Effectiveness of combination of Linagliptin with Dapagliflozin & as a triple combination of Linagliptin + Dapagliflozin + Metformin

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Background and Objective of the Survey

The combination of linagliptin with dapagliflozin, as well as the triple combination of linagliptin, dapagliflozin, and metformin, represents a significant advancement in the management of type 2 diabetes mellitus (T2DM), offering complementary mechanisms of action and improved glycemic control compared to monotherapy or dual therapy regimens.

Linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that works by increasing insulin secretion and decreasing glucagon release, thereby reducing blood glucose levels. Dapagliflozin, on the other hand, is a sodium-glucose co-transporter-2 (SGLT-2) inhibitor that promotes renal glucose excretion, leading to glycosuria and subsequent lowering of blood glucose levels. Metformin is a biguanide that primarily reduces hepatic glucose production and enhances peripheral glucose uptake.

The combination of linagliptin with dapagliflozin offers synergistic effects on multiple pathways involved in glucose homeostasis, resulting in greater reductions in fasting and postprandial blood glucose levels compared to either drug alone. Furthermore, dapagliflozin's mechanism of action is independent of insulin secretion and sensitivity, making it particularly beneficial for patients with T2DM who have insulin resistance or inadequate response to other antidiabetic agents.

The triple combination of linagliptin, dapagliflozin, and metformin provides even greater glycemic control by targeting multiple pathophysiological defects underlying T2DM, including insulin resistance, impaired insulin secretion, and excessive hepatic glucose production. Additionally, metformin's beneficial effects on weight management and cardiovascular risk factors further complement the glucose-lowering properties of linagliptin and dapagliflozin.

The objective of the survey is:

To evaluate the effectiveness of combination of Linagliptin with Dapagliflozin & as a triple combination of Linagliptin + Dapagliflozin + Metformin

Methodology of the Survey

A survey was conducted to evaluate the effectiveness of combination of Linagliptin with Dapagliflozin & as a triple combination of Linagliptin + Dapagliflozin + Metformin. A total of 80 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
- Mechanisms of Action
- Dapagliflozin in Diabetes Mellitus
- Dapagliflozin and Kidney Disease
- Pharmacology/Pharmacodynamics Properties of Dapagliflozin
- Patient Selection and Clinical Perspectives
- Use of Dapagliflozin in Special Situations
- Linagliptin Pharmacology
- Clinical safety

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

Chronic Kidney Disease Management and the Evolution of SGLT-s Inhibitors

The Kidney Disease: Improving Global Outcomes (KDIGO) working group defines Chronic Kidney Disease (CKD) as abnormalities of kidney structure or function present for >3 months, with implications for health. The KDIGO CKD risk score is classified based on estimated glomerular filtration rate (eGFR) and albuminuria. Diabetes and hypertension remain the leading causes of CKD in the United States and worldwide.

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Figure 1. KDIGO CKD staging by GFR and albuminuria categories.

CKD affects 12% of the global population and is a major cause of morbidity and mortality consuming a significant proportion of the health-care resources., According to the United

States Center for Disease Control and Prevention (CDC), 1 in 7 (15%) US adults or a total of 37 million people are estimated to have CKD. Globally, the prevalence of CKD is estimated at 9.1% (697.5 million cases) CKD increases the risk for all-cause mortality, cardiovascular mortality, kidney failure, and other adverse outcomes. In 2018, treating Medicare beneficiaries with CKD cost over $81.8 billion, and treating people with end-stage kidney disease (ESKD) cost and additional $36.6 billion.

Often times, CKD is referred to as the "silent killer" considering that as many as 9 in 10 adults with CKD do not know they have CKD. Global estimates indicate that 1.2 million deaths were attributable to chronic kidney disease in 2017. Additionally, about 2 in 5 adults with severe CKD do not know they have the disease, leading to delayed diagnosis and delivery of care.,

There is no cure for CKD and for decades, management has been focused on delaying its progression and preventing cardiovascular complications. Treatment options have been limited to blood pressure control, reduction of albuminuria and optimization of glycemic control. Clinicians have a few tools to achieve these treatment targets. Guidelines recommend reducing blood pressure to a target of 130/80 mm Hg in most CKD patients. Screening for proteinuria is recommended at the time of diagnosis and at least once a year thereafter. Random measurement of urinary albumin and urinary creatinine is the method of choice.

For almost 20 years, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers were the cornerstone of CKD progression retardation strategies. However, neither class reduced the risk of all-cause mortality in patients with CKD and evidence for their use in patients with CKD without T2D is relatively limited. Results from two landmark clinical trials: Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT), have shown a reduction in CKD progression in diabetic patients by 16–20% compared to placebo and calcium channel blockers., Although renin angiotensin aldosterone blocking drugs reduce the risk of adverse renal outcomes in patients with diabetes, the risk remains high and there is a large need for new treatments that lower the risk of kidney failure and improve cardiovascular risks independent of BP control. Furthermore, despite the above evidence of the benefits of renin aldosterone angiotensin system (RAAS) blockade, a large proportion of patients who meet the criteria for this treatment do not initiate it within 1 year of CKD diagnosis, highlighting a need for new therapies that can slow the progression of CKD.

Table 1. Summary of Trials on SGLT2 Inhibitors with Kidney Outcomes

Trial	**CREDENCE (n = 4401)**	**CANVAS Program (n = 10,142)**	**EMPA-REG OUTCOME (n = 7020)**	**DECLARE-TIMI 58 (n = 17,160)**	**DAPA-CKD (n = 4304)**
Inclusion criteria	eGFR 30 to <90 mL/min/1.73 m^2; UACR >300–5000 mg/g	eGFR ≥30 mL/min/1.73 m^2	eGFR ≥ 30 mL/min/1.73 m^2	CLcr ≥60 mL/min	eGFR 25–75 mL/min/1.73 m^2; UACR 200–5000 mg/g
Drug	Canagliflozin	Canagliflozin	Empagliflozin	Dapagliflozin	Dapagliflozin
Median follow-up	2.6 yr	2.4 yr	3.1 yr	4.2 yr	2.4 yr
Outcomes: RR or HR Comparing SGLT2i with Placebo					
Dialysis, Txp, or death from kidney disease	0.72 (0.54–0.97)	0.56 (0.23–1.32)	0.90 (0.30–2.67)	0.42 (0.20–0.87)	NA
Dialysis, Txp, or sustained eGFR <15 mL/min/1.73 m^2,d	0.68 (0.54–0.86)	0.77 (0.30–1.97)	0.60 (0.18–1.98)	0.31 (0.13–0.79)	0.64 (0.50–0.82)
Loss of kidney function; dialysis, Txp, or sustained eGFR <15	0.66 (0.53–0.81)	0.53 (0.33–0.84)	0.54 (0.40–0.75)	0.53 (0.43–0.66)	0.56 (0.45–0.68)

mL/min/1.73 m^2,d; or death from kidney disease					

Abbreviations: eGFR, estimated glomerular filtration rate; CLcr, creatinine clearance.

