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EXPERT OPINION

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Pharmacokinetics, pharmacodynamics and clinical efficacy of dapagliflozin for the treatment of type 2 diabetes

Marianna Maranghi, Anna Carnovale, Cosimo Durante, Giovanna Tarquini, Giusy Tiseo & Sebastiano Filetti†

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Introduction: Dapagliflozin (DAPA) (Farxiga or Forxiga) is a sodium glucose cotransporter 2 (SGLT2) inhibitor approved for type 2 diabetes mellitus (T2DM) treatment.

Areas covered: The review focuses on the pharmacokinetics (PK), pharmacodynamics(PD) and clinical studies published on DAPA. The authors searched-PubMed database for English language studies describing DAPA characteristics and use in T2DM subjects published through June 2014.

Expert opinion: DAPA exhibits favorable PK and PD properties and is effective in reducing glycemic levels. In addition, DAPA shows beneficial/neutral effects on other risk factors contributing to T2DM metabolic control. Increased risk of genital and urinary infections and episodes of volume depletion represent the major concerns for its use. FDA requires additional data to assess imbalances in bladder cancer and drug cardiovascular safety. The mechanism of action and the very low risk of drug–drug interaction make it an ideal drug for rapidly reducing glucotoxicity and restoring clinical response to other antidiabetic drugs.

Keywords: dapagliflozin, kidney, SGLT2 inhibitors, type 2 diabetes

Expert Opin. Drug Metab. Toxicol. (2015) 11(1):125-137

1. Introduction

According to International Diabetes Federation data, 382 million people worldwide have diabetes and by 2035 this number is expected to rise to 592 million [1]. Of note, this increased prevalence is observed among patients younger than 20 years and older adults (defined as those aged ≥ 65 years), and is related to the increasing rate of obesity, a sedentary lifestyle and to the aging population [1,2]. Type 2 diabetes mellitus (T2DM) comprises 90% of diabetes worldwide [1].

Micro- and macrovascular atherosclerotic complications are the two major causes of high morbidity and costs related to T2DM [3,4]. Patients with T2DM have a two- to fourfold increased risk of developing cardiovascular disease (CVD) and of dying when CVD is present [5]. In 2004 in the USA, heart disease was noted on 68% and stroke on 16% of diabetes-related death certificates among people aged 65 years or older [6].

Insulin resistance (IR) and relative insulin deficiency are traditionally regarded as the main pathophysiologic defects of T2DM [7]. Genetic predisposition, central adiposity and lack of exercise contribute to IR development. IR promotes altered fat metabolism which in turn accelerates β-cell dysfunction and the development of other atherosclerotic risk factors and comorbidities (i.e., atherogenic dyslipidemia, hypertension, chronic inflammation) [7,8]. Increased hepatic glucose production [9], accelerated incretin deficiency/resistance in the gastrointestinal tract [10],

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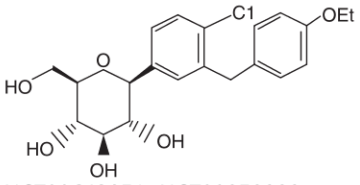
Box 1. Drug summary.

Drug name	Dapagliflozin
Phase	Approved by FDA on January 2014
Indication	In addition to diet and exercise in adults with type 2 diabetes mellitus as monotherapy, or as an add-on to other glucose-lowering agents, including insulin
Pharmacology description	Reversible, highly specific inhibitor of sodium glucose cotransporter 2
Route of administration	Oral
Chemical structure	
Pivotal trial(s)	NCT00643851, NCT00859898, NCT00528879, NCT01042977

hyperglucagonemia in α-cells [11] and increased glucose reabsorption in the kidneys are other mechanisms involved in the diabetic dysregulated metabolism [12].

At present, a wide range of treatments capable of individually targeting these defects are available (**Table 1**), yet the numbers of subjects with poor glycemic control and complications have not decreased over the past 10 years [13].

2. Overview of the markets and unmet needs

A 'modern antidiabetic' drug should improve blood glucose levels while conferring a favorable/neutral (or at least not worse) effect with regard to body weight, blood pressure and lipid abnormalities observed frequently in people with type 2 diabetes.

Indeed, according to FDA antidiabetic agents approval guidance, drugs for the treatment of T2DM should not result in an unacceptable increased risk for CVD [14], the main cause of morbidity and mortality in the population with T2DM.

Lifestyle changes are the first step for the treatment of T2DM: exercise and weight loss improve glycemic levels as well as other CVD risk factors [15]. However, long-term adherence to lifestyle modifications is a key limiting factor for their efficacy.

In many countries, up to nine classes of drugs are available today for the management of diabetes (**Table 1**). Each drug addresses distinct pathogenetic mechanisms of T2DM. They can be used as monotherapy or in addition to metformin (MET), according to the clinical features of the patient and specific features of the drug [16].

Most of these agents potentiate insulin secretion or action thus depending for their effect and durability on residual β-cell function and often exhibiting unfavorable effects on cardiovascular (CV) risk factors and body weight.

