Usage Patterns of Dapagliflozin in Type 2 Diabetes Management

Content

Background and Objective of the Survey	2
Methodology of the Survey	3
Literature Review	4
Survey Form	34
Survey Findings	37
Summary	52
Consultant Opinion	54

Background and Objective of the Survey

Dapagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, has emerged as a valuable addition to the treatment armamentarium for type 2 diabetes mellitus (T2DM) management. Its unique mechanism of action, which promotes urinary glucose excretion, offers several benefits in glycemic control and cardiovascular risk reduction. Usage patterns of dapagliflozin in T2DM management reflect its effectiveness, tolerability, and versatility in various patient populations.

Firstly, dapagliflozin is commonly prescribed as part of dual or triple therapy regimens in patients with inadequately controlled T2DM despite lifestyle modifications and other oral antidiabetic agents. Its glucose-lowering efficacy, when used alone or in combination with other agents such as metformin or sulfonylureas, helps achieve and maintain glycemic targets.

Moreover, dapagliflozin is particularly beneficial in patients with T2DM and established cardiovascular disease (CVD) or those at high cardiovascular risk. Clinical trials have demonstrated that dapagliflozin reduces the risk of major adverse cardiovascular events (MACE), hospitalization for heart failure, and renal events in these patient populations. Therefore, it is often favored in patients with T2DM and concomitant CVD or heart failure.

Additionally, dapagliflozin's favorable safety profile, with a low risk of hypoglycemia and potential weight loss and blood pressure reduction, makes it an attractive option for patients with T2DM who are overweight or have hypertension. Its once-daily oral dosing regimen further enhances convenience and adherence compared to other antidiabetic agents.

The objective of the survey is:

To evaluate the usage patterns of dapagliflozin in type 2 diabetes management

Methodology of the Survey

A survey was conducted to evaluate the usage patterns of dapagliflozin in type 2 diabetes management. A total of 150 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Pharmacological Properties
- Therapeutic Efficacy of Dapagliflozin
- Real-World Studies
- Tolerability of Dapagliflozin
- Adverse Events of Special Interest
- Dosage and Administration
- Place of Dapagliflozin in the Management of T2D
- Benefits of dapagliflozin
- Clinical efficacy of SGLT2i
- Current guidance for Dapagliflozin

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction[1]

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a relatively new class of antihyperglycaemic agents (AHAs) for the treatment of type 2 diabetes (T2D). These agents reduce reabsorption of glucose in the kidneys and facilitate its excretion in the urine by inhibiting the high-capacity glucose transporter SGLT2 located in the proximal convoluted tubule, thereby lowering glucose levels independently of insulin action. This unique mechanism of action of SGLT2 inhibitors complements that of other classes of AHAs, allowing for their use as combination therapy with other AHAs, including insulin. Dapagliflozin is one such SGLT2 inhibitor that is approved for the treatment of T2D in various countries worldwide, including the EU and USA. The pharmacological properties and clinical use of dapagliflozin in adults with T2D have been extensively reviewed previously in *Drugs* . This article, written from an EU perspective, focuses on recent trials, including the large DECLARE-TIMI 58 cardiovascular (CV) outcomes trial in patients with T2D with or without established cardiovascular disease (CVD).

Pharmacological Properties[1]

Dapagliflozin is a highly potent (inhibitory constant 0.55 nmol/L) and reversible SGLT2 inhibitor that is > 1400 times more selective for SGLT2 than SGLT1, the main transporter responsible for glucose absorption in the gut. Dapagliflozin increased the amount of glucose excreted in the urine and improved both fasting (FPG) and post-prandial plasma glucose levels in patients with T2D. Urinary glucose excretion (glucuresis) was seen after the first dose of dapagliflozin, was continuous during the 24 h dosing interval and maintained over the course of therapy. Dapagliflozin-induced glucuresis in patients with T2D was associated with caloric loss and a modest reduction in bodyweight, as well as mild osmotic diuresis and transient natriuresis. The loss in bodyweight with SGLT2 inhibitors is less than that calculated from calorie loss due to glucuresis, which may be because of compensatory mechanisms such as increased energy intake. A modest decrease in blood pressure (BP) was also seen with

dapagliflozin, which may be explained by a decrease in circulating volume because of the diuretic/natriuretic properties of the drug. The effects of dapagliflozin on glycaemic parameters, bodyweight and BP in large clinical trials in patients with T2D.

Dapagliflozin is rapidly absorbed after oral administration, with peak plasma concentrations usually reached within 2 h (fasted state). After a 10 mg dose, the absolute oral bioavailability of dapagliflozin is 78%. The mean steady-state volume of distribution of dapagliflozin is 118 L and it is ≈ 91% protein bound. Dapagliflozin pharmacokinetics are not affected by food to a clinically meaningful extent. Dapagliflozin is largely metabolized by UGT1A9 (an enzyme in the liver and kidneys) to its major inactive metabolite 3-O-glucuronide; the major and other metabolites of dapagliflozin do not contribute to its glucose-lowering effects. Dapagliflozin and its metabolites are largely excreted in the urine, with 75% of a dose recovered in the urine (< 2% as unchanged parent drug) and 21% in the faeces (≈ 15% as unchanged parent drug). After single-dose dapagliflozin 10 mg in healthy subjects, the mean plasma terminal elimination half-life of dapagliflozin was 12.9 h.

Therapeutic Efficacy of Dapagliflozin[1]

Glycaemic and Other Outcomes

Numerous randomized, double-blind, multicentre, phase 3 trials with dapagliflozin as monotherapy and combination therapy have demonstrated its efficacy in improving glycaemic control and reducing bodyweight and BP in a broad spectrum of patients with T2D, including those with high baseline HbA_{1c} (≥ 9%) and the elderly (aged ≥ 65 year. Results from more recent trials, including special populations such as patients with chronic kidney disease (CKD) stage 3A, hypertension or CVD.

Table 1. Efficay of oral dapagliflozin 10 mg once daily as add-on therapy in randomized, double-blind, multicentre, phase 3–4 trials and extensions in patients with T2D

Study (mean diabetes	**Duration (weeks)**	**Treatment (no. of pts)**	**Adjusted mean[a] change from BL [BL]**				**HbA_{1c} < 7% (% of pts)**
			HbA_{1c}[b] (%)	**FPG (mmol/L)**	**BW (kg)**	**SBP[c] (mmHg)**	

duration)							
Matthaei et al. (≈ 9 years)	24	DAPA + MET + SU (108)	− 0.86*** [8.1]	− 1.9*** [9.3]	− 2.7*** [89]	− 4.0*[c] [135]	32***
		PL + MET + SU (108)	− 0.17 [8.2]	− 0.04 [10.2]	− 0.6 [90]	− 0.3[c] [136]	11
	52	DAPA + MET + SU	− 0.8	− 1.5	− 2.9	− 1.0	27
		PL + MET + SU	− 0.2	+ 0.6	− 1.0	+ 1.1	11
Matheiu et al. (≈ 8 years)	24	DAPA + SAX + MET (160)	− 0.82*** [8.2]	− 1.8*** [9.9]	− 1.9*** [86]	− 1.9* [NA]	38***
		PL + SAX + MET (160)	− 0.10 [8.2]	− 0.3 [9.8]	− 0.4 [88]	+ 2.0 [NA]	12
	52	DAPA + SAX + MET	− 0.74	− 1.5	− 2.1	NA	29
		PL + SAX + MET	+ 0.07	+ 0.6	− 0.4	NA	13
Müller-Wieland et al. (≈ 7 years)	52	DAPA + SAX + MET (312)	− 1.2††[d] [8.3]	− 2.1†† [10.4]	− 3.2†† [95]	− 6.4†† [139]	40
		DAPA + MET (311)	− 0.82[d] [8.3]	− 1.6 [10.6]	− 3.5†† [98]	− 5.6†† [138]	20††
		GLIM + MET (309)	− 0.99[d] [8.3]	− 1.5 [10.4]	+ 1.8 [98]	− 1.6 [139]	34
Handelsman et al. (≈ 8 years)	26	DAPA + SAX + MET (232)	− 1.41†† [8.8]	− 1.8††† [9.5]	− 1.9†††	NA	37†
		SIT + MET (229)	− 1.07 [8.9]	− 0.6 [9.7]	− 0.5	NA	25
	52	DAPA + SAX + MET	− 1.29	− 1.4	− 2.3	− 2.6 [130]	33
		SIT + MET	− 0.81	− 0.2	− 0.8	+ 2.5 [129]	20
Frias et al.	28	DAPA + EXN + MET (228)	− 2.0§† [9.3]	− 3.66§†† [10.8]	− 3.6§†† [92]	− 4.3† [131]	45§††

(DURATION-8) (≈ 7 years)		DAPA + PL + MET (227)	− 1.4 [9.3]	− 2.73 [10.5]	− 2.2 [91]	− 1.8† [130]	19
		PL + EXN + MET (230)	− 1.6 [9.3]	− 2.54 [10.5]	− 1.6 [89]	− 1.2 [129]	27
	104 [e]	DAPA + EXN + MET	− 1.70§†	− 2.70§††	− 2.5†	− 3.1†	NA
		DAPA + PL + MET	− 1.06	− 1.20	− 3.0	− 1.1	NA
		PL + EXN + MET	− 1.29	− 1.70	− 0.8	− 0.1	NA
Vilsbøll et al. [e] (NA)	24	DAPA + SAX + MET ± SU (324)	− 1.7[d] [9.0]		− 1.5††	NA	21†f
		INS + MET ± SU (319)	− 1.5[d] [9.0]		+ 2.1	NA	13[f]
	52 [e]	DAPA + SAX + MET ± SU	− 1.51†		− 1.83††	NA	15†††f
		INS + ME ± SU	− 1.26		+ 2.75	NA	7[f]

No statistical comparisons available for two extension studies and nominal *p* values reported for two others

BL baseline, *BW* bodyweight, *DAPA* oral dapagliflozin 10 mg/day, *EXN* subcutaneous exenatide-extended release 2 mg once weekly, *FPG* fasting plasma glucose, *GLIM* oral glimepiride 4 mg/day, *INS* titrated insulin glargine (FPG goal ≤ 5.5 mmol/L), *HbA$_{1c}$* glycated haemoglobin, *MET* oralmetformin ≥ 1500 mg/day, *NA* not available, *PL* placebo, *pts* patients, *SIT* oral sitagliptin 100 mg/day, *SAX* oral saxagliptin 5 mg/day, *SBP* systolic blood pressure, *SU* oral sulfonylurea ≥ 50% of maximum dose

*$p < 0.05$, **$p \leq 0.001$, ***$p < 0.0001$ vs. PL; †$p < 0.05$, ††$p \leq 0.001$, †††$p < 0.0001$ vs. active comparator; §$p < 0.001$ vs. DAPA

[a]Values are least-squares mean in two studies

[b]Primary endpoint for the main study

[c]SBP assessed at week 8 in one study

[d]Noninferiority between treatment groups was demonstrated

[e]Abstract presentation

[f]Proportion of patients achieving target HbA1c < 7% without hypoglycaemia

Table 2. Efficay of oral dapagliflozin 10 mg once daily as add-on to existing antidiabetic therapy in randomized, double-blind, multicentre, phase 3 trials and extensions in patients with T2D and high-risk of cardiovascular complications

Study	**Duration (weeks)**	**Treatment (no. of pts)**	**Adjusted mean change from BL [BL]**				**3-item response[a] (% of pts)**
			HbA_{1c} (%)	**FPG (mmol/L)**	**Bodyweight (kg)**	**SBP (mmHg)**	
In pts with hypertension on ACEi or ARB therapy							
Weber et al.	12	DAPA (302)	− 0.6***[b,c] [8.1]	− 0.7[c] [8.8]	− 1.0[c] [86]	− 10.4**[b,c] [150]	
		PL (311)	− 0.1[b,c] [8.0]	+ 0.4[c] [8.9]	− 0.3[c] [84]	− 7.3[b,c] [150]	
In pts with hypertension on combination antihypertensive therapy							
Weber et al.	12	DAPA (225)	− 0.63***[b,c] [8.1]	− 1.0[c] [9.0]	− 1.44[c] [88]	− 11.9**[b,c] [151]	
		PL (224)	− 0.02[b,c] [8.0]	+ 0.2[c] [8.9]	− 0.59[c] [90]	− 7.6[b,c] [151]	
In pts with CVD							
Leiter et al.	24	DAPA (480)	− 0.3**[b] [8.0]	− 0.8** [9.0]	− 2.5** [95]	− 1.9** [135]	10**[b]
		PL (482)	+ 0.1[b] [8.1]	+ 0.6 [9.2]	− 0.6 [93]	+ 0.9 [135]	1.9[b]
	52	DAPA	− 0.5	− 0.9	− 3.2	− 3.6	10.6
		PL	0.0	+ 0.2	− 1.1	− 0.9	3.1
	24	DAPA (455)	− 0.38***[b] [8.2]	− 0.57* [8.9]	− 2.6*** [93]	− 2.99* [133]	12***[b]

Cefalu et al.		PL (459)	+ 0.08[b] [8.1]	+ 0.35 [8.8]	− 0.3 [94]	− 1.0 [133]	1[b]
	52	DAPA	− 0.44	− 0.96	− 2.9	− 3.40	7
		PL	+ 0.22	− 0.01	− 0.3	+ 0.18	0.7

No statistical comparisons are available for extension studies

ACEi angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BL* baseline, *CVD* cardiovascular disease, *DAPA* dapagliflozin, *FPG* fasting plasma glucose, HbA_{1c} glycated haemoglobin, *PL* placebo, *pts* patients, *SBP* systolic blood pressure

*$p < 0.05$, **$p \leq 0.001$, ***$p < 0.0001$ vs. PL

[a]Defined as the proportion of pts achieving combined reduction in HbA1c of ≥ 5.5%, bodyweight of ≥ 3% and SBP of ≥ 3 mmHg

[b]Coprimary endpoint

[c]Hierarchical testing was used for the coprimary (mean change in seated SBP followed by mean change in HbA1c) and secondary endpoints

In a randomized, double-blind, multinational, phase 3 study in patients inadequately controlled with metformin ($n = 182$), add-on dapagliflozin reduced bodyweight largely by reducing fat mass relative to placebo, with fat mass accounting for approximately two-thirds of the total weight loss. At week 24, patients receiving add-on dapagliflozin 10 mg once daily had significantly lower total bodyweight (primary endpoint; difference from placebo − 2.1 kg; baseline ≈ 92 kg; $p < 0.0001$), smaller waist circumference (− 1.5 cm; baseline ≈ 105 cm $p = 0.0143$) and less fat mass as assessed by dual X-ray absorptiometry (DXA) (− 1.5 kg; baseline ≈ 33 kg; $p = 0.0001$) than those receiving add-on placebo. A rapid decline in bodyweight was seen in the first few weeks of dapagliflozin treatment, with a gradual decline thereafter that had not plateaued at week 24. This change in bodyweight was reflected in the daily spot urinary glucose level, which showed an initial rapid increase and stable levels thereafter, supporting the DXA findings that the loss in bodyweight and fat mass with dapagliflozin was largely because of caloric loss from glucosuria. However, the initial rapid decline in bodyweight in dapagliflozin recipients may partly be because of fluid loss.