Mechanisms of Action

SGLT2 inhibitors inhibit sodium and glucose reabsorption in the proximal tubule, leading to increased sodium and chloride delivery to the macula densa. This results in vasoconstriction in the afferent arteriolar secondary to adenosine-mediated myogenic activation which leads to a reduction in the intra-glomerular pressure and glomerular filtration rate.

Based upon this physiologic action on the kidney, many pathways which lead to the cardiovascular and renal protective effects of SGLT-2 inhibition are triggered and these include natriuresis, reduced intra-glomerular pressure, tubule-glomerular feedback, blood pressure lowering, and reduced oxidative stress and fibrosis.

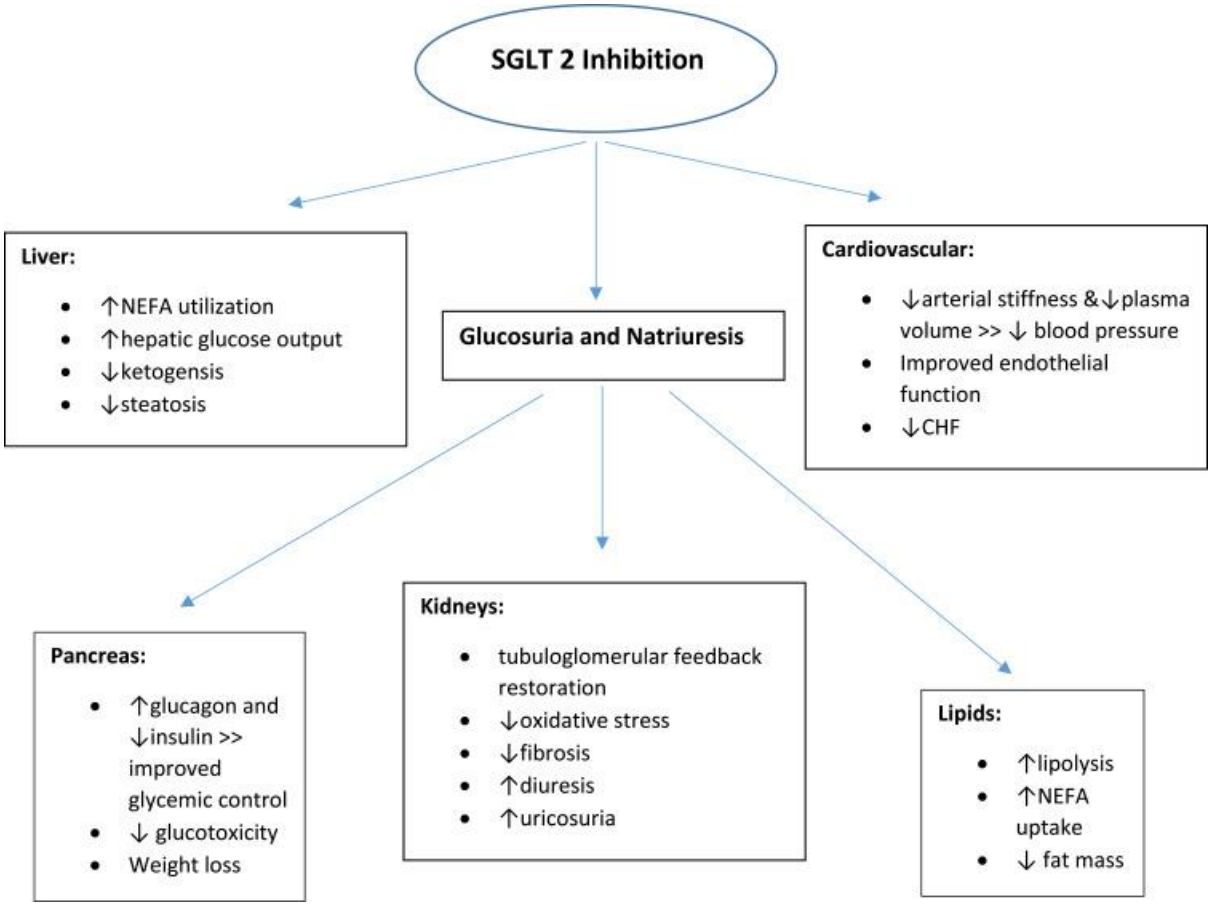

Figure 2. Mechanisms of action of SGLT2 inhibitors.

Dapagliflozin in Diabetes Mellitus

Dapagliflozin is a potent and specific SGLT-2 inhibitor and hence it increases the amount of glucose excreted in the urine and improves both fasting and post-prandial plasma glucose levels in patients with T2D. The glucosuric effect of dapagliflozin results in caloric loss and a modest reduction in bodyweight, as well as mild osmotic diuresis and transient natriuresis. These benefits have been demonstrated by multiple randomized controlled trials.

The glucose-lowering effect of dapagliflozin was similar in patients with or without cardiovascular disease and hypertension., In a pooled analysis of five, Phase 2–3 clinical trials of ≤52 weeks' duration, patients with T2D and a history of heart failure saw an improvement in glycated hemoglobin from baseline (placebo-adjusted mean change −0.55%; baseline 8.2%), bodyweight (−2.7 kg; baseline ≈97 kg) and systolic blood pressure (−2.1 mmHg; baseline ≈134 mmHg) with dapagliflozin 10 mg monotherapy or add-on therapy to other glycemic agents (n = 171) relative to placebo/active comparator (n = 149).

Effect on Blood Pressure

Dapagliflozin achieves modest decrease in blood pressure. This effect may be explained by the diuretic and natriuretic properties of the drug which cause a decrease in circulating volume. That being said, in two mechanistic studies, DAPASALT and DIAMOND, designed to study the effect of dapagliflozin in patients with CKD without T2D, it was demonstrated that during strictly controlled sodium intake, dapagliflozin increased glucosuria but not natriuresis or diuresis. This is probably related to compensatory mechanisms in the kidney that are activated during SGLT2 inhibition which may attenuate the natriuretic/osmotic-induced diuresis. This brings up the question, how can we still have blood pressure reduction if there is no increase in natriuresis? Experts explain this by the positive effects of SGLT-2 inhibition on endothelial function, arterial stiffness and pulse wave velocity.

