic effect of this agent, caution should be paid with respect to volume depletion. Dapagliflozin-induced osmotic diuresis could result in intravascular volume contraction with hypotension, postural dizziness, and syncope. Hypotension due to dapagliflozin-induced osmotic diuresis appears to be at a greater risk among the elderly, in patients with moderate renal impairment, or in subjects taking loop diuretics [36]. Volume depletion may also represent the trigger for few cases of acute renal failure that have prompted a recent US FDA warning.

In summary, dapagliflozin, as well as other SGLT2-I, could benefit T2DM patients who need a diuretic-like effect to optimize BP control, thus adding efficacy to antihypertensive drug regimens.

The panel agrees that: 1. Dapagliflozin reduces blood pressure in a clinically significantly, quantitative and persistent manner providing an additional clinical advantage; 2. Dapagliflozin can be used in patients on anti-hypertensive therapy and blood

pressure already at target; 3. It should be used preferentially used in patients not treated with loop diuretics.

4.3. Body weight

Dapagliflozin in monotherapy as well as in combination therapy exerts a favorable effect on weight loss [37]. Findings suggested that about two-thirds of the weight loss observed with dapagliflozin was attributable to reductions in fat; about one-half was attributable to reductions in fat. Moreover, the reductions in fat mass and waist circumference with dapagliflozin treatment occurred in the context of a sustained elevation in spot urinary glucose excretion, which itself was significantly associated with decreases in fat mass [38]. The gradual reduction in body weight, with decreased waist circumference, is consistent with a reduction of fat mass, which accounts for two-thirds of the total weight loss observed with dapagliflozin [38]. The observed reduction in body weight, however, is less than the one expected on the basis of the average calorie loss (200–300 kcal/day). This is most likely is due to a concomitant increase in caloric intake as a compensatory mechanism [39] and may well account for person-to-person variability of the body weight loss. Since the compensatory mechanism(s) are likely to be modulated by the central nervous system, concomitant use of drugs that may affect appetite and/or satiety may results in a greater body weight loss as it has been recently suggested by the results of the DURATION 8 trial exploring the effect of dapagliflozin plus exenatide once weekly [28]. Since the average body weight decrease with SGLT2-I is less than 3 kg, and predominantly on fat mass, the use of these drugs seems to be useful also in lean patients.

Data pooled from seven studies evaluating dapagliflozin 10 mg as monotherapy or combination therapy over 24 weeks showed that weight loss of 2 kg contributed to 6% of the total HbA1c reduction, to 28% of the overall SBP reduction, and to 24% of the overall DBP reduction [33].

Though the reduction in body weight might exert a favorable effect on glycemic control, the results of studies where dapagliflozin was added on top of sulfonylurea [25], insulin, or metformin [29,38] show a disconnection in temporal profiles between the changes in weight and HbA1c, suggesting that the beneficial effect on glycemic control is not completely related to weight loss.

The panel agrees that: 1. Weight loss with dapagliflozin is clinically relevant; 2. The weight loss and the reduction in glycated hemoglobin with dapagliflozin are only partially related; 3. Dapagliflozin may be used in patients with type 2 diabetes irrespectively of body weight; 4. Normal weight should not necessarily discourage the use of dapagliflozin.

5. Dapagliflozin tolerability

Patients treated with dapagliflozin may have a nonsignificant increased risk of urinary tract infections (UTIs), while they have a clear increased risk of genital infections [40]. In a pooled data analysis from 12 phase II and phase III clinical trials with dapagliflozin both as mono therapy and as add-on therapy, a higher genital infection incidence was observed with dapagliflozin (4–6%) than with placebo (1%) [41,42]. Genital infections are typically mild to moderate in intensity, mainly diagnosed by symptoms, and responsive to standard antifungal therapy, with only few cases of inadequate response. The increased genital infection incidence is more common in women (vulvovaginal mycotic infection, vaginal infection, and vulvovaginal candidiasis) than in men (balanitis, fungal genital infection, and balanitis candida). Generally, the first genital infection episode tends to occur early in the course of treatment, and recurrent infections are uncommon [43]. Patients with a previous personal history of genital infection are more likely to face this problem.

In a UK-based observational study, the overall incidence of UTI was increased among patients with T2DM compared to patients without diabetes [44], with more recent observations suggesting only a mild increase of these episodes with the use of SGLT2-I. UTIs are generally mild to moderate in severity, more common in women, with both sexes responding to standard dose of antimicrobial treatment. Patients already suffering of recurrent UTIs are more likely to experience a relapse while taking either placebo or dapagliflozin. The occurrence of UTI, as monitored in clinical trials, is more frequent soon after initiation of treatment [43].