Additionally, the proportion of patients with a decrease in bodyweight of ≥ 5% was significantly higher in patients receiving dapagliflozin than those receiving placebo (31 vs. 4%; p < 0.0001). Moreover, magnetic resonance imaging in a substudy in 80 patients showed that both visceral and subcutaneous adipose tissues were reduced in dapagliflozin relative to placebo recipients (difference from placebo − 258 and − 185 cm^3, respectively; both nominal $p < 0.05$). The reductions in bodyweight, fat mass and waist circumference with add-on dapagliflozin versus add-on placebo at week 24 were maintained over 102 weeks' therapy.

Patients with Hypertension

Dapagliflozin 10 mg once daily reduced SBP and improved glycaemic control in two phase 3 studies in patients with inadequately controlled T2D and hypertension despite receiving antihypertensive therapy (angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) therapy alone or in combination with one other antihypertensive). At week 12, mean SBP and HbA_{1c} were significantly lower with dapagliflozin than placebo in both studies (first and second coprimary endpoints, respectively) (Table 2). A post hoc analysis of one study suggested that SBP was lowered with dapagliflozin to a greater degree in patients receiving a β blocker or a calcium-channel blocker as their additional antihypertensive drug than in those receiving a thiazide diuretic.

Patients with Cardiovascular Disease

Dapagliflozin 10 mg once daily improved glycaemic control and reduced bodyweight and SBP when added to usual background therapy in two phase 3 studies in patients with inadequately controlled T2D (HbA_{1c} 7–10.5% across the studies) and pre-existing CVD and hypertension. At week 24, in both studies, HbA_{1c} was lowered to a significantly greater extent with add-on dapagliflozin than add-on placebo, and a significantly greater proportion of patients in the dapagliflozin group had a 3-item response than in the placebo group (coprimary endpoints; Table 2). Treatment benefits with dapagliflozin were maintained at week 52 in the extension studies]. A significantly ($p < 0.005$) greater proportion of patients in the dapagliflozin than placebo groups in both studies achieved a target HbA_{1c} of < 7% at week 24 (19 vs. 13%; 16 vs. 8%), with the between-group differences maintained at week 52 (19 vs. 10%; 15 vs. 5%). Efficacy of dapagliflozin was maintained during longer-term treatment in a second extension

of 52 weeks (total 104 weeks' therapy, according to a post hoc pooled analysis of the two studies.

In a pooled analysis of five, phase 2–3 clinical trials of ≤ 52 weeks' duration, patients with T2D and a history of HF had clinically meaningful reductions from baseline in HbA_{1c} (placebo-adjusted mean change − 0.55%; baseline 8.2%), bodyweight (− 2.7 kg; baseline ≈ 97 kg) and SBP (− 2.1 mmHg; baseline ≈ 134 mmHg) with dapagliflozin 10 mg monotherapy or add-on therapy to other AHA regimens (*n* = 171) relative to placebo/active comparator (*n* = 149).

Patients with Renal Impairment

A post hoc analysis of a phase 2/3 study suggested treatment benefit with dapagliflozin in patients with CKD stage 3A (eGFR ≥ 45 and < 60 mL/min 1.73 m^2), with findings supported by the randomized, double-blind, multinational, phase 3 DERIVE study. In DERIVE, patients with inadequately controlled T2D (HbA_{1c} 7–11%), a BMI of 18–45 kg/m^2 who were receiving other AHA regimens and who had CKD stage 3A were randomized to receive 24 weeks of dapagliflozin 10 mg once daily (*n* = 159) or placebo (*n* = 161). At week 24, dapagliflozin significantly (*p* = 0.05) lowered HbA_{1c} (primary endpoint; placebo-adjusted mean change − 0.34; baseline ≈ 8.2%), FPG (− 0.9 mmol/L; baseline ≈ 10 mmol/L), bodyweight (− 1.3 kg; baseline ≈ 90 kg) and SBP (− 3.1 mmHg; baseline ≈ 135 mmHg) relative to placebo. A randomized, double-blind, multinational, phase 3 study (CompoSIT-R) in patients inadequately controlled with metformin ± sulfonylurea (HbA_{1c} 7–9.5%) and who had mild renal impairment (eGFR ≥ 60 to < 90 mL/min/1.73 m^2) showed that the addition of sitagliptin 100 mg once daily (*n* = 307) was noninferior (primary hypothesis) and superior to that of dapagliflozin 10 once daily (*n* = 306) in improving glycaemic control [HbA_{1c} least squares (LS) mean change from baseline − 0.51 vs. − 0.36%; baseline ≈ 7.8% *p* = 0.006].

Cardiovascular and Renal Outcomes

The effects of dapagliflozin on CV and renal outcomes were assessed in the randomized, double-blind phase 3 DECLARE-TIMI 58 trial in patients aged ≥ 40 years with T2D (HbA_{1c} ≥ 6.5 to < 12%) and established atherosclerotic CVD (ASCVD) or multiple risk factors for ASCVD. Patients were also required to have creatinine clearance (CL_{CR}) ≥ 60 mL/min. Patients with multiple risk factors were men aged ≥ 55 years or women aged ≥ 60 years with

one or more of traditional risk factors, such as hypertension, dyslipidaemia [i.e. low-density lipoprotein level > 130 mg/dL (3.36 mmol/L) or use of lipid-lowering therapies] or use of tobacco.

The study was originally designed to assess the effect of dapagliflozin on the primary safety outcome of major adverse CV events (MACE). However, based on the findings of the EMPA-REG OUTCOME trial of empagliflozin that emerged during the conduct of DECLARE-TIMI 58, its study design was modified to include dual primary efficacy outcomes of MACE and the composite of CV death and hospitalization for heart failure (CV death/HHF). The two prespecified secondary endpoints were renal composite outcome (see Table 3 for definition) and death from any cause. At baseline, patients (n = 17,160 randomized) had a mean age of 64 years and 41% had established ASCVD, including coronary artery disease (33% of patients) and heart failure (HF; 10%). The mean duration of diabetes was ≈ 11 years, mean HbA_{1c} was 8.3% and the mean estimated glomerular filtration rate (eGFR) was 85 mL/min/1.73 m^2 (45 and 7% of patients had an eGFR of 60–90 and < 60 mL/min/1.73 m^2, respectively]. Patients were randomized to receive dapagliflozin 10 mg once daily or placebo in addition to other AHAs; use of other AHAs was at the discretion of the treating physician. The median follow-up duration was 4.2 years (69,547 patient-years).

Table 3. Efficacy of oral dapagliflozin 10 mg once daily in in the DECLARE-TIMI 58 cardiovascular outcomes trial

Outcomes	**Event rate (%) [per 1000 patient-years]**		
	DAPA (*n* = 8582)	**PL (*n* = 8578)**	**HR vs. PL (95% CI)**
Primary efficacy outcomes			
CV death or HHF[a]	4.9 [12.2]	5.8 [14.7]	0.83 (0.73–0.95)*[b]
MACE[a]	8.8 [22.6]	9.4 [24.2]	0.93 (0.84–1.03)[b]
Secondary outcomes[c]			
Renal composite[a,d]	4.3 [10.8]	5.6 [14.1]	0.76 (0.67–0.87)
Death from any cause[a]	6.2 [15.1]	6.6 [16.4]	0.93 (0.82–1.04)
Other outcomes[c]			
Additional renal composite[a,e]	1.5 [3.7]	2.8 [7.0]	0.53 (0.43–0.66)
HHF	2.5 [6.2]	3.3 [8.5]	0.73 (0.61–0.88)

MI	4.6 [11.7]	5.1 [13.2]	0.89 (0.77–1.01)
Ischaemic stroke	2.7 [6.9]	2.7 [6.8]	1.01 (0.84–1.21)
Death from CV cause	2.9 [7.0]	2.9 [7.1]	0.98 (0.82–1.17)
Death from non CV cause	2.5 [6.0]	2.8 [6.8]	0.88 (0.73–1.06)

CV cardiovascular, DAPA dapagliflozin, *eGFR* estimated glomerular filtration rate, *HHF* hospitalization for heart failure, *HR* hazard ratio, *MACE* major adverse cardiovascular event (CV death, MI or ischemic stroke), *MI* myocardial infarction, *PL* placebo

*$p = 0.005$

[a]Prespecified outcomes

[b]After demonstrating the noninferiority of DAPA vs. PL ($p < 0.001$) for the primary safety outcome of MACE, superiority (two-sided α level of 0.023) of DAPA over PL was demonstrated for the endpoint of CV death or HHF, but not for MACE

[c]Statistical analyses are hypothesis generating because of hierarchical testing

[d]Defined as ≥ 40% decrease in eGFR to < 60 ml/min/1.73 m^2, end-stage renal disease, or death from renal or CV cause

[e]Defined as ≥ 40% decrease in eGFR to < 60 ml/min/1.73 m^2, end-stage renal disease, or death from renal cause

Dapagliflozin significantly lowered the rate of CV death/HHF versus placebo, but there was no significant between-group difference in the rate of MACE (dual efficacy endpoints assessed after confirming the noninferiority of dapagliflozin and placebo for the primary safety outcome of MACE) (Table 3). As MACE was not lowered to a significant extent with dapagliflozin versus placebo, analyses of secondary and other endpoints (Table 2) conducted hierarchically were only hypothesis generating. The lower rate of the composite endpoint of CV death/HHF in dapagliflozin recipients was attributed to the lower rate of hospitalization for heart failure (HHF) with dapagliflozin than placebo; the rate of CV death was generally similar between the two groups (Table). Sensitivity analyses of the primary efficacy endpoints supported the findings of the primary analysis of the outcomes.

In terms of secondary and other endpoints, results suggest that dapagliflozin reduces the likelihood of progression of renal disease, as indicated by lower incidences of the renal

composite and additional renal composite outcomes in dapagliflozin than placebo recipients (Table 3). For the individual components of the renal outcomes, dapagliflozin relative to placebo was associated with significant reduction in sustained decline in eGFR by ≥ 40% to < 60 mL/min per 1.73 m^2 [hazard ratio (HR) 0.54; 95% CI 0.43–0.67; p< 0·0001), end-stage renal disease (ESRD; HR 0.31; 95% CI 0.13–0.79; p = 0.013), and renal death or ESRD (HR 0.41; 95% CI 0.20–0.82; p = 0.012). The mean decrease from baseline in eGFR was significantly (p < 0.0001) greater with dapagliflozin than placebo at 6 months, but had equalized with placebo by 2 years, and was significantly (p < 0.0001) less than that with placebo by 3 and 4 years after randomization.

The rates of death from any cause, myocardial infarction (MI), ischaemic stroke and death from non-CV causes were generally similar between the two groups (Table 3). CV risk factors were improved with dapagliflozin, including the level of HbA_{1c}, which was lower in dapagliflozin than placebo recipients throughout the trial (average LS mean absolute difference between groups 0.42%; 95% CI 0.40–0.45). Bodyweight (LS mean difference between groups 1.8 kg; 95% CI 1.7–2.0), SBP (2.7 mmHg; 95% CI 2.4–3.0) and diastolic BP (DBP; 0.7 mmHg; 95% CI 0.6–0.9) were also lower with dapagliflozin than placebo during the trial.

Subgroup Analyses

In subgroups analyses, the benefit of dapagliflozin in preventing CV death/HHF was consistent across subgroups, regardless of the history of CVD [patients with ASCVD (HR 0.83; 95% CI 0.71–0.98) or multiple risk factors (HR 0.84; 95% CI 0.67–1.04)], history of HF (yes or no) or baseline eGFR (≥ 90, 60 to < 90, or < 60 mL/min/1.73 m^2) (all p interactions nonsignificant). The rate of MACE did not differ significantly between dapagliflozin and placebo recipients in any subgroup (all p interactions nonsignificant), including patients with ASCVD (HR 0.90; 95% CI 0.79–1.02) or multiple risk factors (HR 1.01; 95% CI 0.86–1.20). Treatment benefit with dapagliflozin relative to placebo in terms of lower rate of progression of renal disease was seen regardless of the history of CVD, HF or CKD at baseline (all p interactions nonsignificant).

A prespecified subgroup analysis suggested robust clinical benefit with dapagliflozin in the high-risk subgroup of patients with T2D and prior MI (median duration from last event 5.4 years) both in terms of MACE and the composite of CV death/HHF. Dapagliflozin significantly reduced MACE by 16% (HR 0.84; 95% CI 0.72–0.99; p = 0.04) in patients with

prior MI (*n* = 3584), but not in those with no prior MI (*n* = 6771; HR 1.00; 95% CI 0.88–1.13) or no prior MI but with established ASCVD (*n* = 3390; HR 0.98; 95% CI 0.81–1.19). The lower rate of MACE in patients with prior MI was largely because of a lower rate of recurrent MI (HR 0.78; 95% CI 0.63–0.95). The absolute risk reduction (ARR) for MACE in patients with prior MI was 2.6% and the number needed to treat (NNT) over 4 years was 39. The treatment benefit with dapagliflozin in terms of MACE appeared to be greater the closer the patients were to the last acute event (*p* interaction trend 0.007), with the greatest benefit in patients with a recent MI (> 12 to 24 months). In contrast to MACE, a treatment benefit (HR < 1) for CV death/HHF was seen with dapaglilozin relative to placebo in all subgroups, i.e. patients with prior MI (HR 0.81; 95% CI 0.65–1.00, *p* = 0.046), those with no prior MI (HR 0.85; 95% CI 0.72–1.00) and patients with no prior MI but with ASCVD (HR 0.87; 95% CI 0.68–1.12); the ARR in the three patient groups was 1.9% (NNT over 4 years was 53), 1.0% and 0.5% respectively.