In two Phase 3 studies, 10 mg once daily of dapagliflozin reduced SBP and improved glycemic control in patients with inadequately controlled type 2 diabetes and hypertension despite their receiving antihypertensive therapy (angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) therapy alone or in combination with one other antihypertensive., SBP reduction was greater when dapagliflozin was added to a β blocker or a calcium-channel blocker when compared to a thiazide diuretic.

Dapagliflozin and Kidney Disease

Table 2. Patients Characteristics in Dapagliflozin Studies

Trial	**DERIVE**	**DECLARE-TIMI 58 (n = 17,160)**	**DAPA-CKD (n = 4304)**	**DAPA-HF (n=4744)**
Inclusion criteria	GFR>45 mL/min/1.73 m^2	CLcr ≥ 60 mL/min	eGFR 25–75 mL/min/1.73 m^2; UACR 200–5000 mg/g	eGFR ≥ 30 mL/min/1.73 m^2
Median follow-up, months	24	50.2	28.8	18
Baseline ACEI or ARB use	132 (82.0%)	13,950 (81%)	1354 (31%)[a]; 2870 (67%)[b]	1332(56.1%)[a] 675 (28.4%)[b] 250 (10.5%)[c]

eGFR, mL/min/1.73 m^2				
≥90	Mean 53.6 (10.6)	8162 (48%)	0 (0)	Mean 66±19.6
60 to <90		7732 (45%)	454 (11%)	
45 to <60		1265 (7%)	1328 (31%)	
30 to <45		NA	1898 (44%)	
		0 (0)	624 (14%)	
Missing		1 (<0.1%)	0 (0)	
UACR, mg/g				
	Mean 29.0 (3.8–8474.0)	11,644 (68%)	NAc	Not reported
30–300		4030 (24%)	NA	
c		1169 (7%)	NA	

Notes: [a]Patients receiving ACEI. [b]Patients receiving ARB. [c]Patients receiving sacubitril/valsartan.

Abbreviations: GFR, glomerular filtration rate; CLcr, creatinine clearance; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; UACR, urine albumin-to-creatinine ratio.

The DERIVE study (Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A), was a double-blind, multinational, phase 3 that evaluated the efficacy and safety of dapagliflozin in patients with type 2 diabetes and chronic kidney disease stage 3A. Patients with T2D and glycated hemoglobin of 7–11% and a BMI of 18–45 kg/m^2 were receiving other glucose-lowering regimens and 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%), fasting blood glucose (−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.

The DECLARE-TIMI 58 trial, a randomized, double-blind phase 3 study, was designed to assess the effects of dapagliflozin on CV and renal outcomes. This study initially excluded patients with CKD, however results from the 2015 EMPA-REG OUTCOME study began to show decreased risk of incident or worsening kidney disease, progression to macroalbuminuria, and doubling of serum creatinine in patients treated with empagliflozin. Similarly, the 2019 CREDENCE trial found that canagliflozin reduced the risk of several cardiovascular and renal

outcomes. The DECLARE-TIMI trial subsequently began to include patients with CKD. The study's two pre-specified secondary endpoints were renal composite outcome 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 the patients) and heart failure (HF; 10%). The mean duration of diabetes was ≈11 years, mean HbA1c was 8.3% and the mean estimated glomerular filtration rate (eGFR) was 85 mL/min/1.73 m^2 (45% and 7% of the 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 glucose-lowering agents at the discretion of the treating physician. The median follow-up duration was 4.2 years (69,547 patient-years). dapagliflozin significantly lowered the rate of CV death/HHF versus placebo, but there was no significant between-group difference in the rate of major adverse cardiovascular events. Secondary analysis results suggested that dapagliflozin decreases the likelihood of progression of renal disease compared with placebo. The reduction in sustained decline in eGFR was ≥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 kidney disease (ESKD; HR 0.31; 95% CI 0.13–0.79; p = 0.013), and renal death or ESKD (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 placebo by 3 and 4 years after randomization.,

The DECLARE-TIMI 58, EMPA-REG OUTCOME and CREDENCE only included patients with diabetes, and whether this benefit would extend to for adults without T2DM was unclear at that point. This formed the question of whether dapagliflozin would affect the progression of chronic kidney disease and cardiovascular death in patients with or without type 2 diabetes and chronic kidney disease characterized by eGFR reduction and microalbuminuria. The Dapagliflozin And Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) study, a multicenter, double-blind, randomized, placebo controlled study, was designed to answer this question. The study included 4304 participants with CKD (defined by eGFR of 25–75 mL/min/1.73 m^2 and albuminuria with albumin-to-creatinine ratio (ACR) of 200–5000 mg/g) with and without T2DM and compared the effect of dapagliflozin to placebo. At least a third of patients without diabetes saw changes associated with ischemic and hypertensive nephropathy, and had chronic glomerulonephritis (especially IgA nephropathy). The study was stopped early after an interim safety analysis found conclusive evidence of the benefit of Dapagliflozin, which demonstrated to reduce the composite endpoint of decline of ≥50% in eGFR, new ESKD, renal mortality, or CVD mortality (9.2% vs 14.5%; HR 0.61; 95% CI 0.51–

0.72; NNT=19). Remarkably, this benefit was similar regardless of T2D status. The medication was also associated with reduction in other endpoints, including all-cause mortality (4.7% vs 6.8%; 0.69; 0.53–0.88; NNT=48). There was a slightly higher risk of major hypoglycemia (0.7% vs 1.3%; P=0.04; NNH=166) with dapagliflozin use.

The study concludes that among patients with chronic kidney disease stages 2 through 4 and elevated levels of albuminuria, regardless of the presence or absence of diabetes, the risk of a sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lowered (39%) when dapagliflozin is used in combination with standard of care treatment with RAAS blockade compared to placebo. The absolute risk reduction was 5.3% over a median time of 2.4 years, dapagliflozin also reduced the relative risk of death from any cause by 31% compared to placebo. The trial was unique in that one-third of patients did not have diabetes, and yet these benefits were the same regardless of diabetes status. This finding contradicts the hypothesis that such drugs mitigate glycemia-related nephrotoxicity.