Furthermore, main limits of current therapies are hypoglycemic risk, route of administration (injection), efficacy on hard CV end points, safe use in subjects with chronic kidney and hepatic disease, risk of drug–drug interaction and costs.

3. Introduction to the compound

Ninety per cent of glucose filtered by the kidney is reabsorbed by the low-affinity/high-capacity sodium glucose cotransporter 2 (SGLT2) [17-19]. Studies in diabetic animals have demonstrated an increased expression of SGLT2 mRNA and increased activity of this protein in diabetic kidneys [20-22]. Agents that inhibit SGLT2 represent a novel class of drug which has recently become available for treatment of T2DM. These drugs increase glycosuria and decreases plasma glucose levels in an insulin-independent manner (**Figure 1**). Furthermore, they improve insulin sensitivity and β-cell function, while increasing hepatic glucose production and glucagon levels, probably as a compensatory response to the reduced levels of glucose and insulin [23,24]. The first non-selective inhibitor of SGLT2/SGLT1 was phlorizin, a β-glucoside comprised two aromatic rings (A and B) joined by an alkyl spacer of three carbons [17] used in research over 150 years for its properties in increasing glucose urinary excretion, reducing hyperglycemia and glucotoxicity and normalizing insulin sensitivity and β-cell function in animals [25,26]. The use of phlorizin in humans was limited by its metabolic instability due to rapid cleavage by glucosidase, low oral bioavailability and lack of selectivity for SGLT2 leading to adverse effects. These limitations led efforts to modify the phlorizin structure to enhance selectivity for SGLT2 and increase stability to β-glucosidase [27]. Modifications in phlorizin structure improved SGLT2:SGLT1 selectivity (1200:1) and affinity for SGLT2 (EC_{50} = 1.1 nM) [17].

Dapagliflozin (DAPA) is a reversible highly specific inhibitor of SGLT2 [27], with a > 1400-fold selectivity for SGLT2 relative to other SGLT, and a > 30,000-fold selectivity for SGLT2 over glucose transporter GLUT1, -2 and -4 and no interaction with several enzymes, transporters and ion channels screened [28]. DAPA inhibits competitively SGLT2 (K_i = 0.5 nM) in humans [28].

Three SGLT2 inhibitors, canagliflozin, DAPA and empagliflozin, are currently approved for use in patients with T2DM in over 30 countries worldwide, including the USA and the European Union and other agents are currently in clinical development [29,30].

4. Chemistry

DAPA is described chemically as (*2S,3R,4R,5S,6R*)-2-[4-chloro-3-(4-ethoxybenzyl) phenyl]-6-(hydroxymethyl) tetrahydro2H-pyran-3,4,5-triol) and its molecular formula is $C_{21}H_{25}ClO_6$. The molecular weight is 408.87. In its chemical structure, the aglycone component is attached to glucose by a

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Table 1. Main characteristics of drugs available for type 2 diabetes treatment.

Therapy	A1c	Weight	Hypoglycemia	Cardiovascular risk factors	Use in kidney failure	Drug–drug interaction	Side effects	Cost
Lifestyle change	↓	↓↓	↔	↓	Safe	None	None	Not expensive
Metformin	↓	↓	↔	↓	With caution*	Possible	Gastrointestinal effects	Not expensive
DPP-IV inhibitor	↓	↔	↔	↔	With caution*	Possible	Long-term safety not established	Expensive
GLP-1 agonist	↓	↓	↔	↓	With caution*	Possible	Gastrointestinal effects Long-term safety not established	Expensive
Sulfonylureas/ Glinides	↓	↑	↑↑	↔	With caution*	Possible	Hypoglycemia	Not expensive
Thiazolinediones	↓	↑	↔	↓	With caution*	Possible	Fluid retention Chronic heart failure Bone fractures Potential increase in MI	Expensive
Acarbose	↓	↔	↔	↔	With caution*	Possible	Gastro-intestinal effects	Expensive
Insulin	↓↓	↑↑	↑↑	↔	Safe	Possible	One to four injections daily monitoring Hypoglycemia	Expensive

*The majority of these drugs cannot be used for eGFR values < 30 ml/min/1.73m^2 and/or dose adjustments are required for eGFR values between 30 and 60 ml/min/1.73m^2.

↑: Mild increase; ↑↑: Moderate increase; ↓: Mild reduction; ↓↓: Moderate reduction; ↔: No effect.

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carbon-carbon bond, which confers metabolic stability against glucosidase enzymes (**Box 1**). DAPA is a Biopharmaceutics Classification System (BCS) Class III compound with BCS Class I-like characteristics of high, pH-independent aqueous solubility, high *in vitro* permeability and good oral bioavailability [31].