Another prespecified subgroup analysis assessed the efficacy of dapagliflozin in patients with T2D and HF with reduced ejection fraction [HFrEF; ejection fraction (EF) < 45%; *n* = 671] and in those without HFrEF [comprising patients with HF without known reduced EF (*n* = 1316) and patients without HF (*n* = 15,173)]. Dapagliflozin reduced CV death/HHF to a greater extent in patients with HFrEF (HR vs. placebo 0.62; 95% CI 0.45–0.86) than in those without HFrEF (HR vs. placebo 0.88, 95% CI 0.76–1.02) (*p* interaction 0.046), with the difference largely because of a reduction in CV death in patients with HFrEF (HR vs. placebo 0.55; 95% CI 0.34–0.90, *p* = 0.02) compared with patients without known HFrEF (HR vs. placebo 1.08; 95% CI 0.89–1.31). All-cause death was also significantly reduced with dapagliflozin relative to placebo in patients with HFrEF (HR 0.59; 95% CI 0.40–0.88, *p* = 0.01), but not in those without known HFrEF (HR 0.97; 95% CI 0.86–1.10) (*p* interaction 0.016). The NNT over 4 years for CV death/HHF, CV death and all-cause death in patients with HFrEF was 11, 19 and 16, respectively. In contrast, HHF was reduced with dapagliflozin regardless of baseline EF, with similar reductions in patients with HFrEF (HR 0.64; 95% CI 0.43–0.95) and without known HFrEF (HR 0.76; 95% CI 0.62–0.92) (*p* interaction 0.45).

Real-World Studies[1]

Several large real-world studies ($n \geq 1900$) supported the efficacy of dapagliflozin in patients with T2D. Dapagliflozin (in addition to other AHAs) for 12 weeks to > 12 − 24 months numerically or significantly improved efficacy outcomes, including HbA_{1c}, bodyweight and SBP in database studies in the UK and USA, a Korean postmarketing study and a prospective, multicentre, observational study in India. During 3–6 months' follow-up in a study based on clinical data from a Canadian registry for patients with T2D (for > 6 months) who received dapagliflozin ($n = 1850$), a dipeptidyl peptidase-4 inhibitor (DPP-4i; $n = 1341$) or a sulfonylurea ($n = 579$), significantly more patients receiving dapagliflozin than those receiving a DPP-4i or a sulfonylurea had HbA_{1c} reduction of ≥ 0.5%, any weight loss and SBP reduction of ≥ 5.0 mmHg (composite primary endpoint; 26 vs. 21 and 15%; $p < 0.05$). Another study, the DARWIN-T2D Italian, multicentre, retrospective study, found that treatment with dapagliflozin ($n = 830$) or a glucagon-like peptide-1 receptor agonist (GLP-1RA; $n = 811$) significantly ($p < 0.05$) reduced HbA_{1c}, bodyweight and SBP. In comparison, treatment with a DPP-4i ($n = 2999$) significantly ($p < 0.05$) reduced two of the three parameters, i.e. HbA_{1c} and bodyweight, and gliclazide (a sulfonylurea; $n = 2111$) significantly ($p < 0.05$) lowered only HbA_{1c}. While the reduction from baseline in HbA_{1c} was generally similar in all four treatment groups (change from baseline − 0.7, − 0.6, − 0.6 and − 0.6%), treatment with dapagliflozin or a GLP-1RA was associated with numerically greater improvements in bodyweight (change from baseline − 2.7 and − 2.4 vs. − 0.5 and − 0.1 kg) and SBP (− 3.0 and − 1.4 vs. − 0.7 and + 0.1 mmHg) than treatment with a DPP-4i or gliclazide.

The efficacy of dapagliflozin in preventing CV events in DECLARE-TIMI 58 was supported by real-world experience in the CVD-REAL Nordic study, based on data from nationwide registries in Denmark, Norway and Sweden for patients with T2D who were prescribed AHAs during 2012–2015. Dapagliflozin ($n = 10,227$ patients) significantly lowered the risk of MACE (non-fatal MI, non-fatal stroke or CV mortality; HR 0.79; 95% CI 0.67–0.94), HHF (HR 0.62; 95% CI 0.50–0.77) and all-cause death (HR 0.59; 95% CI 0.49–0.72) versus DPP-4is ($n = 30,681$) after a mean follow-up of 0.95 years.

Tolerability of Dapagliflozin[1]

Dapagliflozin 10 mg once daily as monotherapy and as add-on therapy to other AHAs was generally well tolerated in patients with T2D in pooled data from 13–30 placebo-/active

comparator-controlled phase 2b/3 clinical trials of 24 to ≤ 208 weeks' duration. In a pooled analysis of 13, placebo-controlled trials of 12–24 weeks' duration, treatment-emergent adverse events (AEs) were reported in 60% (1416/2360) of dapagliflozin and 56% (1279/2295) of placebo recipients, with 4% of patients in each group discontinuing therapy because of these events. The most common (incidence ≥ 3%) treatment-emergent AEs with dapagliflozin were nasopharyngitis (5 vs. 6% with placebo), diarrhoea (3 vs. 4%), headache (3 vs. 4%), upper respiratory tract infections (3 vs. 4%), urinary tract infection (UTIs; 4 vs. 3%) and back pain (4 vs. 2%). Serious adverse events (SAEs) occurred in 5% of patients in each group and resulted in treatment discontinuation in 0.7% of dapagliflozin and 1% of placebo recipients; deaths were infrequent in both groups (0.3 and 0.2%, respectively). In the DECLARE-TIMI 58 trial, significantly more dapagliflozin than placebo recipients discontinued the trial regimen because of AEs (8 vs. 7%; $p = 0.01$), but significantly fewer dapagliflozin than placebo recipients had SAEs (34 vs. 36%; $p < 0.001$) (safety population $n = 8574$ and 8569 in the respective groups). The most common (incidence > 2%) SAEs were unstable angina (2.8 vs. 2.8%) and acute MI (2.7 vs. 2.3%).

Adverse Events of Special Interest[1]

Hypoglycaemia occurred in 14% of dapagliflozin and 12% of placebo recipients in the 13-study pooled analysis. Three major hypoglycaemic events were reported in the dapagliflozin group and two in the placebo group, with most events occurring in patients receiving insulin as background therapy; one event in a patient receiving dapagliflozin plus insulin and metformin resulted in discontinuation of therapy. In DECLARE-TIMI 58, major hypoglycaemic events occurred in significantly fewer dapagliflozin than placebo recipients (0.7 vs. 1.0%; $p = 0.02$).

Genital infections were more frequent with dapagliflozin than placebo in the 13-study pooled analysis (5.5% vs. 0.6%), occurring at least twice as often in women than in men in both treatment groups. All genital infections were of mild or moderate severity, with only 0.2% of patients in the dapagliflozin group and none in the placebo group requiring treatment discontinuation. UTIs were reported in 5% of dapagliflozin and 4% of placebo recipients in this analysis, occurring almost five times more frequently in women than in men, regardless of the treatment group. Most UTIs were of mild or moderate severity, had flora consistent with those in patients with T2D, were not kidney infections and did not require discontinuation of

therapy (UTI-related discontinuation rate ≤ 0.2% in both groups). Most patients with genital infections or UTIs in both treatment groups responded to initial antimicrobial therapy and did not require additional treatment. Results from DECLARE-TIMI 58 supported the findings of the pooled analysis, with genital infections being more common with dapagliflozin than placebo (0.9 vs. 0.1%; $p < 0.001$), while there was no significant between-group in the incidence of UTIs (1.5 vs. 1.6%). Genital infections reported as SAEs were rare in both treatment groups in DECLARE-TIMI 58 (two events in each group). Fournier's gangrene (necrotising fasciitis of the perineum) was reported in one dapagliflozin and five placebo recipients; owing to the risk of this rare, but serious and potentially life-threatening event, patients should be advised to seek medical attention if they experience symptoms, and if Fournier's gangrene is suspected, dapagliflozin should be discontinued and prompt treatment should be instituted.

AEs of renal function occurred in 3% of dapagliflozin and 2% of placebo recipients in the 13-study pooled analysis, occurring more frequently in patients with baseline eGFR < 60 mL/min/1.73 m^2 (vs. ≥ 60 mL/min/1.73 m^2; 19 vs. 1% in the dapagliflozin group) and those aged ≥ 65 years (vs. < 65 years; 8 vs. 2% in the dapagliflozin group). The most common renal AEs were decreased renal creatinine clearance (1.1 vs. 0.7%) and renal impairment (0.8 vs. 0.5%), which were mostly transient, mild/moderate in severity and not accompanied with marked abnormalities of renal function. eGFR declined initially with dapagliflozin and returned towards baseline levels during treatement (mean change from baseline in the dapagliflozin group was − 4.5 and − 1.5 mL/min/1.73 m^2 at weeks 1 and 24, respectively). In DECLARE-TIMI 58, the incidence of acute kidney injury was significantly lower with dapagliflozin than placebo (1.5 vs. 2.0%; $p = 0.002$).

In the 13-study pooled analysis, volume depletion-related AEs (hypotension, hypovolaemia and dehydration) were reported in 1.1% of dapagliflozin and 0.7% of placebo recipients, with half of the events in both groups occurring during the first 8 weeks of therapy (19 and 18% of AEs in the respective groups occurred within the first 2 weeks). Regardless of the treatment group, volume depletion-related AEs were more frequent in patients using loop diuretics than in those not using them (incidence 2.5-fold higher), and in patients with eGFR < 60 mL/min/1.73 m^2 than in those with eGFR ≥ 60 mL/min/1.73 m^2 (incidence ≈ twofold higher). In the dapagliflozin group, patients aged ≥ 65 years were also more likely (incidence ≈ twofold higher) to have volume depletion-related AEs than patients aged < 65 years. In DECLARE-TIMI 58, there was no significant difference between dapagliflozin and placebo

recipients for symptoms of volume depletion (2.5 vs. 2.4%). Dapagliflozin is not recommended for patients receiving loop diuretics.

Treatment with dapagliflozin was associated with small increases in parathyroid hormone, with larger increases seen in patients with higher baseline parathyroid levels]. No bone loss was observed with dapagliflozin during 2 years' therapy in patients with normal or mild renal impairment. Fractures were infrequent with dapagliflozin and placebo in the 13-study pooled analysis (0.3 vs. 0.7%); in DECLARE-TIMI 58, there was no significant between-group difference in fracture rate (5.3 vs. 5.1%).

SGLT2 inhibitors, including dapagliflozin, have been associated with rare cases of diabetic ketoacidosis [DKA; hyperglycaemia (> 250 mg/dL), anion gap acidosis and increased plasma ketones], including life-threatening and fatal cases. In a pooled analysis of 21 placebo-/active comparator-controlled trials of ≤ 208 weeks' duration (n = 5936 in dapagliflozin and 3403 in control groups), one SAE of DKA (which may have occurred because of insulin dose reduction), two AEs of ketonuria and one AE of metabolic acidosis were reported with dapagliflozin versus no events in the control group (estimated incidence of DKA alone 0.02%; 95% CI 0.004–0.059 and of DKA/metabolic acidosis 0.03%; 95% CI 0.01–0.09). In DECLARE-TIMI 58, DKA occurred in significantly more dapagliflozin than placebo recipients (0.3 vs. 0.1%; p = 0.02). Prior to initiating dapagliflozin, factors in patients' history that may predispose them to ketoacidosis should be taken into consideration. The risk of DKA should be considered if non-specific symptoms (e.g. nausea, vomiting, anorexia) occur, and treatment should be discontinued if DKA is confirmed. Patients with euglycaemic DKA (DKA without hyperglycaemia) may need glucose in addition to standard treatment for DKA, and dapagliflozin should be discontinued if DKA occurs.

In a 21-study pooled analysis, although the incidence rate ratio (IRR) associated with dapagliflozin was above 1 for some tumours [bladder (IRR 5.2), breast (2.5), pancreatic (1.8)] and below 1 for other tumours [e.g. blood and lymphatic (0.4), renal tract (0.4)], the overall incidence rate of malignancies did not differ significantly between the dapagliflozin and control groups [1.5 vs. 1.5%; IRR 1.03; 95% CI 0.7–1.5]. In DECLARE-TIMI 58, bladder cancer occurred in fewer dapagliflozin than placebo recipients (0.3 vs. 0.5%; p = 0.02), and there was no between-group difference in the rate of breast cancer (0.4 vs. 0.4%).

Lower limb amputations were reported infrequently in the dapagliflozin and control groups (0.1 vs. 0.2%) in a 30-study pooled analysis of placebo-/active comparator-controlled trials of

≥ 12 weeks' duration (*n* = 9195 in dapagliflozin and 4629 in control groups). The time to amputation was similar in both groups and patients who had an amputation had a high prevalence of risk factors (e.g. neuropathy, CVD, dyslipidaemia and nephropathy). The rate of amputation did not differ significantly between dapagliflozin and placebo recipients in DECLARE-TIMI 58 (1.4 vs. 1.3%).

Cardiovascular Safety

A prespecified meta-analysis of CV events from 21 placebo-/active comparator-controlled phase 2b/3 clinical studies of ≤ 208 weeks' duration indicated that treatment with dapagliflozin was not associated with an increased CV risk in patients with T2D, and suggested a potential CV benefit with treatment, as evidenced by HRs of < 1 for CV outcomes. In the dapagliflozin and control groups, the event rate/100 patient-years (pt-y) of MACE plus unstable angina was 1.5 versus 2.2 in the overall population (HR 0.79; 95% CI 0.58–1.1), 2.9 versus 3.8 in patients with CVD (HR 0.81; 95% CI 0.56–1.16) and 4.2 versus 5.1 in elderly (aged ≥ 65 years) patients with CVD risk (HR 0.82; 95% CI 0.5–1.37). DECLARE-TIMI 58 confirmed the CV safety of dapagliflozin in patients with T2D who had or were at risk of ASCVD, demonstrating noninferiority between dapagliflozin and placebo for the primary composite safety outcome of MACE ($p < 0.001$ for noninferiority), and superiority for one of the two dual composite efficacy outcomes (CV death/HHF) (Table 3).

Dosage and Administration[1]

In the EU, dapagliflozin is approved for use as monotherapy (in patients who are intolerant of metformin) and add-on combination therapy (with other glucose-lowering agents, including insulin) in patients with T2D when diet and exercise alone do not provide adequate glycaemic control. The recommended dose of dapagliflozin is 10 mg once daily administered orally, with or without food. When dapagliflozin is used in combination with insulin or insulin secretagogues (e.g. sulfonylureas), a lower dose of insulin or insulin secretagogues may be required because of an increased risk of hypoglycaemia. Dapagliflozin should not be initiated in patients with GFR < 60 mL/min and its use should be discontinued in patients with GFR persistently < 45 mL/min. No dosage adjustment is required based on renal function or in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment,

dapagliflozin should be initiated at a dose of 5 mg/day, and if well tolerated the dose should be increased to 10 mg/day. Local prescribing information should be consulted for further information, including dosage and administration details, contraindications, warnings and precautions.