The findings in the DAPA-CKD trial led the US Food and Drug Administration in April 2021 to approve dapagliflozin as the first drug that reduces the risk of kidney function decline, kidney failure, cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease who are at risk of disease progression regardless of diabetes status.

The DAPA-CKD results were followed by two sub-analyses. The first aimed to answer the question: is dapagliflozin safe in CKD stage 4 patients? Glenn M. Chertow et al analyzed data of 624 of 4304 (14%) patients in the DAPA-CKD study who had stage 4 CKD (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2). Compared with placebo, dapagliflozin was associated with a significant 27% improvement in the primary composite endpoint time of 50% or more decline in eGFR as well as end-stage kidney disease, or kidney or cardiovascular death in patients with advanced CKD. Furthermore, dapagliflozin significantly lowered both the risks for the kidney and cardiovascular endpoints by 29% and 17%, respectively, and the risk for all-cause mortality by 32%. Compared to placebo, dapagliflozin was superior at preservation of kidney function, with eGFR decreasing by 2.15 vs 3.38 mL/min/1.73 m^2 per year. Rates of serious adverse events including major hypoglycemia, bone fractures, kidney-related events, and amputation were similar between the two groups. It was concluded that the effects of dapagliflozin among patients with stage 4 CKD are similar to those patients with mild-to-moderate CKD. It should be noted that the lower number of participants with eGFR <30 mL/min/1.73 m^2 and the different underlying diseases may have caused a certain bias.

Another pre-specified subgroup analysis was performed to determine whether these outcomes were influenced by the presence or absence of cardiovascular disease. Of the total study population, 37.4% were secondary prevention patients, this group was predominantly males and likely to have diabetes. Additionally, the secondary prevention group had a higher BMI and blood pressure versus other participants. The primary and secondary prevention groups had similar eGFR and median urinary albumin-to-creatinine ratio. Rate of kidney failure was similar between the two groups, but the secondary prevention group had higher rates of adverse cardiovascular outcomes. The primary composite outcome (which included a sustained decline in eGFR of 50% or lower, end-stage kidney disease, and kidney or cardiovascular death) was significantly reduced by dapagliflozin treatment in both the primary and secondary prevention groups. Additionally, dapagliflozin treatment yielded similar reductions in terms of composite outcome of heart failure hospitalization, cardiovascular death, and all-cause mortality. No differences in rates of adverse events were detected between the groups. Based on these data, it was concluded that benefits from dapagliflozin are present in patients with and without cardiovascular disease.

Pharmacology/Pharmacodynamics Properties of Dapagliflozin

Dapagliflozin is rapidly absorbed following oral administration, with peak plasma concentrations usually achieved at 2 hours. Dapagliflozin pharmacokinetics are not affected by food. 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. The mean half-life is 12.9 hrs. Dapagliflozin is largely metabolized in the liver via CYP to an inactive metabolite (dapagliflozin 3-*O*-glucuronide). The drug and its metabolites are mainly excreted in the urine, with 75% of a dose recovered in the urine and 21% in the feces.

Patient Selection and Clinical Perspectives

Renal Indications

As stated above, several clinical trials provided clear and consistent data that SGLT2 inhibitors have marked renal benefits, with preservation of estimated glomerular filtration rate (eGFR) and reduced rates of renal outcomes observed with SGLT2 inhibitors compared with placebo in each of these trials. DAPA-CKD in particular created a paradigm shift in the management of chronic kidney disease (CKD). Current indications for dapagliflozin include chronic kidney disease stages 1–4 (eGFR>25 mL/min/1.73 m^2) with proteinuria (>200 mg/g): To reduce the

risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression. The 2020 Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for management of diabetes and CKD aims to address this issue by providing new clinical recommendations and practical points for clinicians. The guideline recommends treatment with SGLT2i for patients with type 2 diabetes, CKD, and eGFR >30 mL/min per 1.73 m^2 at any level of current glycemic control.

Limitations of use: Dapagliflozin is not recommended in patients with type I diabetes, polycystic kidney disease, or in those who currently require or have a recent history of immunosuppressive therapy for kidney disease.

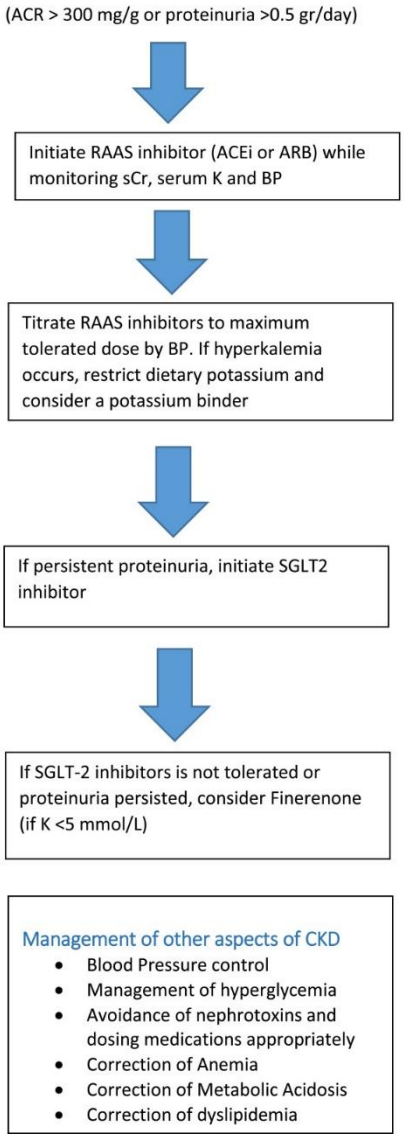

Figure 3. Management of CKD with proteinuria.

Contraindications

- Diabetes mellitus type 1
- Advanced CKD with eGFR <25 mL/min/1.73m^2 (patients may continue 10 mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death and HF)
- Prior diabetic ketoacidosis (DKA)

Precautions

- Frequent bacterial urinary tract infections or genitourinary yeast infections.
- In conjunction with NSAIDs, RAAS inhibitors, and diuretics.
- Peripheral vascular disease, foot ulceration, and neuropathy.
- Patients at high risk for Diabetic Ketoacidosis (DKA).
- Low bone mineral density and high risk for falls and fractures.
- Conditions that predispose to AKI, eg, liver disease and hypovolemia.
- Known history of bladder cancer or at risk of bladder cancer.
- Risk of hypovolemia, eg, ileostomy.
- SGLT-2 inhibitors should be withheld at least 24–48 hours prior to elective surgery, planned invasive procedures, or anticipated severe stressful physical activity and restarted only in stable clinical conditions.
- Patients with severe hepatic impairment were excluded from clinical trials and therefore we recommend avoiding using the drug in this population.