The interruption or discontinuation of dapagliflozin as a result of events of genital infections was rare and occurred in 0–0.2% of on dapagliflozin groups vs. 0% of on placebo [43]. Similarly, patient treated for UTIs did not interrupt study participation or medication due to the infection [41]. Anyhow, patients should be advised about the risk of infection, and it is important to give them proper instructions about seeking medical care if infection is suspected and, most importantly, to keep appropriate self-care.

The panel agrees that: 1. Overall, urinary tract with dapagliflozin are not clinically relevant unless ignored; 2. In the case of an event, dapagliflozin may not be necessarily stopped. 3. The panel remains uncertain as to whether genital infection with dapagliflozin may have clinical relevance: they do not have serious clinical consequences, but may represent a barrier to undertake or continue treatment with a SGLT2-I once patients have experienced one or more events. Whether a history of recurrent UTIs should preclude from prescribing dapagliflozin, the panel did not reach a consensus, and suggests that this should be discussed at the individual level with the person with diabetes to assess his/her understanding of the potential implications of the use of the drug, his/her self-care abilities and overall educational level.

6. Dapagliflozin in special populations

Efficacy and safety of dapagliflozin as monotherapy or in combination with other antidiabetic agents have been determined in a pooled analysis including a large number of patients aged ≥65 years of age compared with those aged <65 years old. Adverse events (AEs) and discontinuations due to AEs were more common in older vs. younger patients and were more frequent with dapagliflozin than placebo, though serious AE frequency was similar. The frequency of hypoglycemia was comparable across age groups and was higher with dapagliflozin than placebo with rare major episodes. UTIs occurred at a similar rate with both treatments in older patients, with no increase vs. younger patients.

Genital infections were more common with dapagliflozin, with no increase in older patients. Volume reduction AEs were uncommon, with a higher frequency with dapagliflozin than placebo in patients ≥75 years old. Dapagliflozin did not increase the risk of fractures or falls regardless of age [45]. AEs of renal function were more common with dapagliflozin than placebo and increased with age. Most of these AEs were limited and transient increases in serum creatinine. Nevertheless, renal function should be monitored carefully in the elderly patient with T2DM.

Clinical trials of dapagliflozin have shown no deleterious effects on renal function. On the contrary, data suggest a potential protective role for SGLT2-I therapy on the kidney [46,47]. The potential nephroprotective effect of SGLT2 inhibitors is further supported by the results of a recent trial showing that in patients with T2DM, CV disease and various degree of chronic kidney disease, empagliflozin therapy for a median of 3.1 years significantly slowed the progression of renal disease and reduced the rate of clinically relevant renal events [48]. The most accredited mechanism responsible for such a protection is the reduction of intraglomerular pressure due to activation of the tubularglomerular feedback. SGLT2-I causes increased Na^+ delivery to the macula densa leading to local adenosine release. Adenosine triggers vasoconstriction of the afferent arteriole with reduction of intraglomerular pressure [49–51]. In addition, reduced glucose passage across the proximal tubular cells may lead to decreased oxidative stress, inflammation, and tubuleinterstitial fibrosis [52].

Under stress conditions or in the presence of reduced insulin availability, SGLT2-I may increase the risk of diabetic ketoacidosis (DKA) as previously discussed. Most cases of DKA under treatment with SGLT-2 inhibitors were reported in individuals with type 1 diabetes or autoimmune diabetes and/or under conditions of infection, alcohol intake, or surgery [53]. In more than 18,000 patients exposed to dapagliflozin in the randomized controlled T2DM study program, including DECLARE (Dapagliflozin Effect on Cardiovascular Events), the frequency of reported events suggestive of DKA (blinded and unblinded events) was less than 0.1% (Data on file).

The panel agrees that: 1. There is no evidence for a negative effect of dapagliflozin on long-term renal function 2. Ketoacidosis may occur under states of insulin deficiency often associated with stress events; therefore, it should be largely recognizable and preventable. 3. The panel did not reach consensus with regards of the use of dapagliflozin in people >75 years old. The recommendation is to use caution and evaluate the risk-to-benefit on the individual level.

7. Dapagliflozin and CV risk

Dapagliflozin addresses three cardiovascular disease (CVD) risk factors: hyperglycemia, body weight, and BP [54,55], the triad characterizing the metabolic syndrome mostly associated with CVD [56].