Place of Dapagliflozin in the Management of T2D[1]

The aim of treatment in T2D is to prevent complications and optimize patient quality of life. The 2018 American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus guidelines and the 2019 ADA guidelines recommend a patient-centred approach for the management of glycaemia and CV risk factors in T2D. Glycaemic targets should be individualized based on the risk of adverse events (e.g. hypoglycaemia and bodyweight gain), patient characteristics (e.g. comorbidity and patient frailty) and patient preference and goals. Several classes of AHAs with different mechanisms of action are available for use in T2D. Metformin (unless contraindicated or not tolerated) and comprehensive lifestyle changes (including bodyweight management and physical activity) are first-line therapy. The choice of other AHAs should be individualized based on patient factors (including history of CVD, bodyweight, hypoglycaemic risk and CKD), the cost of treatment and patient preference. CVD is the major cause of mortality in T2D, with MI and stroke accounting for ≈ 80% of all deaths. Therefore, it is important that the AHA selected to improve glycaemic control in patients with T2D does not aggravate, and preferably improves, CV risk factors and reduces CV morbidity and mortality.

SGLT2 inhibitors are a relatively new class of oral AHAs that reduce plasma glucose levels by increasing urinary glucose excretion. Because of their insulin-independent mechanism of action, SGLT2 inhibitors can be combined with other AHAs (including insulin) with minimal risk of hypoglycaemia. Currently approved SGLT2 inhibitors in the EU include dapagliflozin, canagliflozin, empagliflozin and ertugliflozin, which are administered orally once daily. Dapagliflozin is a potent, highly selective SGLT2 inhibitor with proven efficacy and safety in patients with T2D. In well-designed phase 3–4 clinical trials, dapagliflozin once daily as monotherapy and combination therapy with other AHAs, provided effective glycaemic control and reduced bodyweight and BP in a broad spectrum of T2D patients, including those with hypertension and/or CVD. Evidence from real-world studies supported the efficacy of dapagliflozin in patients with T2D.

Additionally, dapagliflozin was noninferior in terms of MACE and significantly lowered the rate of CV death and HHF relative to placebo in the large DECLARE-TIMI 58 CV outcomes trial in patients at high risk for CV events, with the between-group difference largely attributed to a lower rate of HHF with dapagliflozin. Dapagliflozin also reduced the likelihood of progression of renal disease, although statistical significance of these findings was not demonstrated because of hierarchical testing. The CV and renal benefits with dapagliflozin were consistent across subgroups, suggesting treatment benefits across a broad patient population, regardless of history of ASCVD, HF or CKD at baseline. Other subgroup analyses suggested that dapagliflozin reduced both MACE and CV death/HHF in high-risk patients with T2D and prior MI, and reduced CV death/HHF to a greater extent in patients with HFrEF than in those without HFrEF (mainly because of a larger reduction in CV death in patients with HFrEF). The ongoing phase 3 DAPA-HF trial in patients with confirmed HFrEF and the phase 3 DELIVER and phase 4 PRESERVED-HF trials in patients with preserved ejection fraction HF are further evaluating the effects of dapagliflozin in these patient subgroups, while the phase 3 DAPA-CKD trial in patients with CKD is assessing whether dapagliflozin delays the progression of kidney disease.

Dapagliflozin was generally well tolerated, with a low risk of hypoglycaemia and drug class-related AEs, including AEs of volume depletion, lower limb amputations, acute kidney injury and bladder cancer. DKA (rare) and genital infections (common), also drug-class related, were reported more frequently with dapagliflozin than placebo; Fournier's gangrene was reported in one dapagliflozin and five placebo recipients in DECLARE-TIMI 58.

In addition to DECLARE-TIMI 58, CV and renal benefits with SGLT2 inhibitors were also seen in the EMPA-REG OUTCOME trial of empagliflozin and the CANVAS Program for canagliflozin. EMPA-REG OUTCOME exclusively enrolled patients with ASCVD, while DECLARE-TIMI 58 and the CANVAS Program had only 41% and 65% of patients with established ASCVD. In all three CV outcomes trials, a more consistent and robust effect of SGLT2 inhibitors was seen for the prevention of HF and renal outcomes than in terms of atherosclerotic CV events. This difference may be because of the mechanism of action of SGLT2 inhibitors on the kidney and other effects, such as natriuresis, reduction in BP and improvement in endothelial function. Across the trials, SGLT2 inhibitors also appeared to moderately reduce the risk of MACE in patients with ASCVD, but not in patients with multiple risk factors. However, in contrast to results from EMPA-REG OUTCOME, the rate of CV

death and all-cause death was not significantly reduced in DECLARE-TIMI 58, which may be because of differences between the drugs or between the study designs.

Results from a recent meta-analysis of the three CV outcome trials of SGLT2 inhibitors were consistent with the findings from the individual trials, demonstrating robust benefits in terms of reducing HHF and progression of renal disease, and moderate benefits in terms of MACE, largely in patients with ASCVD. Several mechanisms have been proposed to explain the CV benefits with SGLT2 inhibitors, including improvement in ventricular loading conditions, improvement in cardiac metabolism and bioenergetics, inhibition of myocardial Na^+/H^+ exchange, reduction of necrosis and cardiac fibrosis, as well as alteration in adipokines, cytokine production and epicardial adipose tissue mass

Among other AHAs that have been assessed in CV outcome trials, the GLP-1RAs liraglutide (LEADER) and semaglutide (SUSTAIN-6) significantly reduced the likelihood of MACE in patients with T2D, while exenatide (EXSCEL) and lixisenatide (ELIXA) did not demonstrate either a CV benefit or harm. No significant effect of GLP-1RAs on HHF was observed in the CV outcome trials. Results from a recent meta-analysis suggested that SGLT2 inhibitors reduced the risk of HHF to a greater extent than GLP-1RAs (SGLT2 inhibitors vs. GLP-1RAs: HR 0.71), while there was no significant difference between SGLT2 inhibitors and GLP-1RAs for the reduction in the risk of MACE (GLP-1RAs vs. SGLT2 inhibitors: HR 1.02). In CV outcome trials assessing DPP-4is, sitagliptin (TECOS), saxagliptin (SAVOR-TIMI 53) and alogliptin (EXAMINE) demonstrated CV safety, but no CV benefit, although saxagliptin was associated with a 27% greater ($p = 0.007$) risk of HHF than placebo. In terms of renal outcomes, unlike SGLT2 inhibitors that significantly reduced albuminuria and the decline in eGFR, GLP-1RAs were generally associated with significant reductions in albuminuria, but had no significant effect on eGFR, while the effect of DPP-4is on renal outcomes is unclear and needs further assessment.

CV benefits with SGLT2 inhibitors have also been seen in large real-world studies, including the observational CVD-REAL study that enrolled > 300,000 propensity score-matched T2D patients across six countries (USA, UK, Norway, Denmark, Sweden and Germany). Treatment with an SGLT2 inhibitor was associated with a lower risk of death (HR 0.49; $p < 0.001$) and HHF (HR 0.61; $p < 0.001$), as well as a modestly lower risk of MI (HR 0.85; $p = 0.05$) and stroke (HR 0.83; $p = 0.02$) in patients newly initiated on an SGLT2 inhibitor (of the exposure time, 53, 42, and 5% of patients received canagliflozin, dapagliflozin and empagliflozin,

respectively) or another AHA (*n* = 154,528 patients/group). In a subgroup analysis, SGLT2 inhibitors reduced the risk of HF regardless of pre-existing CVD, a finding consistent with the results of clinical CV outcome trials. Cardioprotective effects of SGLT2 inhibitors were also seen in the CVD-REAL Nordic (Denmark, Norway and Sweden; *n* = 40,908) and CVD-REAL 2 (Asia Pacific, the Middle East and North American regions; *n* = 235,064) studies, which showed that initiation of an SGLT2 inhibitor was associated with a lower risk of CV events (including MACE and HHF) and all-cause death.

Given the CV benefits of SGLT2 inhibitors and GLP-1RAs, the recent ADA/EASD consensus guidelines and the ADA guidelines recommend that history of CVD be considered very early during treatment selection for patients with T2D. In patients with established ASCVD who do not achieve HbA_{1c} target with metformin (or if metformin is not tolerated or contraindicated), the addition of an SGLT2 inhibitor or GLP-1RA with proven CVD benefit is recommended. In those with HF or CKD, the addition of an SGLT2 inhibitor with evidence of reducing HF and/or CKD progression is preferred, and if the SGLT2 inhibitor is not tolerated or contraindicated, the addition of a GLP-1RA with proven CKD benefit is recommended. If HbA_{1c} still remains above target and further intensification is required (or SGLT2 inhibitor or GLP-1RA is not tolerated), the guidelines recommend addition of the other drug class with proven CV benefit (GLP-1RA or SGLT2 inhibitor), a DPP-4i (if not on GLP-1RA; not saxagliptin in the setting of HF), basal insulin, a thiazolidinedione (avoid in the setting of HF) or sulfonylurea. SGLT2 inhibitors are also recommended as second- and subsequent-line options for patients without history of ASCVD or CKD and with a compelling need to minimize hypoglycaemia or bodyweight.

To conclude, oral dapagliflozin once daily improves glycaemic control, bodyweight and BP, and reduces the risk of CV death/HHF and possibly progression of renal disease, providing an important option for the management of a broad patient population, regardless of the history of CVD.

Benefits of dapagliflozin[2]

Dapagliflozin has proved to be an effective therapeutic agent improving glycemic control in a diverse range of people with T2DM. It is effective when used as monotherapy, and in combination with metformin, glimepiride, pioglitazone, sitagliptin and insulin. Additionally,

dapagliflozin acts independently of insulin secretion or action and is thus unlikely to cause hypoglycaemia.

Although not fully understood, SGLT2 inhibition caused by dapagliflozin sequentially corrects and effects multiple metabolic and hemodynamic risk factors particularly associated with diabetes and CVD. In addition to plasma glucose reduction, glucosuria produces a negative energy balance and in combination with fluid loss secondary to osmotic diuresis contributes to weight reduction. Previous studies have shown a total bodyweight loss of over 2 kg in 24 weeks following a combination of dapagliflozin 10 mg and metformin. It also promotes urinary excretion of sodium, which in turn reduces plasma volume and blood pressure. Systolic blood pressure has been reduced by 3–5 mmHg compared with placebo in those taking dapagliflozin 10 mg. Dapagliflozin is also associated with lowering of uric acid levels and albuminuria.

Clinical efficacy of SGLT2i[2]

Following the controversy surrounding rosiglitazone over a decade ago, the Centre for Drug Evaluation and Research at the FDA in the USA published guidance mandating any new glucose-lowering drugs intended for the treatment of Type 2 diabetes to rule out a statistically significant unacceptable increase in CV risk. Prespecified primary composite end point outcomes required for evaluation of CV risk included CV mortality, nonfatal MI and nonfatal stroke. This is known as the classic three-point Major Adverse Cardiovascular Events (MACE). Often other end points are included under the umbrella term of MACE including hospitalization for HF, unstable angina and overall mortality. More recent trials use the three-point MACE system, particularly as different end points and heterogeneity among trials makes comparison of similar studies difficult and superiority is difficult to ascertain. Since the release of FDA guidance in 2008, multiple large-scale CV outcome trials have provided new insights into how the disease process can be modified by some treatment approaches, causing a dramatic shift in therapeutic approach in T2DM from a focus on reducing HbA1c to recognition of the importance of reducing CV risk.

Unlike many earlier glucose-lowering drugs, the associations of cardiometabolic and hemodynamic advantageous characteristics of SGLT2 inhibitor treatment, alongside supporting evidence raised the hypothesis that they would reduce the CV risk in T2DM independently of their glucose-lowering effects. This meant that while fulfilling the requirements set out by the FDA, some of the CV outcomes trials with SGLT2i were powered for superiority as well as noninferiority with placebo. Prior to the results of the Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction 58 trial (DECLARE-

TIMI 58), the Phase II and III trials with dapagliflozin, collected information on CV events. In a meta-analysis investigating CV outcomes from these studies, there was no suggestion of increased risk for major adverse CV events; furthermore, there was evidence of potential CV benefit, particularly reduction in hospitalization for HF and a decreased incidence of MI and other MACE events in patients with pre-existing CVD.

While the DECLARE-TIMI 58 trial was ongoing, two other SGLT2i CV outcome trials were published, with empagliflozin (the EMPA-REG OUTCOME trial) and canagliflozin (the CANVAS trials), respectively. EMPA-REG OUTCOME included 7020 patients with T2DM and established CVD, randomized to 10 or 25 mg of empagliflozin or placebo and followed for a median time of approximately 3 years. There was a 14% relative risk reduction (RRR) of the three-point MACE primary outcome in patients on empagliflozin therapy versus placebo (hazard ratio [HR]: 0.86; 95% CI: 0.74–0.99; p = 0.04 for superiority). Considerable benefit was seen in the empagliflozin group with respect to CV mortality (38% RRR), any-cause death (32% RRR) and hospitalization secondary to HF (35% RRR). No statistically significant differences were seen with rates of MI or stroke. The CANVAS trials included 10,142 patients with T2DM. Unlike EMPA-REG OUTCOME, 65.6% of participants had established CVD and the remainder were at high risk of CVD with multiple risk factors. Canagliflozin reduced the three-point MACE primary outcome by 14% (HR: 0.86; 95% CI: 0.75–0.97; p = 0.02 for superiority). It also observed a 33% RRR in HF-associated hospitalization. No statistically significant reduction in CV-related mortality was seen. In both trials, the efficacy of three-point MACE outcomes was more apparent in patients with pre-existing CVD. On the other hand, further subanalysis of the trials confirmed the reduction of HF hospitalization was beneficial among a wide range of patients including those without established CVD.

CV outcomes with dapagliflozin in the DECLARE-TIMI 58 trial

DECLARE-TIMI 58 was a multicenter, randomized, double-blind, placebo-controlled, Phase III trial designed to evaluate the effect of dapagliflozin 10 mg once daily on CV outcomes in patients with T2DM with either established atherosclerotic CVD or with risk factors. The trial was originally designed with the primary hypothesis that dapagliflozin does not increase incidence of MACE and will reduce the incidence of CV events. As described previously, published data from the EMPA-REG study revealed significant benefit with regard to RRR of hospitalization secondary to HF- and CV-related death. In response, the primary outcome was amended to include hospitalization due to HF and CV death and thus there were two coprimary end points; MACE and the composite of hospitalization for HF and CV death. Secondary

outcome measures included time to all-cause mortality and time to first event of renal composite end point (confirmed sustained ≥40% decrease in estimated glomerular filtration rate [eGFR] to eGFR < 60 ml/min/1.73 m^2 and/or ESRD and/or renal or CV death) within a time frame of up to 6 years. From 2013 to 2018 (median of 4.2 years), 17,160 participants with T2DM and either established CVD (n = 6974) or multiple risk factors (n = 10,186) were studied. Patients treated with dapagliflozin achieved better glucose control during the trial (0.42%; 95% CI: 0.40–0.45) versus placebo, but the differences tended to attenuate over time. A placebo-subtracted weight reduction of 1.8 kg was seen in those on dapagliflozin and placebo-subtracted systolic and diastolic blood pressure reduction of 2.7 and 0.7 mmHg, respectively.