5. Pharmacodynamics

DAPA induces in a dose-dependent manner increase in urinary glucose related to filtered load (plasma glucose × glomerular filtration rate [GFR]) [31]. Doses ≥ 20 mg/day determine maximal increases in urinary glucose excretion in patients with T2DM [31]. Pharmacodynamic (PD) changes, assessed by urinary glucose excretion, are dependent on plasma glucose level and renal function (estimated by GFR) [31]. In fact, in patients with moderate-to-severe kidney disease receiving DAPA less increase in urinary glucose excretion is observed as compared with patients with normal renal function probably due to lower filtered load (plasma glucose × GFR) [32].

6. Pharmacokinetic and metabolism

Orally administered DAPA rapidly reaches peak plasma concentrations within 1 – 2 h (T_{max}) [31,32]. Food co-administration reduces the rate of absorption with no decrease in total exposure [31,32]. DAPA has extensive extravascular distribution (mean volume distribution 118 L) and 91% of the drug binds to plasma proteins [31,32]. Metabolism occurs predominantly by uridine diphosphate-glucuronosyltransferase-1A9 (UGT1A9) to the major metabolite DAPA 3-*O*-glucuronide (this metabolite is not an SGLT2 inhibitor at clinically relevant exposures) [31,32]. Experimental data suggest a major role for the kidney expressed UGT1A9 isoform in the production of DAPA 3-*O*-glucuronide [33].

Less than 10% is eliminated by oxidative metabolism. DAPA is not appreciably cleared by renal excretion (< 2% of dose is recovered in urine as parent) [31,32]. DAPA 3-*O*-glucuronide elimination occurs mainly via renal excretion, with 61% of a DAPA dose being recovered as its metabolite in urine. The half-life for orally administered DAPA (10 mg) is 12.9 h. No relevant differences were observed in DAPA exposure with respect to age, race, sex, body weight, food or presence of T2DM [31,32].

6.1 Drug interactions

Co-administration of DAPA with other antidiabetic drugs (MET, pioglitazone [PIO], glimepiride [GLI], sitagliptin [SITA]) in healthy volunteers did not impact the drug's pharmacokinetic (PK) features [31,32,34]. Reciprocally, DAPA did not interfere with the PK of the other drugs [31,32,34]. A trend for slightly greater exposure to GLI and increased incidence of hypoglycemia was detected when DAPA was co-administered with GLI in patients with T2DM [31,32]. Co-administration of DAPA with simvastatin, valsartan,

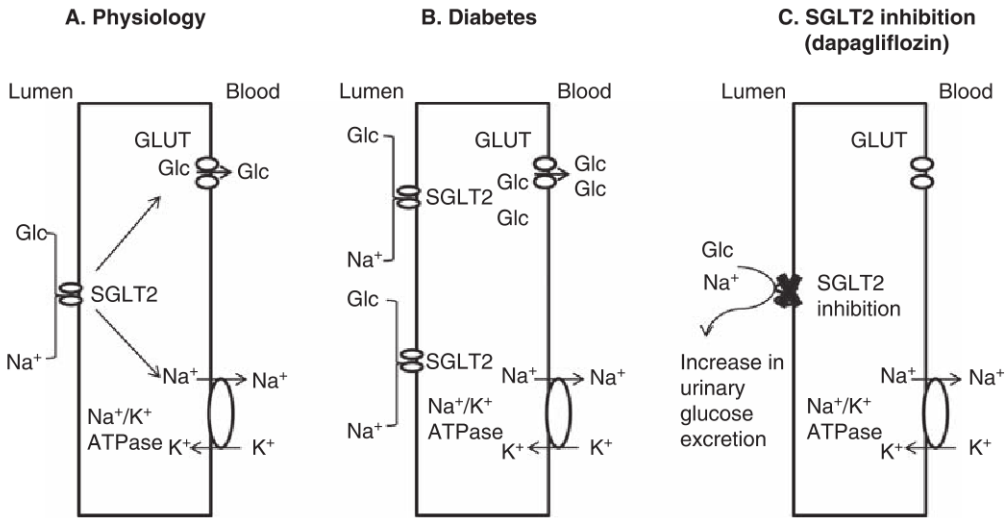

Figure 1. SGLT2, GLUT, Glc (Glucose). (A) One-hundred-eighty grams of glucose are filtered and completely reabsorbed by the kidney daily. Ninety percentage of glucose reabsorption is mediated by the low-affinity/high capacity transporter SGLT2 located in the S1 segment of the proximal tubule. Intracellular glucose is then passively transported into the blood by GLUT on the basolateral side of proximal tubule cells. **(B)** The capacity of glucose reabsorption is increased in diabetic subjects. SGLT2 mRNA expression and activity are increased in diabetic animals. Patient with type 2 diabetes have an increased glucose tubular transport maximum as a maladaptive response to chronic high blood glucose levels which contributes to hyperglycemia. **(C)** Inhibition of SGLT2 by dapagliflozin leads to increased urinary glucose excretion, thus reducing blood glucose levels

GLUT: Glucose transporter; SGLT2: Sodium glucose cotransporter 2.

warfarin, digoxin and bumetanide (medications commonly used for reducing CV risk factors or comorbidities associated with T2DM) did not result in clinically relevant interactions [31,32]. Only a mild increase in exposure to R-warfarin and S-warfarin was detected with no change in international normalized ratio [34-36].