Prior to Initiating Dapagliflozin, Clinician Should

- Obtain a baseline kidney function (sCr, albuminuria/proteinuria) and liver function tests.
- Assess and correct hypovolemia as it is optimal to start therapy when the patient is euvolemic. Consider reducing the dose of diuretic therapy by 25–50% at the initiation of dapagliflozin.
- Decrease the dose of insulin and oral hypoglycemic agents to reduce the risk of hypoglycemia.

Dosing

Dose of 10 mg once daily can be taken any time of day with or without food.

For patients with reduced liver function, a starting dose of 5 mg is recommended.

In impaired renal function: if eGFR ≥45 mL/minute/1.73 m^2, no dosage adjustment is necessary.

In patients with eGFR 25 to <45 mL/minute/1.73 m^2, no dosage adjustment is necessary, but caution should be used.

In patients with eGFR <25 mL/minute/1.73 m^2, dapagliflozin should not be initiated; however, patients previously established on dapagliflozin may continue 10 mg once daily. This is consistent with the DAPA-CKD trials enrollment.

Monitoring During Treatment

Clinicians should monitor the following during treatment with dapagliflozin:

- Fasting blood sugar and glycated hemoglobin
- Renal function (BUN and sCr)
- Volume status and blood pressure

Even though most clinicians argue for the need to monitor renal function in all patients following the initiation of SGLT2 inhibitors, a recent report published in the Clinical Journal of American Society of Nephrology (CJASN) indicates that there is no need to have a routine monitoring strategy to check kidney function or electrolytes, unless there is a clinical concern about volume depletion in specific individuals, such as in patients with BP <120/70 mm Hg, sign/symptoms of volume depletion (eg, orthostatic symptoms), a regimen of high-dose diuretics, and perhaps among elderly patients. This recommendation is predicated on the concept that the risk of AKI is not increased, eGFR dipping is not associated with kidney injury, and that ultimately dipping should not affect management or continuation of therapy. Furthermore, unlike RAAS inhibitors, SGLT2 inhibitors do not cause hyperkalemia after initiation. Therefore, patients can safely undergo blood work at a subsequent follow-up appointment to avoid additional cost and unnecessary anxiety around an eGFR dip. The authors hope that this strategy will decrease the barriers to initiating guidelines-recommended therapy, particularly in the primary care setting. Monitoring renal function 4 weeks after initiating SGLT2 inhibitors is recommended for high-risk patients (prior episodes of kidney injury, advanced CKD and patients at risk of volume depletion). If serum creatinine rose >30% of baseline value, clinicians need to reassess blood pressure and volume status with consideration to reduce/hold diuretics, liberalize fluid intake or holding SGLT-2 inhibitors.

Clinicians should ask patients who are taking insulin or insulin secretagogues to monitor fasting and pre-meal glucose levels for the first few weeks following initiation or dose escalation of dapagliflozin.

Insulin dosing should be decreased by 10% to 20% and insulin secretagogue dosing by 50% if blood glucose fall <80 mg/dL.

Use of Dapagliflozin in Special Situations

Use in the Elderly

Special consideration should be given when prescribing dapagliflozin to elderly patients as they are predisposed to intravascular volume depletion. Clinicians should monitor for symptoms such as hypotension, orthostatic hypotension, dizziness, syncope, and dehydration before prescribing dapagliflozin.

The cardiovascular and renal benefits of dapagliflozin in elderly patients were evaluated in a sub-analysis of DECLARE-TIMI 58 trial, which included a large cohort of elderly and very elderly patients (65–75 and >75 years old). Similar results were noted across all age groups indicating that the overall efficacy and safety of dapagliflozin were consistent regardless of age.

Dapagliflozin and Pregnancy

(SGLT2) inhibitors are not recommended for patients with type 2 diabetes mellitus planning to become pregnant. This is based on adverse effects on renal development observed in animal studies. Similarly due to the potential for serious adverse reactions in the breastfeeding infant, breastfeeding is not recommended by the manufacturer. Patients of child-bearing age should use effective contraception during therapy. Transition to a preferred therapy should be initiated prior to conception and contraception should be continued until glycemic control is achieved.

Dapagliflozin in Patients Who Received Kidney Transplant

Little is known about the safety and efficacy of SGLT2i in the kidney transplant setting. Concerns regarding increased risk of urinary tract infections, diabetic ketoacidosis and acute kidney injury limit their use in this patient population. In a single center, retrospective analysis of 50 adult kidney transplant recipients who were followed for a period of 6 months, improvement in weight (−2.95 kg [SD 3.54, P = <0.0001 (CI: 3.53, 1.50)]), hypomagnesemia (0.13 [SD 1.73, P = 0.0004 (CI: 0.06, 0.20)]) and insulin usage (−3.7 units [SD 22.8, P = 0.17]) was observed. Similar rate of UTIs was observed in patients receiving treatment compared to a control group. No incidence of DKA or amputations was observed. While conclusions cannot be accurately drawn from a single-center retrospective studies like this one and while randomized research is needed to further validate these results, this data serves as a hypothesis for future studies. In the meantime, the use of dapagliflozin should be avoided in the first-year post kidney transplant.

Linagliptin Pharmacology[2]

Mechanism of Action

Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). This activity, in turn, increases the plasma concentrations of active incretin hormones, thereby stimulating the release of insulin in a glucose-dependent manner and decreasing circulating levels of glucagon. GLP-1 and GIP are involved in the physiological regulation of glucose homeostasis. Both hormones increase the biosynthesis of insulin and its secretion from pancreatic beta cells in the presence of normal or elevated levels of blood glucose. In addition, GLP-1 reduces glucagon secretion from pancreatic alpha-cells, resulting in a reduction in glucose output in the liver.