Although dapagliflozin was noninferior for MACE events, there was no statistically significant reduction (8.8% in the dapagliflozin group and 9.4% in the placebo group; HR: 0.93; 95% CI: 0.84–1.03; p = 0.17). However, among patients with established CVD the rate of MACE was lower in the dapagliflozin group (13.9%) compared with placebo (15.3%); which is of interest although not statistically significant. The same benefit was not seen in those without established CVD.

For the other coprimary end point, patients treated with dapagliflozin had a lower rate of the composite outcome of CV mortality and hospitalization for HF (HR: 0.83; 95% CI: 0.73–0.95; p = 0.005). This was largely driven by the reduction in hospitalization for HF (HR: 0.73; 95% CI: 0.61–0.88), with a RRR of 17 and 27%, respectively, which was consistent across an extensive range of patients irrespective of a history of atherosclerotic disease or HF, whereas the reduction in CV death was not significant.

A prespecified subgroup analysis of DECLARE specifically focused on patients within the trial with a history of MI (n = 3584). Due to their high baseline risk, it was hypothesized that this specific group would gain an even greater benefit from dapagliflozin therapy. In patients with prior MI, there was a 16% RRR and 2.6% absolute risk reduction of MACE, whereas no significant risk reduction was noted in those without a history of MI including those with established CVD. There was also a 19% RRR of CV death and a 15% RRR of hospitalization for HF in those with a prior MI.

Another subanalysis of DECLARE explored the effect of dapagliflozin on HF and mortality, found that HF was reduced in patients with T2DM with or without HF and reduced ejection fraction and reduced CV mortality in those with T2DM with HF and reduced ejection fraction.

Renal & other outcomes in DECLARE-TIMI 58[2]

In a prespecified secondary analysis, the incidence of cardiorenal events, defined as a sustained decline of at least 40% in eGFR to less than 60 ml/min per 1.73 m^2, end-stage renal disease or death from renal or CV causes was 4.3% in those taking dapagliflozin and 5.6% in those taking placebo (HR: 0.76; 95% CI: 0.67–0.87). Excluding CV death, the HR for the renal composite outcome was 0.53; 95% CI: 0·43–0·66; this lower rate of renal disease progression was consistent among those with and without established CVD, HF and or chronic kidney disease.

In previous trials of SGLT2i, there have been conflicting data reports of some infrequent adverse events, notably amputations, bladder cancer, fractures and severe genital and urinary tract infections, making it difficult to ascertain genuine conclusions. The DECLARE trial specifically reported these events including incidence of amputations, fractures, stroke, severe genital and urinary tract infections, diabetic ketoacidosis (DKA) and bladder cancer. Compared with placebo, rates of major hypoglycemia, acute kidney injury and bladder cancer were lower with dapagliflozin and no statistical difference was found between the two groups in the incidence of amputations, fractures, stroke, volume depletion or hypersensitivity. Higher rates of DKA were seen in patients on dapagliflozin (0.3 vs 0.1%; p = 0.02) of which more than 80% were using insulin at baseline. Genital infections that led to discontinuation of dapagliflozin or thought to be serious adverse events in both male and female patients were seen more frequently with dapagliflozin treatment (0.9 vs 0.1%; HR: 8.36; 95% CI: 4.19–16.68; p < 0.001), albeit serious adverse events were rare with only two events occurring in each group. Out of the six reported cases of Fournier's gangrene, only one was within the dapagliflozin group.

New evidence on dapagliflozin in HF: the DAPA-HF trial[2]

During the European Society of Cardiology (ESC) Congress in September 2019, the results of the Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction Trial (DAPA-HF) were presented for the first time and results subsequently published. DAPA-HF was a randomized, placebo-controlled Phase III trial lasting a median of 18.2 months involving 4744 patients with New York Heart Association (NYHA) class II, III or IV HF and an ejection fraction of 40% or less. Prior to the completion of the trial, most evidence surrounding dapagliflozin and HF reduction was obtained from populations who for the large part did not have HF at baseline. The trial, completed across 410 centers in 20 countries, was thus designed to measure the efficacy and safety of dapagliflozin in subjects with pre-existing HF with reduced ejection fraction irrespective of a diagnosis of T2DM.

Assigned treatment of dapagliflozin 10 mg once daily or placebo was given in conjunction with recognized standard drug therapy for HF including angiotensin-converting enzyme inhibitor, angiotensin receptor blocker or sacubitril/valsartan; and a β-blocker (unless contraindicated or not tolerated); as well as a mineralocorticoid receptor antagonist, if indicated. Patients requiring standard HF device therapy such as an implantable cardioverter defibrillator (26%) and/or cardiac resynchronization therapy (8%) were also included.

The primary outcome included a composite of CV death or worsening HF defined as hospitalization or an urgent visit resulting in intravenous therapy for HF. Secondary outcomes included a composite of hospitalization for HF or CV death, total number of hospitalizations for HF, CV death, a composite of worsening renal function and death from any cause.

The primary composite outcome (worsening HF or death from CV causes) favorably with dapagliflozin, occurring in 16.3% of dapagliflozin patients compared with 21.2% of placebo patients (HR: 0.74; 95% CI: 0.65–0.85; $p < 0.001$). It was recorded within the trial duration that 21 patients would need to be treated with dapagliflozin to prevent one primary event.

A first event of worsening HF was seen in 10% of patients on dapagliflozin versus 13.7% of patients on placebo (HR: 0.70; 95% CI: 0.59–0.83). Less than 10% of dapagliflozin patients were hospitalized for HF compared with over 13% of placebo patients. Death from CVD occurred in 9.6% of the dapagliflozin group compared with 11.5% of the placebo group, while death from any cause occurred in 11.6 and 13.9%, respectively. Incidence for secondary outcomes of hospitalization for HF- or CV-related death was lower in those taking dapagliflozin. Between the treatment groups, no difference was seen in renal composite outcomes.

Initially, 42% of all patients had T2DM, with a new diagnosis of T2DM later being made in around 3% of patients in each cohort. Notably, primary outcomes were consistent among patients with and without diabetes. NYHA classes III and IV seemed to benefit less compared with NYHA class II.

No statistically significant side effects were observed, and adverse events rarely required the discontinuation of treatment.

Impact of dapagliflozin[2]

Although dapagliflozin did not result in three-point MACE reduction across the general population, it did suggest modest benefit in those who had pre-existing CVD. Importantly, dapagliflozin did produce superior outcomes to placebo in prevention of HF hospitalization and improved renal outcomes among a broad range of patients with T2DM, irrespective of

prior CVD, HF or renal disease. Moreover, most of the patients did not have a known history of HF, so the prevention of new clinical HF is notable. Additional benefits of dapagliflozin therapy as validated by DECLARE included lowering plasma glucose, blood pressure reduction and weight loss. Notably, all of which positively contribute to the metabolic syndrome and pathophysiological processes related to complications and CV events.

More recently, the results of DAPA-HF, which shows a reduction for risk of worsening HF and CVD, present a clear benefit of dapagliflozin therapy in patients with HF and reduced ejection fraction irrespective of the presence or absence of diabetes. The effectiveness of dapagliflozin in patients with and without diabetes supports the idea that it has benefits beyond those directly related to glucose lowering.

Dapagliflozin and other drugs of the class have more notable dominance in impacting HF and renal disease due to their action on the kidneys. This is also true for many features of the metabolic syndrome by which dapagliflozin and other SGLT2i impact. The chain of events grossly simplified relates to glycosuria and natriuresis. Whereby downstream effects involving natriuresis lower blood pressure and plasma volume, which in turn reduces arterial stiffness and reduces myocardial stretch. Natriuresis also increases tubuloglomerular feedback, causing afferent arteriole constriction, which then triggers a reduction in intraglomerular hypertension and hyperfiltration. The impact of glycosuria on the other hand includes weight loss through negative energy balance, which also impacts blood pressure. Weight loss also contributes to a reduction in epicardial fat, helping to increase cardiac contractility and reduce inflammation and fibrosis. The modest reduction in plasma uric acid may also impact atherosclerosis risk. Glycosuria also reduces HbA1c, the core purpose of treatment which as already known reduces atherosclerosis, inflammation and glucose toxicity. The collective features together create a unique cardiac and renal protective system.

Current guidance for Dapagliflozin[2]

Dapagliflozin was formally approved by the EMA for use in the European Union in 2012, followed by the US FDA in 2014. Known by its brand names Farxiga (the USA) and Forxiga (EU), it is licensed as 5 or 10 mg doses for the use in adults with T2DM to improve glycemic control in conjunction with diet and exercise. Dapagliflozin 10 mg is contraindicated for the use in patients with Type-1 diabetes due to risk of hypoglycemia and DKA as per FDA and EMA guidance. However, based on emerging research, EMA has approved the use of dapagliflozin 5 mg for the treatment of uncontrolled Type-1 diabetes despite optimal insulin therapy and a BMI ≥27 kg/m^2 to be used in conjunction with insulin and appropriate guidance

and risk awareness. As mentioned, most common side effects include urinary tract and genital mycotic infections with a specific warning and awareness against less likely but possible DKA.

Currently, the management of T2DM UK guidance published by the National Institute of Clinical Excellence has not incorporated the most recent evidence of the use of dapagliflozin or other SGLT2i in the realm of CV risk protection, but an update is planned for 2020. However, as data have been released from SGLT2i trials and related research over the years, their benefits in reducing major CV events in patients with pre-existing CVD have been increasingly recognized internationally. In 2016, European guidelines for CVD prevention were revised to include consideration of early SGLT2i use in the course of diabetes management in those with established CVD. Last year, the American Diabetes Association and the European Association for the Study of Diabetes released a consensus statement on management of hyperglycemia in T2DM. The report recommends using a SGLT2i in patients with pre-existing CVD irrespective of glucose control due to the benefits of MACE reduction. Following the findings from DECLARE of a reduction in progression of chronic kidney disease, the American Diabetes Association and FDA, respectively, updated its position statement and drug label, lowering the eGFR threshold to 45 from 60 ml/min/1.73 m^2 in an attempt to provide safe beneficial outcome to a wider patient group. In addition, the DECLARE subanalysis mentioned earlier that focuses on patients with previous history of MI adds to current recommendations encouraging that patients with T2DM and previous MI be considered for SGLT2i to reduce CV risk.

Despite DECLARE evidently demonstrating reduction of hospitalization for HF regardless of previous CV history, the present guidelines have largely focused on initiating treatment in those established CVD. The data suggest that dapagliflozin could also be considered in patients with T2DM without pre-existing CVD or HF. However, in August 2019, the ESC-released guidelines in collaboration with the European Association for the Study of Diabetes recommending the use of dapagliflozin or other SGLT2i in those with T2DM and CV or in those with T2DM who are at high risk of CV or HF. Following this and based on the results from DECLARE in October 2019, the FDA approved dapagliflozin in reducing risk of HF-associated hospitalization in adults with T2DM and multiple CV risk factors or pre-existing CVD.

In 2019, a systematic review by Zelniker *et al*. compared the effects of GLP-1 RA and SGLT2i for prevention of major adverse CV events and renal outcomes in T2DM. The study concluded that in trials which had been reported to date, similar reduction of MACE was achieved in both groups in patients with established CVD. However, SGLT2i have a higher impact in preventing

hospitalization for HF and progression of kidney disease. Renoprotection was also confirmed in the recent CREDENCE trial, which compared the renal outcomes of patients with T2DM and albuminuric chronic kidney disease taking 100 mg of canagliflozin versus placebo.

The latest DAPA HF data suggest that dapagliflozin could be used as an adjunct to standard HF therapy in those with HF and a reduced ejection fraction and should be considered in future HF guidance.

References:

1. Dhillon S. Dapagliflozin: A Review in Type 2 Diabetes [published correction appears in Drugs. 2019 Dec;79(18):2013]. Drugs. 2019;79(10):1135-1146.
2. Al-Bazz, Dalal Y; Wilding, John PH. Dapagliflozin and cardiovascular outcomes in patients with Type 2 diabetes. *Future Cardiology*. 2020;16(2),77–88.

Survey Form

1) What is your preferred second-line therapy for patients with Type 2 Diabetes who have failed to achieve glycemic control with metformin alone?

a) Dapagliflozin
b) Sulfonylureas
c) DPP-4 inhibitors
d) GLP-1 receptor agonists

2) What is your perception of the cardiovascular safety profile of Dapagliflozin compared to other antidiabetic medications?

a) Superior
b) Similar
c) Inferior
d) Not sure

3) How do you determine the appropriateness of Dapagliflozin therapy in elderly patients with Type 2 Diabetes?

a) Consideration of renal function and frailty
b) Assessment of cognitive function and fall risk
c) Evaluation of potential drug interactions
d) All of the above

4) What proportion of your patients with Type 2 Diabetes and comorbid obesity are prescribed Dapagliflozin?

a) Less than 10%
b) 10% - 25%
c) 25% - 50%
d) More than 50%

5) How do you monitor renal function in patients receiving Dapagliflozin therapy?

a) Regularly assess serum creatinine and eGFR
b) Perform urinalysis for albuminuria
c) Order renal ultrasound for structural abnormalities
d) Refer patients to a nephrologist for comprehensive evaluation

6) What percentage of your patients with Type 2 Diabetes are currently prescribed Dapagliflozin?

a) Less than 10%
b) 10% - 25%
c) 25% - 50%
d) More than 50%

7) How frequently do you encounter patients who have experienced significant weight loss while on Dapagliflozin therapy?

a) Frequently
b) Occasionally
c) Rarely
d) Never

8) In your experience, what is the most common reason for discontinuing Dapagliflozin therapy among your patients?

a) Adverse gastrointestinal effects
b) Genitourinary tract infections
c) Concerns about diabetic ketoacidosis
d) Other

9) How do you evaluate the effectiveness of Dapagliflozin therapy in lowering blood glucose levels in your patients?

a) Regularly monitor HbA1c levels
b) Assess fasting blood glucose levels
c) Utilize continuous glucose monitoring systems
d) Rely on patient-reported symptoms

10) What is your primary consideration when initiating Dapagliflozin therapy in a patient with Type 2 Diabetes and established cardiovascular disease?

a) Lowering blood glucose levels
b) Reducing cardiovascular risk
c) Managing weight and metabolic parameters
d) Avoiding hypoglycemia

11) How often do you adjust the dosage of Dapagliflozin in your patients?

a) Every 3 months
b) Every 6 months
c) Annually
d) As needed based on clinical response

12) What is your approach to managing potential adverse effects of Dapagliflozin, such as dehydration and hypotension?

a) Adjust the dosage of Dapagliflozin
b) Prescribe additional medications to manage symptoms
c) Educate patients on hydration and monitoring blood pressure
d) Refer patients to a specialist for further evaluation

13) How frequently do you encounter patients with Type 2 Diabetes who are resistant to Dapagliflozin therapy?