Rifampicin and mefenamic acid are two potential modulators of UGT1A9, by inducing and inhibiting the enzyme, respectively. As expected, rifampicin significantly decreased AUC (-22%) of DAPA and mefenamic acid increased DAPA AUC (+ 51%) [34].

6.2 Renal and hepatic impairment

Renal impairment is common in T2DM, especially in older adults (defined as those aged ≥ 65 years) [37]. In patients with reduced kidney function, when DAPA was administered at the dose of 20 mg/day daily, plasma concentration of the drug and of its metabolite DAPA 3-*O*-glucuronide increased. In patients with renal impairment (defined as an estimated creatinine clearance between 80 and 20 ml/min but not receiving dialysis), PD effects are attenuated compared with those with normal renal function. Steady-state renal glucose clearance is reduced by 42, 83 and 84% in subjects with mild, moderate and severe renal impairment, respectively [38]. Probably, with decreasing renal function the efficacy of DAPA is reduced due to the fact that less glucose is delivered and filtered by the kidney and less is available to be reabsorbed. Because of decreased clinical efficacy, DAPA should not be initiated in subjects with estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2 [39].

DAPA mean C_{max} values are 12, 12 and 40% higher in patients with mild, moderate and severe hepatic impairment, respectively, compared with healthy subjects following a single 10 mg oral dose of the drug. Mean AUC with the last concentration extrapolated to infinity values are 3, 36 and 67% higher in patients with mild, moderate and severe hepatic failure, respectively. These findings suggest that systemic exposure to DAPA is related to the degree of hepatic impairment [40]. There is no dose adjustment suggestion for patients with mild or moderate hepatic failure and a risk–benefit assessment should be performed in patients with severe hepatic impairment, since safety and efficacy of this drug have not been studied in this population [39].

7. Clinical efficacy

7.1 Phase I and IIa studies

There were 28 clinical pharmacology studies conducted in 728 subjects, encompassing healthy subjects (560), subjects with T2DM (130) and subjects with renal (20) and hepatic (18) impairment [32].

In early Phase III studies, the dose selection of DAPA was narrowed to 10 mg since this dose consistently showed greater glycosuria, diuresis and benefits in terms of glycemic goals reduction with a similar safety profile [41,42]. In Europe,

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DAPA 10 mg has been proposed as the starting daily dose, while in the USA DAPA 5 mg is the recommended one. Furthermore, the 5 mg dose may be appropriate for subjects at risk for volume depletion [32].

7.2 Phase IIb and III studies

An extensive DAPA development program, including 24 studies, placebo (PBO) and active comparators, > 11000 subjects recruited and with durations ranging from 12 weeks to 4 years has been established [32]. In these studies, DAPA produced consistent and sustained reductions in glycated hemoglobin (HbA1c) as monotherapy (**Table 2**), particularly in those groups of patients with higher baseline HbA1c levels [43-46]. Instead, HbA1c decrease in the range of 0.4 – 0.7% as compared with PBO were observed when DAPA (5 or 10 mg) was added to MET [47-50], SITA [51], GLI [52], PIO [53] or insulin [54,55] in patients with treatment failure (**Tables 2**,**3**,**4**,**5**). Furthermore, DAPA reduced the weight gain associated with PIO and insulin therapy [53-55] and as a consequence a decrease in daily dose of insulin was required [54,55].

Few head-to-head studies have been performed to compare DAPA with antidiabetic drugs. In particular, DAPA 10 mg was non-inferior in reducing HbA1c levels to extended-release (XR) MET up to 2000 mg [45] and to glipizide (GLIP) up to 20 mg (**Table 5**) [56,57]. DAPA treatment was associated with better weight loss and fasting plasma glucose values as compared with XR MET [45] and with less hypoglycemia and weight loss as compared with GLIP (**Table 5**) [56,57].

Subjects with T2DM carrying early- or late-stage disease had similar HbA1c reductions on DAPA therapy compared with PBO [58].

A limited number of studies or subcohort analyses were also conducted in subjects with prior CVD, in older adults and in subjects with renal impairment. A similar HbA1c reduction was observed in subjects with prior CVD or CV risk factors [59]. On the contrary, in older adults a smaller HbA1c reduction was found [59]. The reduced renal function with advancing age may explain this finding [59]. Indeed, in subjects with moderate renal impairment (eGFR between 30 and 59 ml/min/1.73m^2), DAPA 10 mg did not produce greater HbA1c reduction compared with PBO [60].

Treatment with DAPA is also associated with weight decrease (from -0.46 to -2.16 kg) being faster over the first few weeks, followed by a more gradual decline and maintained over time in extended studies [32,43-58]. Free water loss and increased caloric loss may contribute to this effect. Weight loss seems to derive predominantly from loss of fat mass, mostly from visceral abdominal tissue than from subcutaneous abdominal tissue [49,50].