The other DPP-4 inhibitors currently available in the U.S.—saxagliptin (Onglyza, Bristol-Myers Squibb) and sitagliptin (Januvia, Merck)—also act by slowing the inactivation of incretin hormones.[,]

Chemical Structure[2]

Although the three FDA-approved DPP-4 inhibitors share a common mechanism of action, each has unique chemical features. Linagliptin, for example, has a xanthine-based structure, which may be a key factor in the drug's long terminal elimination half-life (more than 100 hours). The long half-life of linagliptin may be more beneficial for patients who occasionally miss their doses of medication, compared with the substantially shorter half-lives of saxagliptin and sitagliptin (2.5 and 12.4 hours, respectively).[,]

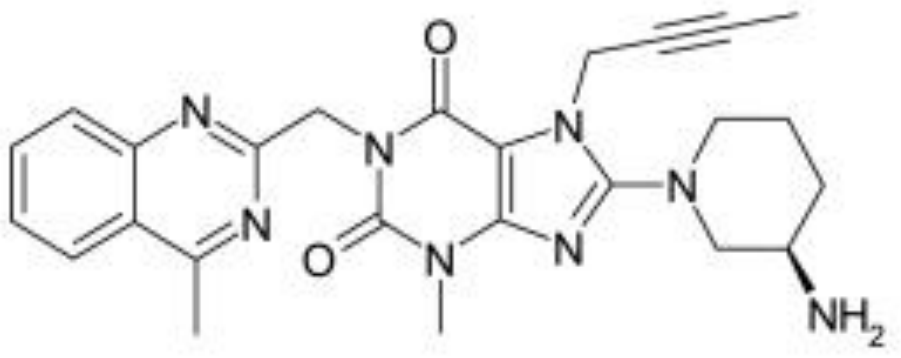

Figure 4. Chemical structure of linagliptin. (From package insert.)

Enzyme Binding[2]

Linagliptin binds tightly, but not irreversibly, to the DPP-4 enzyme. Tightly bound inhibitors are important; once they are attached to the target enzyme, the enzyme's function remains inhibited even after the free drug has been eliminated from the systemic circulation or removed from the specific site of action. This pharmacological feature may explain linagliptin's 24-hour inhibition profile. In a study of multiple oral doses of linagliptin in men with type-2 diabetes, the 5- and 10-mg doses provided DPP-4 inhibition of more than 80% at 24 hours after dosing.

Pharmacodynamics[2]

Thomas and colleagues evaluated the *in vitro* potency and selectivity of linagliptin and compared it with the other DPP-4 inhibitors. The relative *in vitro* potencies of DPP-4 inhibition among the three FDA-approved compounds, expressed as half the minimal inhibitory concentration (IC_{50}), were 1 nM for linagliptin, 19 nM for sitagliptin, and 50 nM for saxagliptin. In addition, linagliptin is 40,000-fold more selective for DPP-4 than for DPP-8 or DPP-9, whereas the corresponding selectivity for sitagliptin and saxagliptin is more than 2,500-fold and less than 100-fold, respectively." Thus, linagliptin selectively inhibits DPP-4 activity, but not DPP-8 or DPP-9 activity, *in vitro* at concentrations that approximate therapeutic exposures.

Pharmacokinetics[2]

Several studies have described the pharmacokinetic profile of linagliptin in both healthy subjects and patients with type-2 diabetes.'⁻

After the administration of increasing intravenous (IV) doses of linagliptin in healthy men, the absolute bioavailability of linagliptin 10 mg was found to be approximately 30%. Linagliptin showed nonlinear pharmacokinetics after IV infusions of 0.5 to 10 mg. The steady-state volume of distribution increased with dose, from 380 to 1,540 L.

In a study of men with type-2 diabetes who received oral linagliptin (1 mg, 2.5 mg, 5 mg, or 10 mg) once daily for 12 days, the drug's terminal half-life ranged from 113 to 131 hours for all dosing groups. Similar half-lives were reported in the healthy men receiving increasing IV doses of linagliptin (126–139 hours).

Healthy Japanese men showed elimination half-lives ranging from 96.9 to 175.0 hours after receiving single escalating oral doses of linagliptin (1 mg, 2.5 mg, 5 mg, and 10 mg) once daily for 12 days. The labeling for linagliptin states that the drug's half-life is more than 100 hours.

The metabolism and disposition of linagliptin were evaluated in healthy subjects who were given the radiolabeled drug orally as 5 mg or intravenously as 10 mg. The apparent total clearance of linagliptin was 374 mL/minute, and the mean terminal half-life was 155 hours. The major metabolite of linagliptin (the *S*-3-hydroxypiperidinyl derivative) accounted for at least 10% of the systemic exposure of the parent compound after oral administration. The half-life of the metabolite was 10.8 hours. Most of the linagliptin dose was eliminated unchanged after both oral and IV administration. Oral linagliptin was eliminated primarily via the fecal route (84.7%). The cytochrome P450 (CYP) 3A4 enzyme was responsible for the metabolism of linagliptin.

Clinical safety[2]

Early safety data for linagliptin were provided by several dose-ranging studies.[7–] Evaluating the safety and tolerability of linagliptin in healthy male volunteers, Hüttner et al. found that linagliptin was well tolerated up to doses of 600 mg. The incidence of drug-related AEs was similar for linagliptin and placebo (30% vs. 31%, respectively). Linagliptin (1, 2.5, 5, or 10 mg) was also well tolerated in a study of men with type-2 diabetes. In this study, the rate of AEs was lower for linagliptin than for placebo (54% vs. 75%, respectively), and no serious AEs or hypoglycemic episodes occurred in either treatment group. Similarly, in a study of linagliptin (1–10 mg) in healthy Japanese men, no AEs were considered to be drug-related, and there were no episodes of hypoglycemia.

The clinical safety of linagliptin has been assessed more than 4,000 patients who had type-2 diabetes. In placebo-controlled trials, nasopharyngitis was an AE that occurred in at least 5% of the linagliptin patients (n = 2,566) and more frequently than in the placebo patients (n = 1,183) (5.8% vs. 5.5%, respectively). Other AEs reported in clinical studies of linagliptin included hypersensitivity and myalgia. In the linagliptin clinical trial program, pancreatitis occurred in 8 of 4,687 patients receiving linagliptin and in none of the 1,183 patients receiving placebo.

Hypoglycemia[2]

Hypoglycemia rarely occurs during treatment with linagliptin. According to the product labeling, the incidence of - hypoglycemia was similar for linagliptin and placebo when linagliptin was administered as monotherapy or in combination with metformin or pioglitazone in placebo-controlled trials. In a study of monotherapy with linagliptin (5 mg) in patients with

inadequately controlled type-2 diabetes, 0.6% of the linagliptin group and 0.3% of the placebo group experienced hypoglycemic events.

In another placebo-controlled study of linagliptin monotherapy (1, 5, or 10 mg), no episodes of hypoglycemia were reported in patients with type-2 diabetes. In the study of initial combination therapy with linagliptin and pioglitazone in patients with inadequately controlled type-2 diabetes, 1.2% of the active-treatment group experienced hypoglycemia compared with 0% of the placebo group. Similarly, the study of linagliptin, when added to metformin, reported no hypoglycemic events for the linagliptin or placebo groups.