a) Frequently
b) Occasionally
c) Rarely
d) Never

14) In your opinion, what is the role of Dapagliflozin in patients with Type 2 Diabetes who have a history of cardiovascular events?

a) Primary therapy for cardiovascular risk reduction
b) Adjunct therapy to standard cardiovascular medications
c) Limited role due to safety concerns
d) Not sure

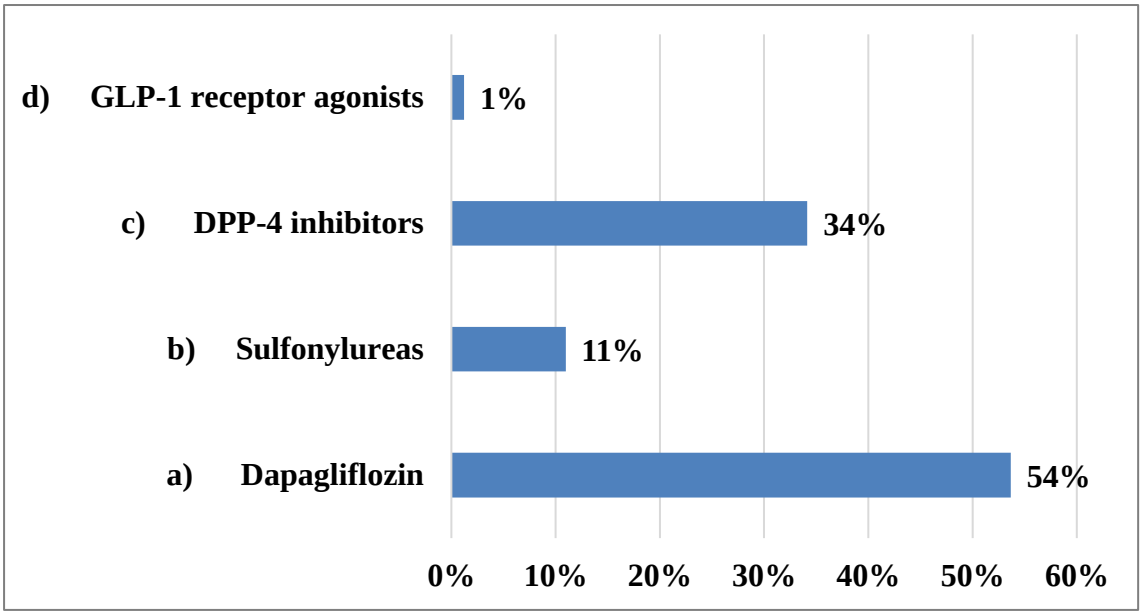
15) What is your opinion on the cost-effectiveness of Dapagliflozin compared to other antidiabetic medications?

a) Very cost-effective
b) Somewhat cost-effective
c) Not very cost-effective
d) Not sure

Survey Findings

1) What is your preferred second-line therapy for patients with Type 2 Diabetes who have failed to achieve glycemic control with metformin alone?

a) Dapagliflozin
b) Sulfonylureas
c) DPP-4 inhibitors
d) GLP-1 receptor agonists



According to 54% of doctors, their preferred second-line therapy for patients with Type 2 Diabetes who have failed to achieve glycemic control with metformin alone is Dapagliflozin.

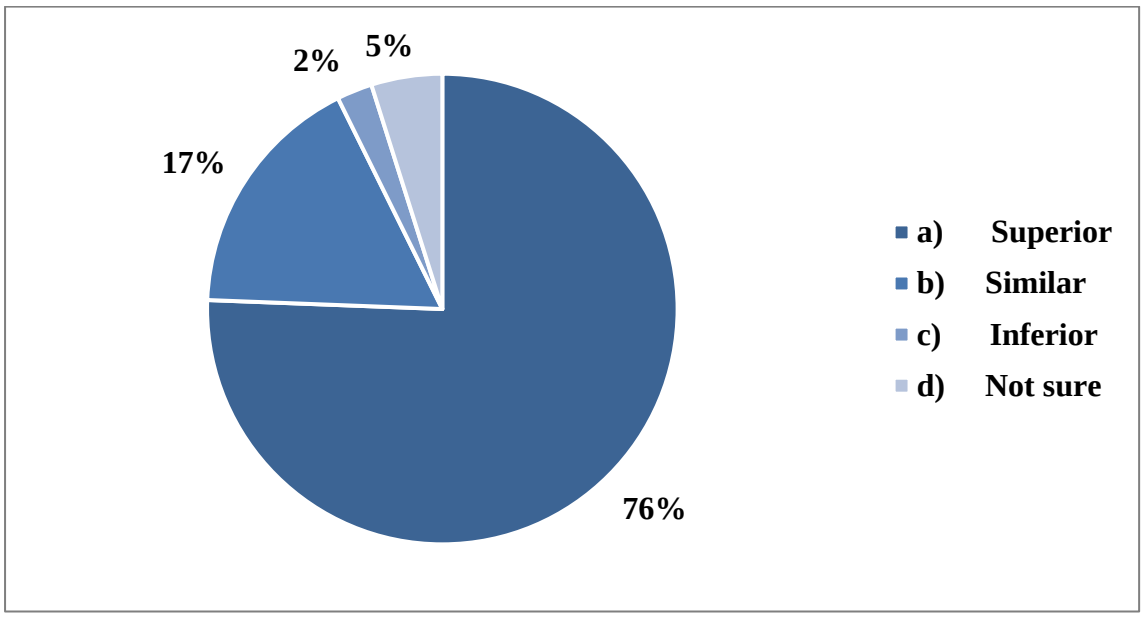
2) What is your perception of the cardiovascular safety profile of Dapagliflozin compared to other antidiabetic medications?

a) Superior

b) Similar

c) Inferior

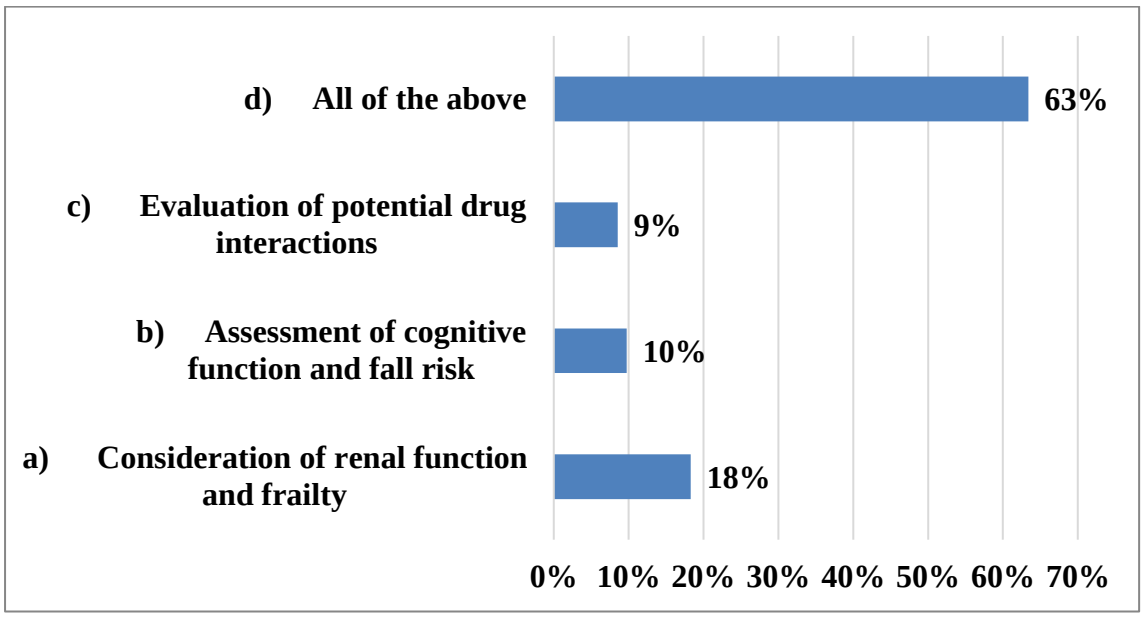
d) Not sure



Majority of doctors perceive the cardiovascular safety profile of Dapagliflozin compared to other antidiabetic medications as superior.

3) How do you determine the appropriateness of Dapagliflozin therapy in elderly patients with Type 2 Diabetes?

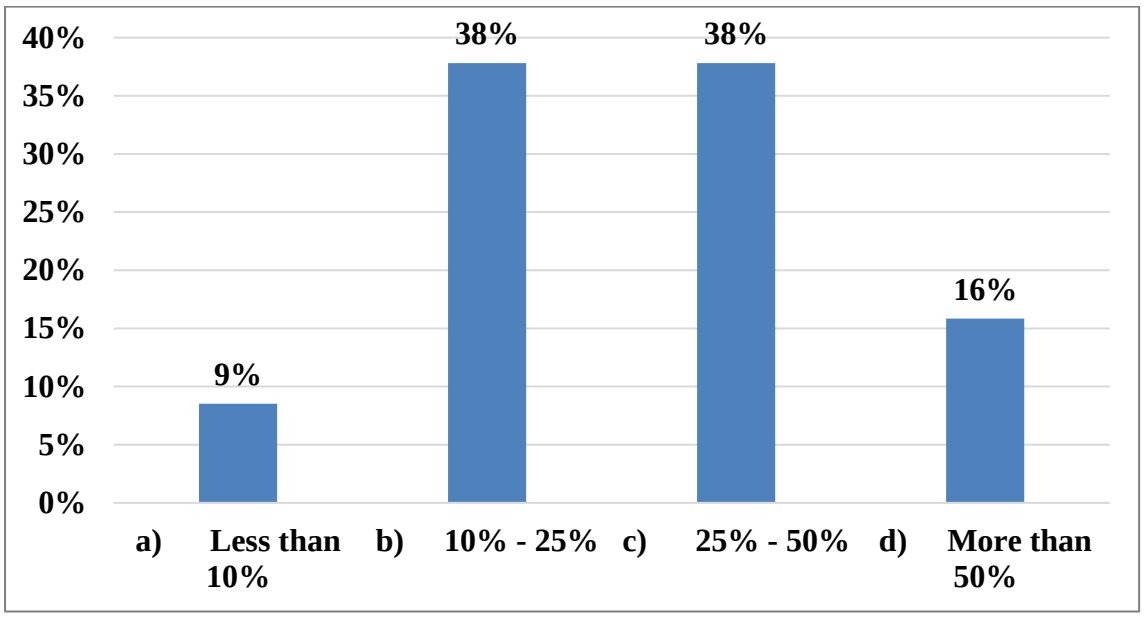
a) Consideration of renal function and frailty
b) Assessment of cognitive function and fall risk
c) Evaluation of potential drug interactions
d) All of the above



Majority of doctors determine the appropriateness of Dapagliflozin therapy in elderly patients with Type 2 Diabetes by consideration of renal function and frailty, assessment of cognitive function and fall risk and evaluation of potential drug interactions.

4) What proportion of your patients with Type 2 Diabetes and comorbid obesity are prescribed Dapagliflozin?

a) Less than 10%
b) 10% - 25%
c) 25% - 50%
d) More than 50%



As per 38 % of doctors, 10-25% of their patients with Type 2 Diabetes and comorbid obesity are prescribed Dapagliflozin whereas as per another 38%, the percentage is 25-50.

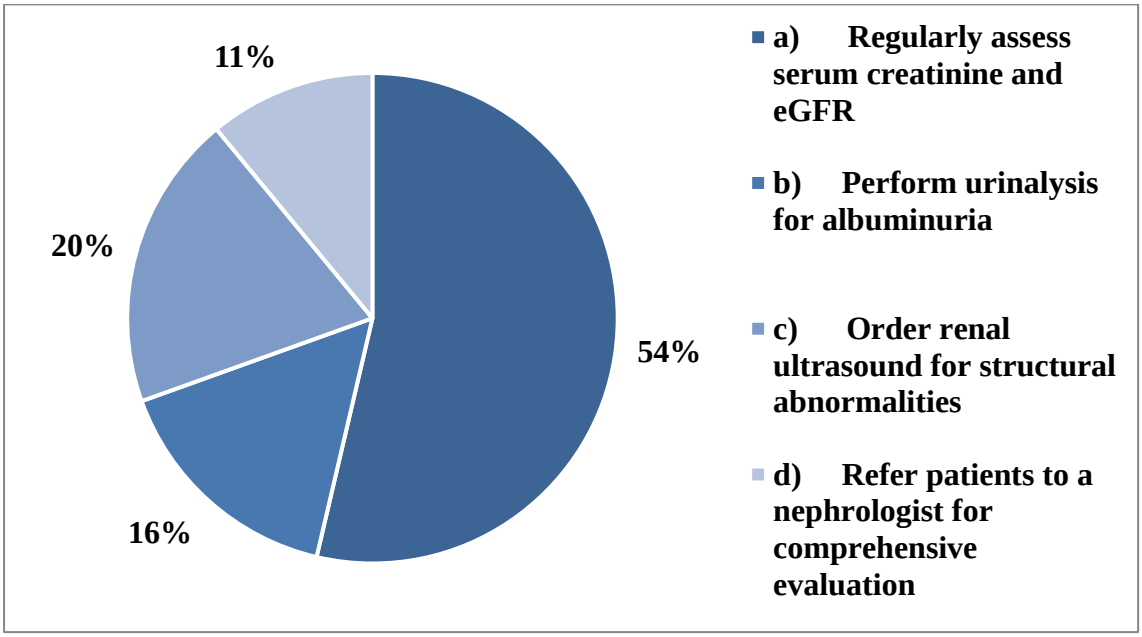
5) How do you monitor renal function in patients receiving Dapagliflozin therapy?

a) Regularly assess serum creatinine and eGFR

b) Perform urinalysis for albuminuria

c) Order renal ultrasound for structural abnormalities

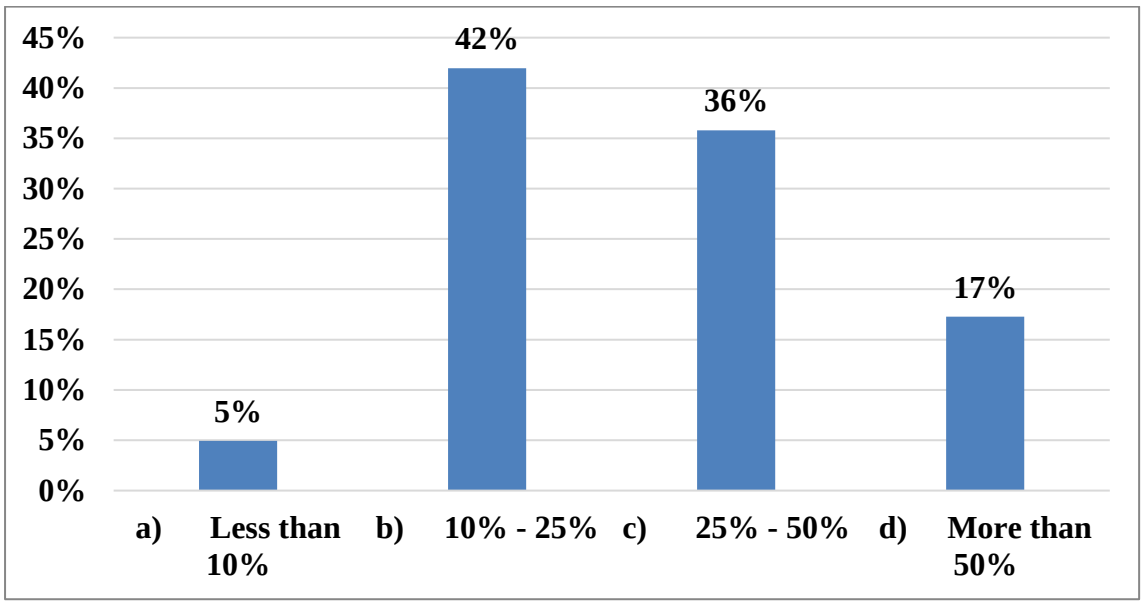
d) Refer patients to a nephrologist for comprehensive evaluation



54% of doctors monitor renal function in patients receiving Dapagliflozin therapy by regularly assessing serum creatinine and eGFR.