The use of DAPA is associated with modest reduction of systolic BP (SBP) (-1.3 to -5.3 mmHg PBO corrected) [32,43-58]. Episodes of orthostatic hypotension were reported in clinical studies, especially in patients treated with diuretics. This effect on BP, probably linked to the osmotic diuresis, was not dose-dependent and not accompanied by any notable changes in heart rate; no cases of hypotension and/or syncope were reported [42].

Treatment with DAPA is also associated in some studies with a mild favorable, effect on triglycerides and high-density lipoprotein cholesterol (**Tables 2**,**3**,**4**,**5**), and with a decrease in serum uric acid [32,36]. Whether these changes translate into CV events reduction and benefits need to be clarified.

8. Safety

8.1 Major events

Major and common adverse clinical events in DAPA clinical studies were genital infection (GI) and urinary tract infection (UTI), volume depletion episodes and bladder cancer [32,43-58,61].

These infections were generally of mild or moderate intensity and did not generally require the need to interrupt treatment. No clear dose–response relationship between DAPA and GIs and UTIs was demonstrated [62,63]. Events of UTIs and GI were more common in females than males, and *Escherichia coli* and fungal infections were typical detected pathogens [62,63].

Events of volume depletion (hypotension/hypovolemia/dehydration) were infrequent but more common in patients treated with DAPA 10 mg relative to PBO, in particular in the subgroups of patients ≥ 65 years of age, patients receiving loop diuretics or patients with decreased eGFR [32].

Of note, health-related quality of life is unchanged by DAPA use [64,65].

Bladder cancer occurred in 9 out of 5478 patients treated with DAPA, compared with 1 out of 3136 control patients [61,66]. Ongoing studies will investigate this to determine if there is a causal relationship between DAPA treatment and bladder cancer.

Five cases of elevated aspartate transaminases or alanine transaminases greater than three-times the upper limit of normal levels were found in DAPA trials. Of the total, two could not be attributed to another cause, resulting in possible DAPA-induced hepatic injury [61]. In light of these findings, the FDA is requiring more post-marketing studies for evaluating bladder cancer and CV risk and a pharmacovigilance program to monitor liver abnormalities associated with DAPA use [39,67].

8.2 Minor events

In clinical trials, in monotherapy, hypoglycemic episodes, although being common, were similar to PBO arm. Instead, when DAPA was added to SU or insulin hypoglycemic episodes were more frequent, but not more severe [43-58].

In clinical studies, a slight transient increase in blood urea nitrogen (1.5 – 1.8 mg/dL) and creatinine was noted [68].

9. Regulatory affairs

On January 2014, the FDA approved DAPA tablets once-daily as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

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Table 2. Comparison studies on dapagliflozin efficacy in drug naïve patients.