Concerning lipids, small changes in fasting lipid profile were reported with SGLT2-I, including an increase in high-density and low-density lipoproteins and a decrease in triglycerides [57]. In general, dapagliflozin appears to induce not a significant effect on lipid levels in individual studies [58]. Whether these changes in lipid profile represent a clinically significant effect remains unknown.

Reduction in levels of uric acid has consistently been reported with SGLT2-I: this effect is mediated by the facilitated glucose transporter member-9, a urate transporter, which secretes urate back into the urine in exchange for glucose [50]. Dapagliflozin has also a modest but significant effect on uric acid elimination [59].

Albuminuria predicts morbidity and mortality, as well as CV and renal outcomes in patients with T2DM. Dapagliflozin resulted in greater reductions in albuminuria compared with placebo in patients receiving renin–angiotensin system blockade with microalbuminuria or macroalbuminuria at baseline [60]. The long-term effects of dapagliflozin on urinary albumin/creatinine ratio (UACR) were demonstrated also in patients with increased albuminuria and impaired renal function. Dapagliflozin treatment was associated with a persistent 40% reduction in UACR [46]. After an initial decline, estimated glomerular filtration rate (eGFR) remained stable for the 2 years of the study in the dapagliflozin group, as opposed to a progressive decline in patients receiving placebo. Thus, reductions in albuminuria, along with an indication of a long-term delay in worsening eGFR, suggest that dapagliflozin may exert a favorable effect on preventing/delaying progression of renal disease.

A significant reduction in CV composite end point along with a significant reduction of hospitalization for heart failure has been reported in the EMPA-REG CV OUTCOME trial employing empagliflozin. A CV outcome trial testing safety/superiority of dapagliflozin is currently ongoing (see below). At the present time, data on CV risk with dapagliflozin rely on pooled and meta-analyses. These analyses suggest that dapagliflozin is associated with no increase in the CV risk in terms of primary composite end point (time to first event of CV death, myocardial infarction [MI], stroke, and hospitalization for unstable angina) and secondary composite end point (time to first event including events of the primary composite end point plus unplanned coronary revascularization and hospitalization for heart failure) and with a decrease in hospitalization for heart failure. Another recent meta-analysis has reported similar potential beneficial effect on CV outcomes of all SGLT2-I considered [61]. A simulated projection by using the Archimedes model showed that adding dapagliflozin to other antidiabetic agents further decreases CV and microvascular complications associated with T2DM over a 20-year period [62]. Thus, dapagliflozin has the potential for a beneficial effect both in the overall population and in those with a history of CV disease [8].

The panel concurs with: 1. The reduction in cardiovascular events, in secondary prevention, can influence the choice of using a SGLT2 inhibitor in patients with high cardiovascular risk and previous events; 2. The reduction in cardiovascular events, in secondary prevention, can influence the choice of using a SGLT2 inhibitor even in patients with cardiovascular risk without previous events; 3. The reduction in uric acid observed with dapagliflozin is clinically relevant; 4. The reduction in albuminuria is clinically relevant.

5. The panel did not reach consensus with respect to the extent to which the effects of dapagliflozin on lipid profile may influence the choice of treatment. It was, however, the

impression that the ongoing CV outcome trials will provide better evidence to guide an educated choice.

7.1. The role of the Multicenter Trial Evaluating the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58) (DECLARE)

The long-term effect of dapagliflozin on CV outcomes will be elucidated after completion of an ongoing placebo-controlled trial that was planned to randomize approximately 17,150 patients with T2DM at high risk for CV events, either with known CV disease (secondary prevention cohort) or at least two CV risk factors (primary prevention cohort). DECLARE-TIMI 58 is an event-driven trial, with an estimated median follow-up of a median of 4.5 years. It is expected to end in 2019 and is currently the largest ongoing SGLT-2-I outcome trial: therefore, it should be powered to answer the question as to whether dapagliflozin may confer CV benefits, as well as addressing other safety-related questions. DECLARE is designed to test the primary efficacy objective, i.e. to determine whether when added to background therapy, dapagliflozin, when added to background therapy and compared with placebo, will reduce risk of CVD, nonfatal MI, or nonfatal ischemic stroke. Moreover, it will test a primary safety objective, i.e. to establish that dapagliflozin compared with placebo will not increase the risk of CV death, nonfatal MI, or nonfatal ischemic stroke. Hospitalization for unstable angina or heart failure, as well as all-cause mortality, will also be investigated.