Weight Gain[2]

DPP-4 inhibitors appear have a neutral effect on weight.' Forst et al. reported mean weight loss of 0.15, 0.57, and 1.27 kg with linagliptin 1 mg, 5 mg, and 10 mg, respectively. Conversely, in a study by Gomis et al., combination therapy with linagliptin and pioglitazone caused significantly greater weight gain over 24 weeks of treatment compared with placebo plus pioglitazone (+2.3 vs. +1.2 kg, respectively; $P = 0.01$); however, the changes from baseline were minimal. A similar decrease in body weight was observed for linagliptin/metformin versus placebo/metformin in a 24-week study. Further, there were no significant differences in body weight between linagliptin plus a sulfonylurea, compared with a placebo plus a sulfonylurea in an 18-week study.

QT Interval Prolongation[2]

No significant changes in electrocardiographic parameters were observed in clinical studies of linagliptin.'–

In a randomized, placebo-controlled, double-blind, four-period crossover study, Ring et al. evaluated the potential for linagliptin to prolong the QT interval at therapeutic and supratherapeutic doses. A total of 44 patients were assigned to receive a single dose of linagliptin 5 mg, linagliptin 100 mg (20 times the recommended dose), moxifloxacin (Avelox, Merck) 400 mg, or placebo. Neither the 5-mg dose nor the 100-mg dose of linagliptin increased the QT interval, corrected for heart rate.

Linagliptin was well tolerated, and there were no clinically relevant electrocardiographic (ECG) changes or relevant changes in other safety parameters.

Contraindications[2]

Linagliptin should not be prescribed for patients with a history of a hypersensitivity reaction to this drug, such as urticaria, angioedema, or bronchial hyperreactivity.

Dosage and administration[2]

The recommended dosage of linagliptin is 5 mg once daily. The tablets may be taken with or without food. No dosage adjustments are necessary for patients with renal or hepatic impairment.

Drug interactions[2]

The efficacy of linagliptin may be reduced when the drug is coadministered with a strong CYP3A4 or P-glycoprotein inducer (e.g., rifampin). Sulfonylureas should be used with caution during treatment with linagliptin.

The pharmacokinetic characteristics of linagliptin were not altered by the concomitant administration of simvastatin (Zocor, Merck), digoxin (Lanoxin, Glaxo-SmithKline), glyburide, warfarin (Coumadin), metformin, or pioglitazone.

Abstracts

A Randomized, Double-Blind, Parallel-Group Phase III Trial Investigating the Glycemic Efficacy and Safety Profile of Fixed-Dose Combination Dapagliflozin and Linagliptin Over Linagliptin Monotherapy in Patients with Inadequately Controlled Type 2 Diabetes with Metformin

Abstract

Introduction: The aim of the study was to evaluate the efficacy and safety of fixed-dose combination (FDC) of dapagliflozin (10 mg) and linagliptin (5 mg) in comparison to linagliptin 5 mg (Trajenta) in patients with insufficiently controlled type 2 diabetes mellitus (T2DM) on metformin monotherapy.

Methods: The double-blind, randomized, multicentric, parallel-group phase III trial screened 287 adult patients with T2DM (age 18-65 years) from 16 sites across India. The recruited subjects were undergoing metformin monotherapy ≥ 1000 mg/day for at least 28 days. Patients with HbA1c of 7.5-10.5% (58-91 mmol/l) (n = 232) after 2 weeks of run-in period with linagliptin monotherapy and placebo dapagliflozin/linagliptin on metformin monotherapy were randomized (1:1) in parallel to once daily dapagliflozin/linagliptin 10/5 mg or linagliptin 5 mg for 16 weeks. Patients were stratified on the basis of HbA1c (≤ 9.0% and > 9.0%; ≤ 75 mmol/l and > 75 mmol/l)). A total of 225 subjects completed 16 weeks of treatment, 115 patients in the test group and 110 patients in the reference group.

Results: Dapagliflozin/linagliptin ($p = 0.0003$) exhibited a greater change in HbA1c from baseline than linagliptin ($p < 0.0001$) in 16 weeks (mean reduction, - 1.28% vs - 0.83%). Test group showed a significant decrease in fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and body weight compared to the reference group. The FDC was well tolerated with adverse events being more frequent in the reference group. No serious adverse events (SAEs) were reported in the study.

Conclusion: Dapagliflozin/linagliptin combination is a novel dipeptidyl peptidase 4 (DPP4)/sodium-glucose co-transporter 2 (SGLT2) inhibitor FDC approved in India for patients with T2DM. Potential limitations of this study are a small dose of dapagliflozin (10 mg) in the FDC, a short study duration (30 weeks) and a high minimum threshold for HbA1c (≤ 7.5%; ≤ 53 mmol/l). Results indicate the FDC to be a superior therapeutic option over linagliptin for patients with T2DM on metformin monotherapy.

Pharmacokinetics of a Fixed-Dose Combination Product of Dapagliflozin and Linagliptin and Its Comparison with Co-Administration of Individual Tablets in Healthy Humans

Abstract

Dapagliflozin, a selective sodium–glucose co-transporter-2 inhibitor, and linagliptin, a competitive, reversible dipeptidyl peptidase-4 inhibitor, are commonly prescribed antidiabetic medications in general clinics. Since there are several merits to combining them in a fixed-dose combination product, this study investigated the pharmacokinetic equivalence between the individual component (IC) and fixed-combination drug product (FCDP) forms of dapagliflozin and linagliptin. A randomized, open-label, single-dose crossover study was conducted. All participants (n = 48) were randomly allocated to group A (period 1: ICs, period 2: FCDP) or group B (period 1: FCDP, period 2: ICs), and each group received either a single dose of IN-C009 (FCDP) or single doses of both dapagliflozin and linagliptin. There was no statistically significant difference found between the pharmacokinetic variables of FCDP and IC. The values of estimated geometric mean ratios and the 90% confidence interval for both maximum concentration and area under the plasma drug concentration–time curve were within the range of 0.8–1.25 for both dapagliflozin and linagliptin. The results of the clinical study demonstrated comparable pharmacokinetic characteristics between IC and FCDP forms of dapagliflozin and linagliptin. The combined use of dapagliflozin and linagliptin was safe and tolerable in both formulations.