Study	Comparison	Phase	Population N (*A1c*)	Weeks	Mean A1c change (%)‡	Mean body weight change (kg)‡	Mean lipid profile change (%)*			Mean blood pressure change (mmHg)*‡		Adverse events (%)	
							Total cholesterol	High-density lipoprotein cholesterol	Triglyceride	Systolic blood pressure	Diastolic blood pressure	Urinary tract infection	Genital infection
Bailey *et al.* (2012) [43]	PBO	III	282 (*7 – 10%*)	24	+0.02	–0.96 (–1.74, –0.19)	+3.77	+3.74	–5.18	+0.8	+0.2	1.5	2.9
	DAPA 1 mg				-0.68 #	–2.69 (–3.44, –1.94)§	+1.03	+0.94	–6.44	–3.7	–1.1	4.2	1.4
	DAPA 2.5 mg				–0.72 (–0.95, –0.49) #	–2.64 (–3.38, –1.90)§	+2.21	–0.05	–7.83	–3.1	–2.0	1.4	6.8
	DAPA 5 mg				–0.82 (–1.06, –0.58) #	–2.69 (–3.47, –1.91)§	+1.98	+1.89	–5.89	–4.6	–1.9	2.9	2.9
Ferrannini *et al.* (2010) [44] (main cohort)	Morning dose	III	485 (*7 – 12%*)	24			–	–	–				
	PBO				–0.23 (–0.43, –0.02)	–2.2 (–3.3, –1.3)				–0.9	–0.7	4.0	1.3
	DAPA 2.5 mg				–0.58 (–0.80, –0.36)	–3.3 (–4.2, –2.3)				–4.6	–2.8	4.6	7.7
	DAPA 5 mg				–0.77 (–0.99, –0.55)¶	–2.8 (–3.8, –1.9)				–2.3	–1.7	8.0	7.8
	DAPA 10 mg				–0.89 (–1.10, –0.67)#	–3.2 (–4.0, –2.3)				–3.6	–2.0	5.7	12.9
	Evening dose												
	DAPA 2.5 mg				–0.83 ± 0.11	–3.8 ± 0.5				–4.0	–3.2	7.5	9.0
	DAPA 5 mg				–0.79 ± 0.11	–3.6 ± 0.5				–5.2	–2.0	11.8	4.4
	DAPA 10 mg				–0.79 ± 0.10	–3.1 ± 0.4				–2.3	–1.0	6.6	2.6
	Morning dose (A1c ≥ 10.1%)				–								
	n = 74				2.88 ± 1.41	–2.1 ± 3.4				–5.7	–3.3	8.8	5.9
	DAPA 5 mg				–2.66 ± 1.26	–1.9 ± 3.5				–2.5	–2.9	15.4	17.9
	DAPA 10 mg												
Henry *et al.* (2012)–Study 1 [45]	MET + PBO	III	598 (*7.5 – 12%*)	24	–1.35 (–1.53, –1.18)	–1.29 (–1. 76, –0.82)	–	–	–	–1.8	–0.4	7.5	2.0
	PBO + DAPA 5 mg				–1.19 (–1.36, –1.02)	–2.61 (–3.07, –2.15)				–4.2	–3.0	7.9	6.9
	MET + DAPA 5 mg				–2.05 (–2.23, –1.88)**‡‡	–2.66 (–3.14, –2.19)‡‡				–2.9	–2.2	7.7	6.7
Henry *et al.* (2012) Study 2 [45]	MET + PBO	III	638 (*7 – 12.5%*)	24	–1.44 (–1.59, –1.29)	–1.36 (–1.83, –0.89)	–	–	–	–1.2	0.0	4.3	2.4
	PBO + DAPA				–1.45 (–1.59, –1.31)	–2.73 (–3.19, –2.27)				–4.0	–1.9	11	12.8
	10 mg MET + DAPA 10 mg				–1.98 (–2.13, –1.83)**‡‡	–3.33 (–3.80, –2.86)‡‡				–3.3	–1.8	7.6	8.5
List *et al.* (2009) [46]	PBO MET	IIb	389 (*7 – 10%*)	12	–0.18 ± 0.10	–1.2 (–2.0, –0.4)	–	–	–	+ 2.4	+0.3	5.6	0
	DAPA 2.5 mg				–0.73 ± 0.10	–1.7 (–2.4, –0.9)				–0.4	–0.6	10.7	2
	DAPA 5 mg				–0.71 ± 0.09¶	–2.7 (–3.4, –1.9)				–3.1§	+0.8	6.8	3
	DAPA 10 mg				–0.72 ± 0.09¶	–2.5 (–3.3, –1.8)				–2.9§	–0.3	10.3	2
	DAPA 20 mg				–0.85 ± 0.11¶	–2.7 (–3.5, –1.8)				–6.4§	–2.6	10.6	2
	DAPA 50 mg				–0.55 ± 0.09§	–3.4 (–4.1, –2.6)				–4.3§	–0.5	16.9	7
					–0.90 ± 0.10¶	–3.4 (–4.1, –2.6)				–2.6	+0.1	16.1	7

Data are presented as: *mean; ‡mean ± SD from descriptive statistics or estimate of mean (95% CI). For each estimate of difference in change p-values are provided as: §($p < 0.05$ vs placebo); ¶($p < 0.001$ vs placebo); #($p < 0.0001$ vs placebo); **($p < 0.0001$ DAPA + MET vs DAPA + PBO); ‡‡($p < 0.0001$ DAPA + MET vs MET + PBO).

DAPA: Dapagliflozin; GI: Genital infections; MET: Metformin; PBO: Placebo.

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Table 3. Comparison studies on dapagliflozin versus placebo as add-on therapy to metformin.

Study	Comparison	Phase	Population N (A1c)	Weeks	Mean A1c change (%)‡	Mean body weight change (kg)‡	Mean lipid profile change (%)*			Mean blood pressure change (mmHg)*		Adverse events (%)	
							Total cholesterol	High-density lipoprotein cholesterol	Triglyceride	Systolic blood pressure	Diastolic blood pressure	Urinary tract infection	Genital infection
Bailey CJ (2010)	MET + PBO	III	546	24	–0.30 (–0.44, –0.16)	–0.9 (–1.4, –0.4)	+2.7	+0.4	+2.1	–0.2	–0.1	8	5
	MET + DAPA 2.5 mg		(7 – 10%)		–0.67 (–0.81, –0.53) ¶	–2.2 (–2.7, –1.8) #	+2.9	+1.8	–2.4	–2.1	–1.8	4	8
	MET + DAPA 5 mg				–0.70 (–0.85, –0.56) #	–3.0 (–3.5, –2.6) #	+2.2	+3.3	–6.2	–4.3	–2.5	7	13
	MET + DAPA 10 mg				–0.84 (–0.98, –0.70) #	–2.9 (–3.3, –2.4) #	+4.2	+4.4	–6.2	–5.1	–1.8	8	9
BaileyCJ (2013)	MET + PBO	III	339	102	–0.02 (–0.20, +0.23)	+1.36 (0.53, +2.20)	–	–	–	+1.5	–1.0	8	5.1
	MET + DAPA 2.5 mg		(7 – 10%)		–0.48 (–0.68, –0.29) ¶	–1.10 (–1.91, –0.29) #				+0.7	–0.1	8	11.7
	MET + DAPA 5 mg				–0.58 (–0.77, –0.39) #	–1.70 (–2.48, –0.91) #				–1.1	–1.5	8.8	14.6
	MET + DAPA 10 mg				–0.78 (–0.97, –0.60) #	–1.74 (–2.51, –0.96) #				–0.3	–1.2	13.3	12.6
Bolinder *et al.* (2012) [49]	MET + PBO	III	182	24	–0.10	–0.88	–	–	–	+0.1	+0.3	2.2	0
	MET + DAPA 10 mg		(6.5 – 8.5%)		–0.39 #	–2.96#				–2.7	–0.7	6.6	3.3
Bolinder, *et al.* (2014) [50]	MET + PBO	III	184	102	+0.12(–0.02, +0.27)	–2.12 (–2.97, –1.27)	–	–	–	–	–	7.7	1.1
	MET + DAPA 10 mg		(6.5 – 8.5%)		–0.30 (–0.43, –0.16)	–4.54 (–5.43, +3.66)						6.6	2.2