To date, preliminary results are available for the CV safety study of canagliflozin (CANVAS, CANagliflozin cardioVascular Assessment Study), while the EMPAREG-OUTCOME trial for empagliflozin has been already published [63,64]. Interim analysis suggests that canagliflozin is not associated with an increased risk of major adverse cardiovascular events (MACE), even if an increased risk for stroke was found within the first 30 days of therapy. CANVAS will continue until 420 3-point MACEs will be accrued. Regrettably, this will result in relatively limited power for evaluation of the potential for CV benefits, due to a relatively smaller number of events. For this reason, MACE from CANVAS and CANVAS-R, planning to recruit 5700 individuals with T2DM with change in albuminuria as the primary outcome, will be combined to increase the statistical power to detect the effect on primary 3-point MACE end point.

In the EMPA-REG, 7020 patients with established CV disease were enrolled. This trial has shown that in patients with T2DM, in secondary prevention, empagliflozin, irrespectively of dosing, was able to reduce the primary end point (CV death, nonfatal MI, and nonfatal stroke).

The panel agrees that: 1. The DECLARE study will provide information on the use of dapagliflozin in patients with type 2 diabetes also in primary prevention; 2. The DECLARE study will offer more robust evidence on the role of SGLT2 inhibitors in terms of CV safety, being the study with the largest population compared to the other cardiovascular outcome trials with SGLT2 inhibitors.

The Panel did not reach consensus with respect to which extent the design of DECLARE is similar to that of the CV outcome trial using SGLT2-I. It was indeed felt that while the DECLARE population differs from that of EMPA-REG OUTCOME, more information should be gained for the DECLARE population for a more educated comparison with CANVAS

8. Expert opinion

Dapagliflozin is effective in lowering plasma glucose concentration in patients with T2DM and shows a good safety profile. Dapagliflozin can be utilized in combination with all other anti-hyperglycemic agents at all stages of the disease. However, its efficacy, as for the other drugs in the class, is limited in the presence of reduced GFR. Due to its good safety profile, dapagliflozin can be used in the elderly patients with T2DM, though caution should guide its prescription in these individuals due to the potential risk of dehydration and reduced carbohydrate intake and in those on diuretic treatment. Despite a consistent amount of phase II, phase III, real-world evidence, and randomized controlled trials, the exact role of this class of drugs in the management of diabetes mellitus is still unclear. According to the most recent American Diabetes Association guidelines on the management of hyperglycemia in patients with T2DM, SGLT2-I is one of the six treatment options that may be considered as combination therapy with metformin if the HbA1c target is not achieved after 3 months of metformin monotherapy at maximum tolerated doses [65]. Moreover, dedicated renal outcome trials are needed to confirm that SGLT2-I, in addition to their glycemic and BP benefits, may provide nephroprotective effect. Part of the skepticism toward their use derives also from the fact that their mechanism of action is not completely clarified: for this reason, additional mechanistic studies are needed to comprehensively understand their benefit beyond their ability to increase glycosuria.

Dapagliflozin positively modifies also other risk factors for CV disease like BP and body weight: these effects are being tested in the CV outcome trial, the DECLARE, which will communicate whether this class of these drugs will be disease modifiers also in patients with T2DM in primary prevention. Notwithstanding the benefits, AEs such as UTIs, genital infections, and the risk of dehydration and hypotension, especially in elderly patients under diuretic therapy, and of ketoacidosis in those withdrawing carbohydrate intake should always be considered when dapagliflozin is prescribed.

9. Five-year view

The mechanism(s) of action not only in the kidney but also in the CV system will be clarified. New SGLT2-I will be available so that they will be able not only to abrogate more efficiently the SGLT2 but also to influence intraglomerular blood flow beyond their ability to modify macula densa sodium–chlorine interactions.

Key issues

- Dapagliflozin decreases blood glucose by abrogating the glucose reabsorption by the proximal tubule in the kidney.
- Dapagliflozin can be utilized in combination with all other anti-hyperglycaemic agents at all stages of the disease.
- Its efficacy, as for the other drugs in the class, is limited in the presence of reduced GFR.

- Dapagliflozin, beside hyperglycaemia, positively modifies other risk factors for CV disease like blood pressure and body weight.
- Most important adverse events are UTIs, genital infections, the risk of dehydration and hypotension especially in elderly patients.

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