6) What percentage of your patients with Type 2 Diabetes are currently prescribed Dapagliflozin?

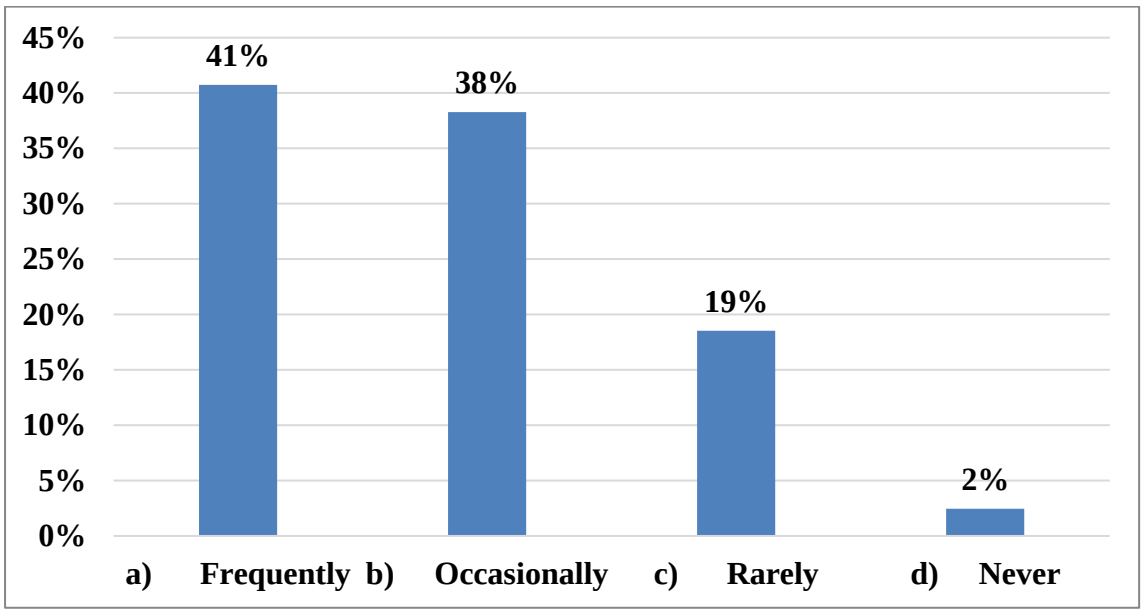
a) Less than 10%
b) 10% - 25%
c) 25% - 50%
d) More than 50%



According to 42% of doctors, 10-25% of their patients with Type 2 Diabetes are currently prescribed Dapagliflozin.

7) How frequently do you encounter patients who have experienced significant weight loss while on Dapagliflozin therapy?

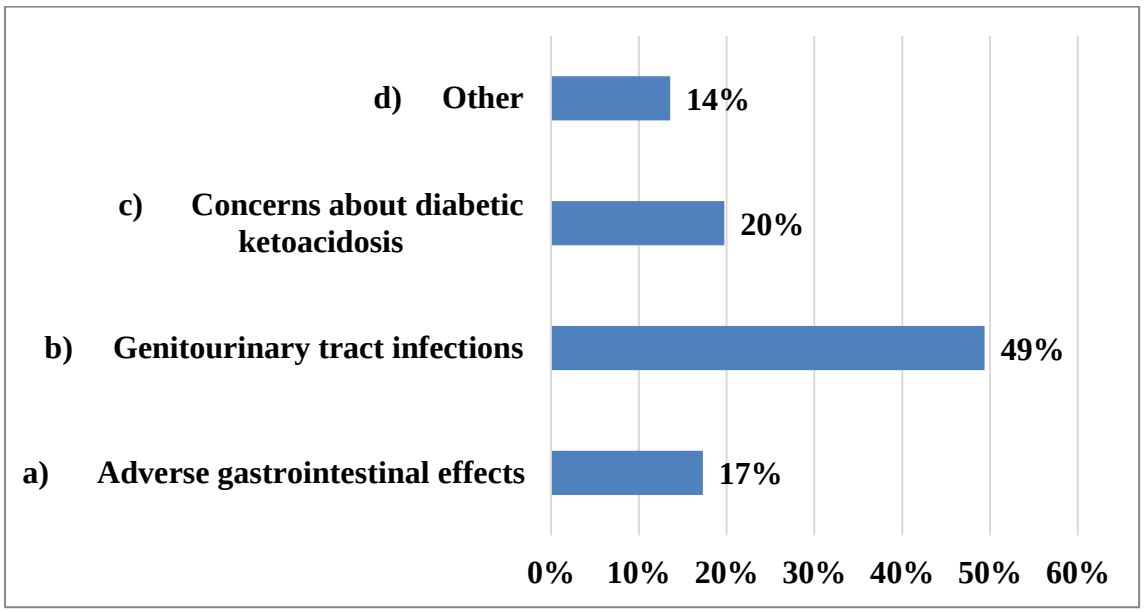
a) Frequently
b) Occasionally
c) Rarely
d) Never



As per 41% of doctors, they frequently encounter patients who have experienced significant weight loss while on Dapagliflozin therapy.

8) In your experience, what is the most common reason for discontinuing Dapagliflozin therapy among your patients?

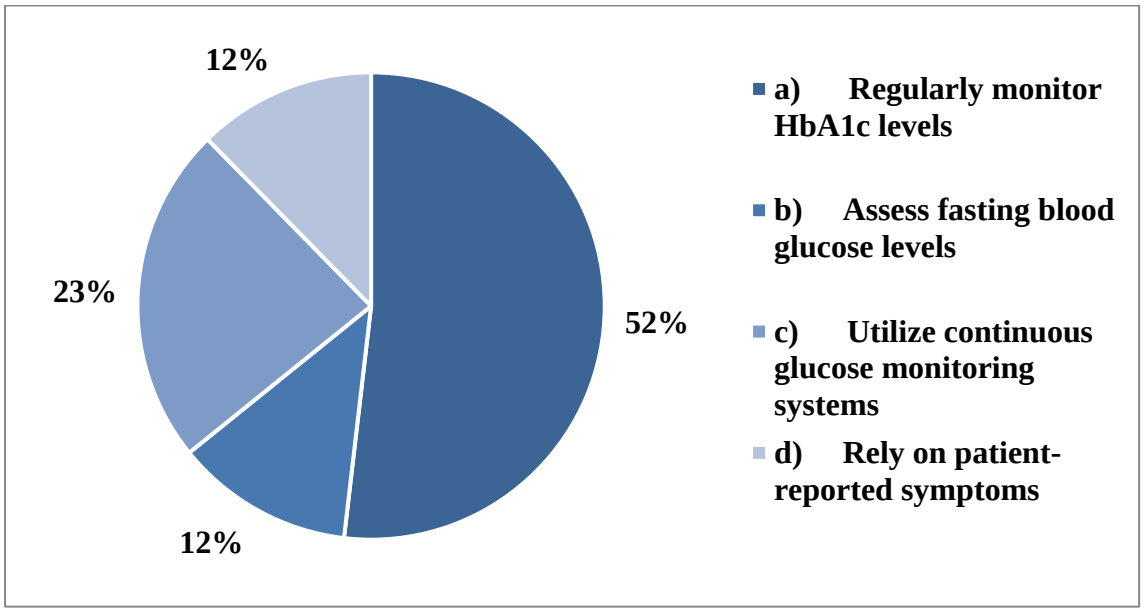
a) Adverse gastrointestinal effects
b) Genitourinary tract infections
c) Concerns about diabetic ketoacidosis
d) Other



In the experience of 49% of doctors, the most common reason for discontinuing Dapagliflozin therapy among their patients is genitourinary tract infections.

9) How do you evaluate the effectiveness of Dapagliflozin therapy in lowering blood glucose levels in your patients?

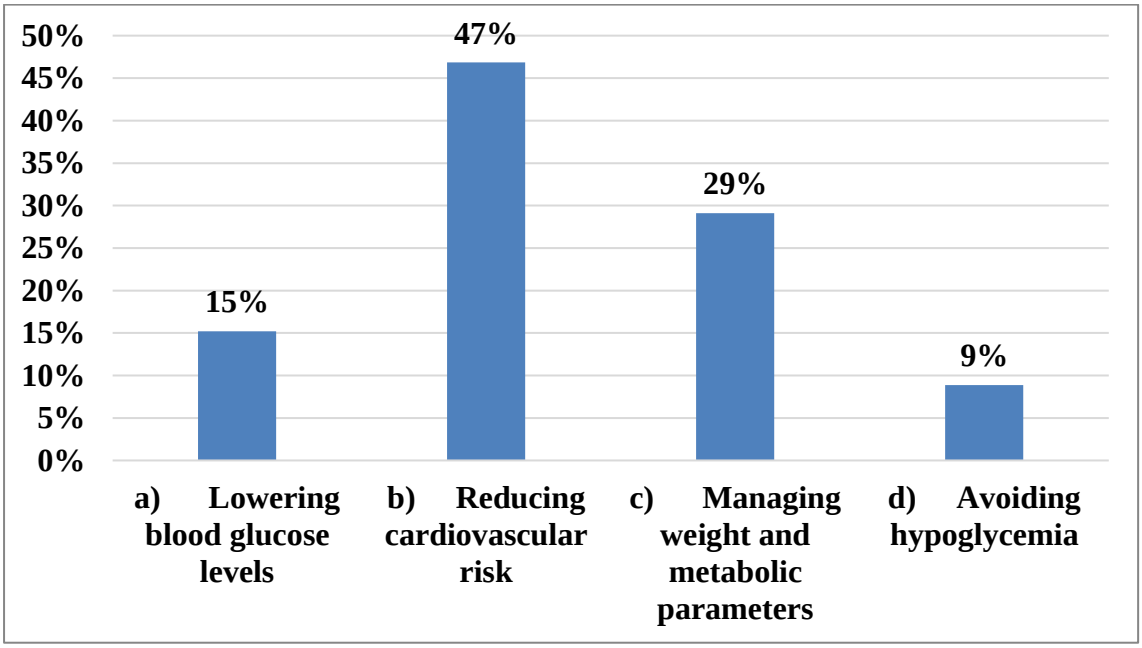
a) Regularly monitor HbA1c levels
b) Assess fasting blood glucose levels
c) Utilize continuous glucose monitoring systems
d) Rely on patient-reported symptoms



More than half the doctors surveyed, 52%, evaluate the effectiveness of Dapagliflozin therapy in lowering blood glucose levels in their patients by regular monitoring of HbA1c levels.

10) What is your primary consideration when initiating Dapagliflozin therapy in a patient with Type 2 Diabetes and established cardiovascular disease?

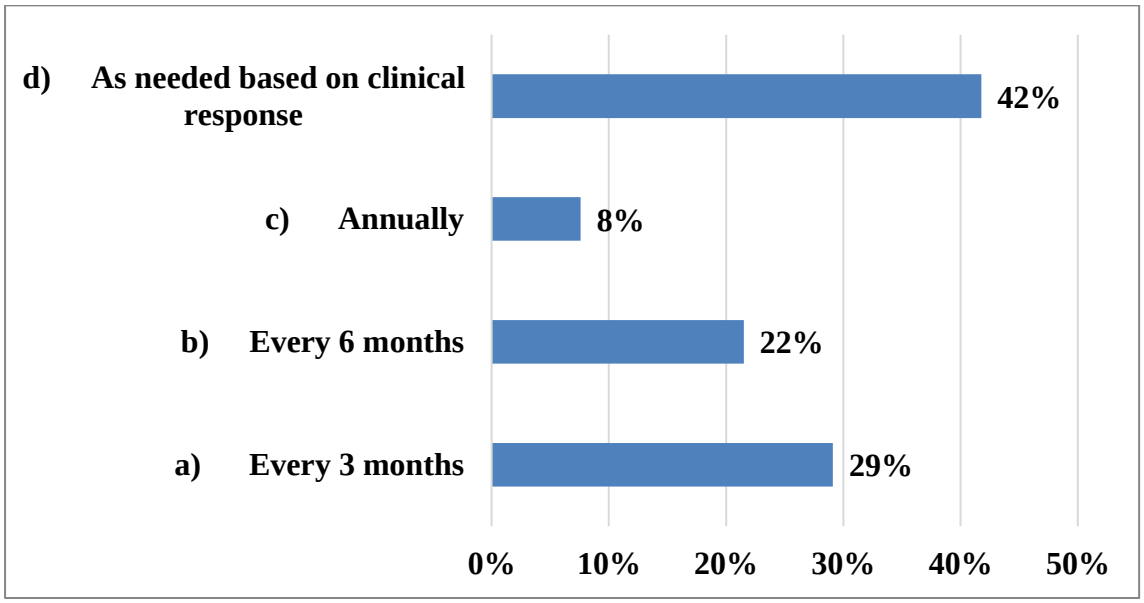
a) Lowering blood glucose levels
b) Reducing cardiovascular risk
c) Managing weight and metabolic parameters
d) Avoiding hypoglycemia



According to 47% of doctors, their primary consideration when initiating Dapagliflozin therapy in a patient with Type 2 Diabetes and established cardiovascular disease is reducing cardiovascular risk.

11) How often do you adjust the dosage of Dapagliflozin in your patients?