Metformin dose is ≥ 1500 mg/day for all studies.

Data are presented as: *mean; ‡mean ± SD from descriptive statistics or estimate of mean (95% CI). For each estimate of difference in change p-values are provided as: ¶($p < 0.001$ vs placebo); #($p < 0.0001$ vs placebo).

DAPA: Dapagliflozin; GI: Genital infections; MET: Metformin; PBO: Placebo.

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Table 4. Comparison studies on dapagliflozin versus placebo as add-on other therapies (glimepiride, insulin, pioglitazone, sitagliptin).

Study	Comparison	Phase	Population N (A1c)	Weeks	Mean A1c change (%)‡	Mean body weight change (kg)‡	Mean lipid profile change (%)*			Mean blood pressure change (mmHg)*		Adverse events (%)		
							Total cholesterol	High-density lipoprotein cholesterol	Triglyceride	Systolic blood pressure	Diastolic blood pressure	Urinary tract infection	Genital infection	Hypoglycemia
Strojek *et al.* (2011) [52]	GLI + PBO	III	597 (7 – 10%)	24	–0.13	–0.72	–	–	–	–	–	+6.2	0.7	4.8
	GLI + DAPA 2.5 mg				–0.58#	–1.18						+3.9	3.9	7.1
	GLI + DAPA 5 mg				–0.63#	–1.56§						+6.9	6.2	6.9
	GLI + DAPA 10 mg				–0.82#	–2.26#						+5.3	6.6	7.9
Wilding *et al.* (2012) [55]	INS ± OAD + PBO	III	808 (7.5 – 10.5%)	48	–0.47	+0.82	–	–	–	–	–	+5.1	2.5	51.8
	INS ± OAD + DAPA 2.5 mg				–0.79¶	–0.96¶						+7.9	6.4	60.4
	INS ± OAD + DAPA 5 mg				–0.96¶	–1.00¶						+10.8	9.9	55.7
	INS ± OAD + DAPA 10 mg				–1.01¶	–1.61¶						+10.2	10.7	53.6
Wilding *et al.* (2009) [54]	INS + OAD + PBO	IIb	71	12	+ 0.09	–1.90	–4.42 (–11.7,+3.5)	–0.26	–12.63	+2.8	+0.3	–	4.3	13.0
	INS + OAD + DAPA 10 mg		(7.5 – 10%)		–0.61	–4.50	–2.03 (–9.0,+5.5)	–-1.60	–2.33	–7.2	–1.2	+4.2	–	29.2
	INS + OAD + DAPA 20 mg				–0.69	–4.30	+10.00 (+2.11.+18.5)	+2.61	+3.08	–6.1	–3.9		20.8	25.0
Rosenstock J (2012)	PIO + PBO	III	480 (7 – 10.5%)	24	–0.42	+1.64	–	–	–	+1.3	+0.7	–	–	–
	PIO + DAPA 5 mg				–0.82¶	+0.09#				–0.8	–1.0			
	PIO + DAPA 10 mg				–0.97#	–0.14#				–3.4	–3.1			
Rosenstock J (extension)	PIO+ PBO	III	480 (7 – 10.5%)	48	–0.54	+ 2.99	–	–	–	+2.0	+0.4	+7.9	2.9	0.7
	PIO + DAPA 5 mg				–0.95	+ 1.35				–1.0	–0.7	+8.5	9.2	2.1
	PIO + DAPA 10 mg				–1.21	+ 0.69				–2.2	–2.4	+5.0	8.6	0
Jabbour *et al.* (2014) [51]	SITA + PBO	III	432 (7 – 10%)	24	+0.1	–0.1	–	–	–	–4.0	–	–	–	–
	SITA + DAPA 10 mg				–0.5#	–1.9#				–7.1				
	SITA + MET + PBO				0.0	–0.5				–2.4				
	SITA + MET + DAPA 10 mg				–0.4#	–2.4#				–6.0				

Data are presented as: *mean; ‡mean ± SD from descriptive statistics or estimate of mean (95% CI). For each estimate of difference in change p-values are provided as: ¶($p < 0.001$ vs placebo); #($p < 0.0001$ vs placebo).
DAPA: Dapagliflozin; GI: Genital infections; GLI: Glimepiride; OAD: Oral antidiabetic agents; PBO: Placebo; PIO: Pioglitazone; SITA: Sitagliptin.

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Table 5. Comparison studies on dapagliflozin versus glipizide as add-on therapy to metformin.

Study	Comparison	Phase	Population N (A1c)	Weeks	Mean A1c change (%)‡	Mean body weight change (kg)‡	Mean lipid profile change (%)*			Mean blood pressure change (mmHg)*		Adverse events (%)		
							Total cholesterol	High-density lipoprotein cholesterol#	Triglyceride	Systolic blood pressure**	Diastolic blood pressure‡‡	Urinary tract infection	Genital infection	Hypoglycemias
Nauck *et al.* (2011) [56]	MET + GLIP 5 mg	III	814	52	–0.52 (–0.60, +0.44)	+1.44 (+1.09, +1.78)	–0.59	–0.16	–0.76	+0.8	–0.4	+6.4	2.7	39.7
	MET + DAPA 2.5 mg		(6.5 – 10%)		–0.52 (–0.60, +0.44)	–3.22 (–3.56, –2.87)¶	+1.5	+5.88	–1.10	–4.3	–1.6	+10.8§	12.3	3.4
Nauck *et al.* (2014) extension [57]	MET + GLIP 5 mg	III	432	104	–0.14 (–0.25, –0.03)	+1.40 (+0.90, +1.80)	–	–	–	+1.2	–	+9.8	2.9	45.8
	MET + DAPA 2.5 mg		(6.5 – 10%)		–0.32 (–0.42, –0.21)§	–3.70 (–4.20, –3.20)				–2.7		+14.7	16.7	4.2

Metformin dose is ≥ 1500 mg/day.

Data are presented as: *mean; ‡mean ± SD from descriptive statistics or estimate of mean (95% CI). For each estimate of difference in change p–values are provided as: § ($p < 0.05$ vs glipizide); ¶($p < 0.0001$ vs glipizide); #difference versus MET + GLIP 0.156 mmol/l (95% CI 0.104, 0.210); **Difference versus MET + GLIP –5.0 mmol/l (95% CI –6.7, –3.4); ‡‡Difference versus MET + GLIP –1.2 mmol/l (95% CI –2.3, –0.2.).

DAPA: Dapagliflozin; GI: Genital infections; GLIP: Glipizide; MET: Metformin.

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10. Conclusion

DAPA is an orally active highly selective SGLT2 inhibitor that improves glycemic control in T2DM by reducing renal glucose reabsorption leading to urinary glucose excretion. DAPA metabolism occurs predominantly in the liver and kidney by UGT1A9 to the major inactive metabolite DAPA 3-*O*-glucuronide. DAPA is demonstrated to be effective in reducing HbA1c levels as monotherapy and as add-on therapy to a wide range of frequently used T2DM medications. Furthermore, it has shown non-inferiority for HbA1c-lowering compared with MET and GLIP in head-to-head studies.

DAPA demonstrated additional benefits by modestly reducing weight and SBP, showing a very low risk for drug–drug interactions and a low risk of hypoglycemia particularly if not used in combination with insulin or sulfonylureas.

Major limitations in its clinical use include the lack of efficacy and safety in subjects with moderate and severe renal impairment, and concerns regarding the increased risk of UTI, GI and episodes of volume depletion, particularly in the elderly as for the others SGLT2 inhibitors. Additional data are needed to definitively clarify imbalances in bladder cancer risk and to assess the drug CV risk effect.

11. Expert opinion

Selective SGLT2 inhibitors, including DAPA, represent a novel class of drugs for T2DM treatment, whose strength is the independence from insulin level or action for their efficacy in lowering glucose levels. In fact, DAPA's mechanism of action results in the direct elimination of glucose in the urine, being therefore complementary to the mechanisms of other antidiabetic drug classes.

Furthermore, in clinical studies DAPA has shown a favorable/neutral profile on other factors important for T2DM metabolic control and altered by other frequently used antidiabetic drugs. DAPA's safety profile is acceptable; however, the FDA requires long-term clinical trials and post-marketing studies to further investigate DAPA's CV and safety profiles.

While health-related patient quality of life seem unchanged by DAPA use, its use is less advisable in older adults due to its reduced efficacy and side effects.

An overweight/obese patient with newly diagnosed T2DM and high HbA1c levels represents the ideal candidate for DAPA therapy as second- or third-line agent. In fact, we think that the drug could be very effective in the early stages of glycemic failure, rapidly reducing glucotoxicity and restoring clinical response to other antidiabetic drugs whose mechanism action is insulin-dependent.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

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