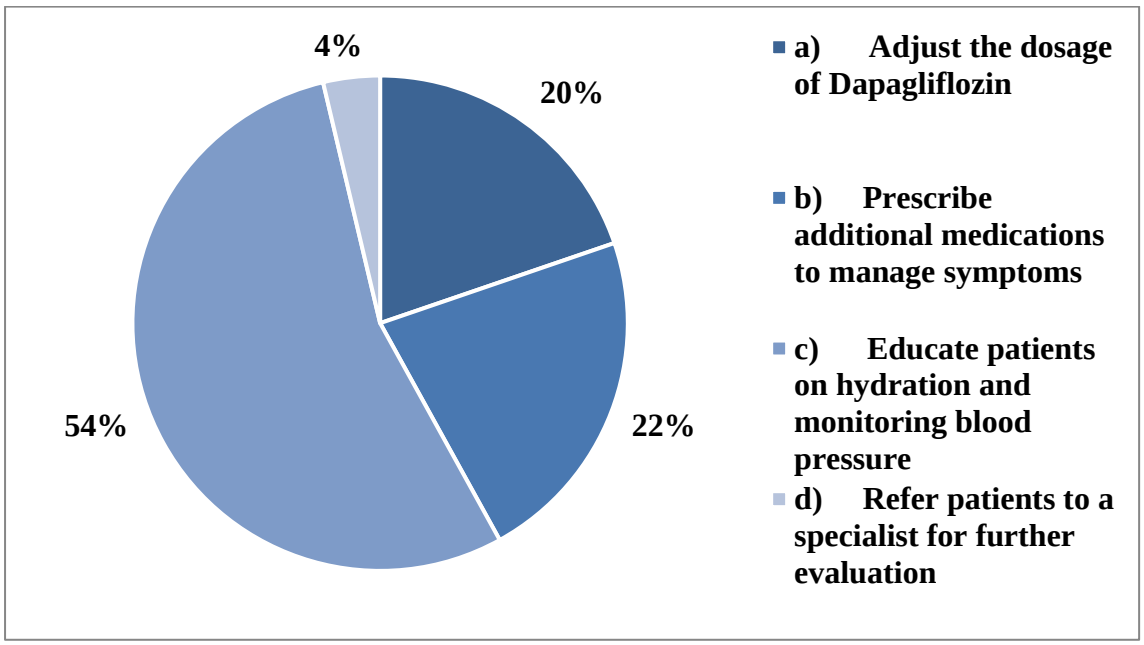
a) Every 3 months
b) Every 6 months
c) Annually
d) As needed based on clinical response



42% of doctors adjust the dosage of Dapagliflozin in their patients as needed based on clinical response.

12) What is your approach to managing potential adverse effects of Dapagliflozin, such as dehydration and hypotension?

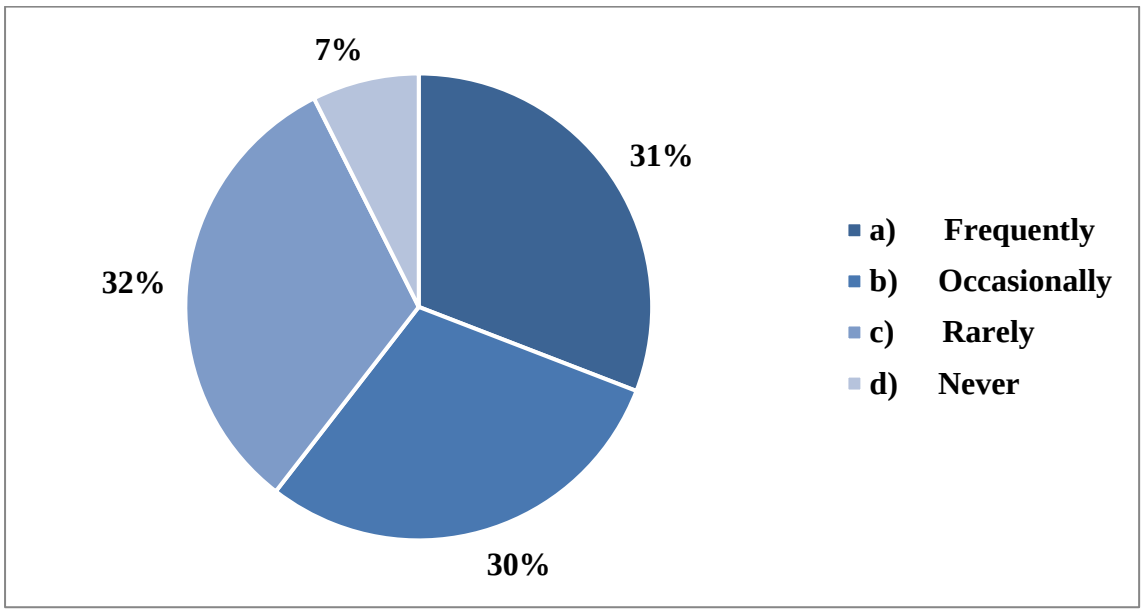
a) Adjust the dosage of Dapagliflozin
b) Prescribe additional medications to manage symptoms
c) Educate patients on hydration and monitoring blood pressure
d) Refer patients to a specialist for further evaluation



According to 54% of doctors, they educate patients on hydration and monitoring blood pressure for managing potential adverse effects of Dapagliflozin, such as dehydration and hypotension.

13) How frequently do you encounter patients with Type 2 Diabetes who are resistant to Dapagliflozin therapy?

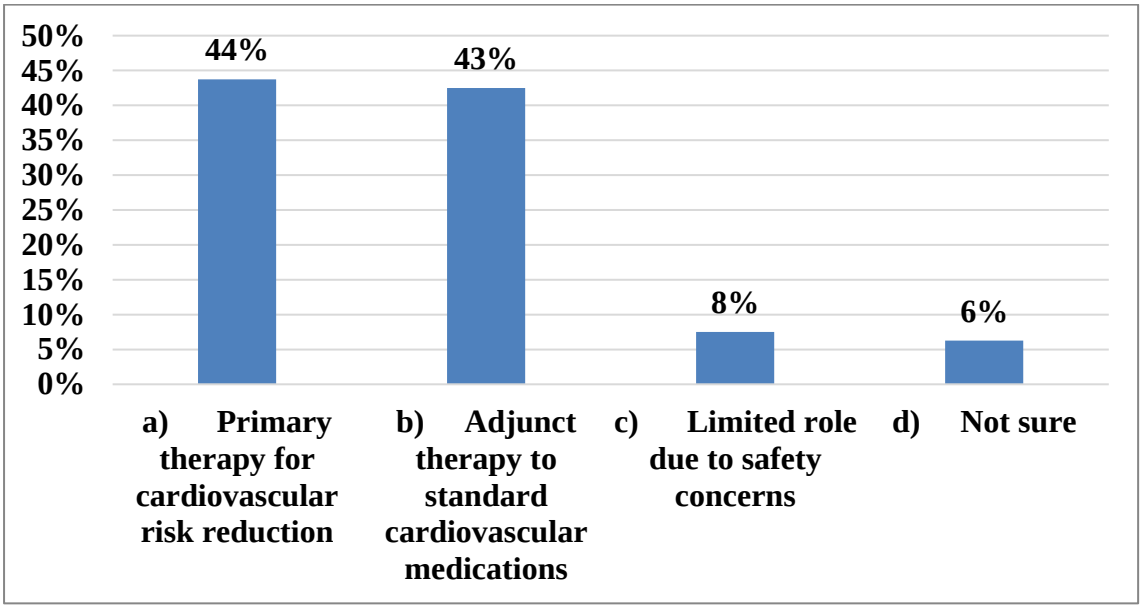
a) Frequently
b) Occasionally
c) Rarely
d) Never



32% of doctors rarely encounter patients with Type 2 Diabetes who are resistant to Dapagliflozin therapy.

14) In your opinion, what is the role of Dapagliflozin in patients with Type 2 Diabetes who have a history of cardiovascular events?

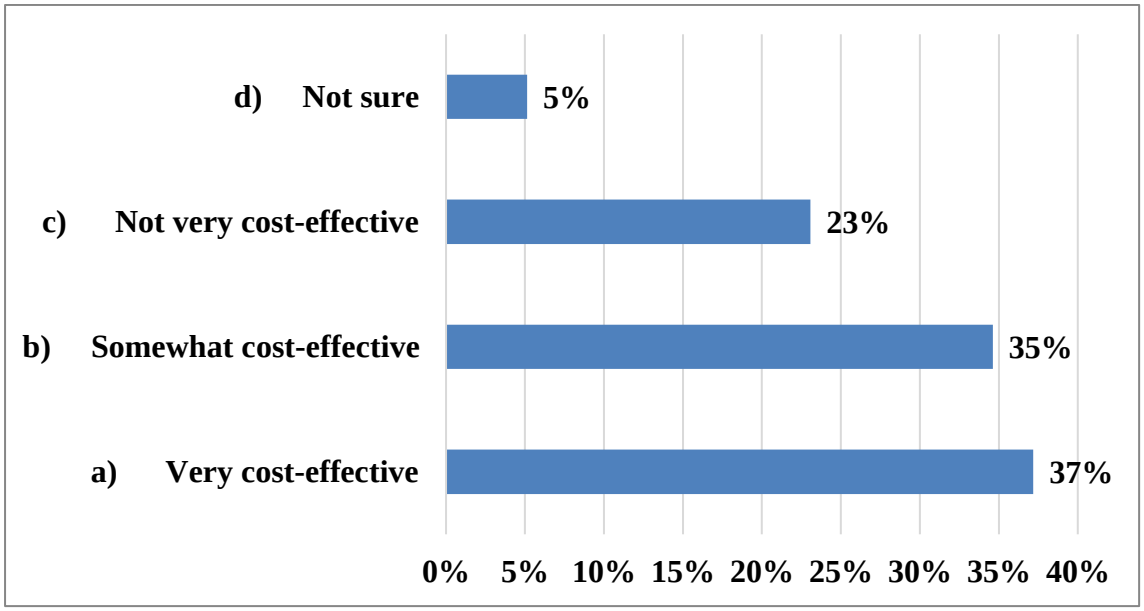
a) Primary therapy for cardiovascular risk reduction
b) Adjunct therapy to standard cardiovascular medications
c) Limited role due to safety concerns
d) Not sure



In the opinion of 44% of doctors, Dapagliflozin works as primary therapy for cardiovascular risk reduction in patients with Type 2 Diabetes who have a history of cardiovascular events.

15) What is your opinion on the cost-effectiveness of Dapagliflozin compared to other antidiabetic medications?

a) Very cost-effective
b) Somewhat cost-effective
c) Not very cost-effective
d) Not sure



37% of doctors believe Dapagliflozin is very cost-effective compared to other antidiabetic medications.

Summary

- According to 54% of doctors, their preferred second-line therapy for patients with Type 2 Diabetes who have failed to achieve glycemic control with metformin alone is Dapagliflozin.
- Majority of doctors perceive the cardiovascular safety profile of Dapagliflozin compared to other antidiabetic medications as superior.
- Majority of doctors determine the appropriateness of Dapagliflozin therapy in elderly patients with Type 2 Diabetes by consideration of renal function and frailty, assessment of cognitive function and fall risk and evaluation of potential drug interactions.
- As per 38 % of doctors, 10-25% of their patients with Type 2 Diabetes and comorbid obesity are prescribed Dapagliflozin whereas as per another 38%, the percentage is 25-50.
- 54% of doctors monitor renal function in patients receiving Dapagliflozin therapy by regularly assessing serum creatinine and eGFR.
- According to 42% of doctors, 10-25% of their patients with Type 2 Diabetes are currently prescribed Dapagliflozin.
- As per 41% of doctors, they frequently encounter patients who have experienced significant weight loss while on Dapagliflozin therapy.
- In the experience of 49% of doctors, the most common reason for discontinuing Dapagliflozin therapy among their patients is genitourinary tract infections.
- More than half the doctors surveyed, 52%, evaluate the effectiveness of Dapagliflozin therapy in lowering blood glucose levels in their patients by regular monitoring of HbA1c levels.
- According to 47% of doctors, their primary consideration when initiating Dapagliflozin therapy in a patient with Type 2 Diabetes and established cardiovascular disease is reducing cardiovascular risk.
- 42% of doctors adjust the dosage of Dapagliflozin in their patients as needed based on clinical response.

- According to 54% of doctors, they educate patients on hydration and monitoring blood pressure for managing potential adverse effects of Dapagliflozin, such as dehydration and hypotension.
- 32% of doctors rarely encounter patients with Type 2 Diabetes who are resistant to Dapagliflozin therapy.
- In the opinion of 44% of doctors, Dapagliflozin works as primary therapy for cardiovascular risk reduction in patients with Type 2 Diabetes who have a history of cardiovascular events.
- 37% of doctors believe Dapagliflozin is very cost-effective compared to other antidiabetic medications.

Consultant Opinion

Preferred Second-Line Therapy:

Encourage the adoption of Dapagliflozin as a preferred second-line therapy for patients with T2DM who have failed to achieve glycemic control with metformin alone, as preferred by 54% of doctors in the survey.

Cardiovascular Safety Profile:

Highlight the perceived cardiovascular safety profile of Dapagliflozin compared to other antidiabetic medications, as perceived by the majority of doctors, to promote its use in patients with T2DM and cardiovascular comorbidities.

Patient Selection and Monitoring:

Emphasize the importance of considering renal function, frailty, cognitive function, fall risk, and potential drug interactions when determining the appropriateness of Dapagliflozin therapy, especially in elderly patients with T2DM.

Weight Loss and Adverse Effects:

Educate healthcare providers and patients about the potential for significant weight loss as a beneficial effect of Dapagliflozin therapy and the management of adverse effects such as genitourinary tract infections.

Monitoring and Evaluation:

Encourage regular monitoring of renal function, HbA1c levels, and cardiovascular risk factors in patients receiving Dapagliflozin therapy to assess its effectiveness and safety.

Dosage Adjustment and Patient Education:

Advocate for individualized dosage adjustments of Dapagliflozin based on clinical response and educate patients on hydration and blood pressure monitoring to manage potential adverse effects like dehydration and hypotension.

Cost-Effectiveness:

Highlight the perceived cost-effectiveness of Dapagliflozin compared to other antidiabetic medications, as believed by 37% of doctors, to support its inclusion in treatment regimens and formulary decisions.

Primary Therapy for Cardiovascular Risk Reduction:

Consider the use of Dapagliflozin as primary therapy for cardiovascular risk reduction in patients with T2DM who have a history of cardiovascular events, as suggested by 44% of doctors.

By implementing these recommendations and addressing the opportunities identified in the survey, healthcare providers and pharmaceutical companies can enhance the management of T2DM and improve patient outcomes in clinical practice.

NOTES

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Developed by:

Weston Medical Education Foundation of India

CTS-77, Shop No.11, Swapna Siddhi CHS LTD, Akurli Road Near Malad Sahakari Bank
Kandivali (E), Mumbai - 400101. M: 9322615653 I W: www.wmefi.co.in