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2. Freeman MK. Efficacy and safety of linagliptin (tradjenta) in adults with type-2 diabetes mellitus. *P T*. 2011;36(12):807-842.
3. Jain A, Vispute A, Dange A, et al. A Randomized, Double-Blind, Parallel-Group Phase III Trial Investigating the Glycemic Efficacy and Safety Profile of Fixed-Dose Combination Dapagliflozin and Linagliptin Over Linagliptin Monotherapy in Patients with Inadequately Controlled Type 2 Diabetes with Metformin. *Diabetes Ther*. 2024;15(1):215-227.
4. Park JW, Kim JM, Noh JH, et al. Pharmacokinetics of a Fixed-Dose Combination Product of Dapagliflozin and Linagliptin and Its Comparison with Co-Administration of Individual Tablets in Healthy Humans. *Pharmaceutics*. 2022;14(3):591.

Survey Form

1) As per your opinion, which is the unmet medical need in patients with type 2 diabetes mellitus (T2DM)?

A. Combination therapy to address multiple pathophysiological mechanisms of hyperglycemia in order to achieve glycemic control
B. Additional treatments that provide both glycemic and non-glycemic benefits, as the control of diabetes comorbidities is needed in most of the patients
C. Reducing the occurrence of hypoglycaemia or weight gain
D. Treatment regimens which focuses on reduction of cardiovascular risk

2) Which is the most preferred Dipeptidyl peptidase 4 (DPP-4) inhibitor in your current clinical practice?

A. Linagliptin
B. Vildagliptin
C. Sitagliptin
D. Saxagliptin
E. Teneligliptin

3) Which is the most preferred Sodium glucose co-transporter-2 (SGLT-2) inhibitor in your current clinical practice?

A. Dapagliflozin
B. Empagliflozin
C. Canagliflozin
D. Remogliflozin

4) In your clinical practise how often do you find the need to initiate therapy for T2DM with a combination?

A. <25%
B. 26-50%
C. 51-75%
D. >75%

5) At what HbA1c level would you consider initiating a dual combination therapy for T2DM?

A. 7-9%
B. 9-11%
C. >11%

6) Do you have a clinical experience of concomitantly prescribing a Linagliptin plus Dapagliflozin combination therapy?

A. Yes
B. No

7) In your opinion, what would be the ideal dose for Linagliptin and Dapagliflozin fixed drug combination?

A. Linagliptin 2.5mg + Dapagliflozin 5mg
B. Linagliptin 5mg + Dapagliflozin 5mg
C. Linagliptin 2.5mg + Dapagliflozin 10mg
D. Linagliptin 5mg + Dapagliflozin 10mg

8) In which patient population would the combination Linagliptin and Dapagliflozin be preferred?

A. Newly diagnosed patients with Type 2 Diabetes
B. Patients with T2DM and impaired renal function
C. Obese patients with Type 2 Diabetes
D. Patients with Uncontrolled diabetes
E. Patients with T2DM and elevated risk of cardiovascular disease

9) Which of the clinical advantage do you perceive with the usage of Combination of Linagliptin and Dapagliflozin:

A. Significant reduction in hyperglycemia.
B. Comparitively better renal outcomes in patients with renal impairment.
C. Negligible risk of weight gain.
D. Negligible risk of hypoglycemia.
E. Lesser occurrence of urinary tract infections.

10) In your opinion, what would be the preferred dose of Metformin to be added to a combination of Linagliptin and Dapagliflozin?

A. Metformin 500 mg
B. Metformin 1000 mg

11) As per your opinion, what can be the average duration for Linagliptin + Dapagliflozin + Metformin Therapy in patient with T2DM?

A. <6 months
B. 6 months to 1 year
C. >1 year to 5 years
D. Life-long

12) In your clinical practise, when do you consider to escalate the dose of Dapagliflozin and Metformin for a patient with T2DM already on a lower strength fixed drug combination of Linagliptin + Dapagliflozin + Metformin?

A. Uncontrolled glycaemic levels
B. Further reduce the risk of cardiovascular diseases

13) In your opinion, in what age group can the combination of Linagliptin + Dapagliflozin+ Metformin be preferred?

A. 20-40 years old
B. 40-60 years old
C. >60 years old

Survey Findings

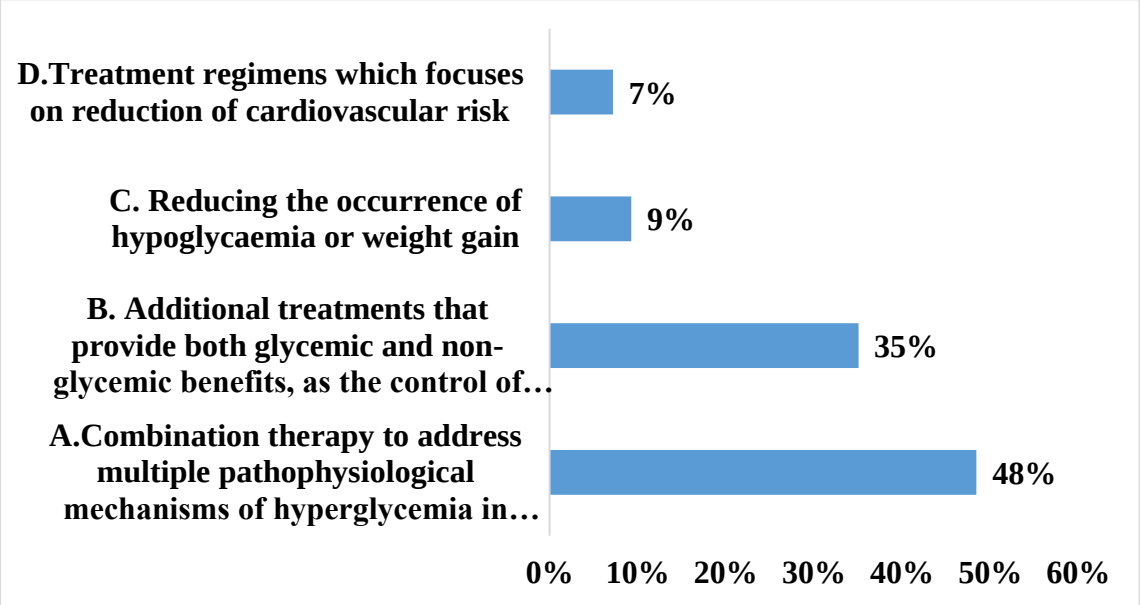
1) As per your opinion, which is the unmet medical need in patients with type 2 diabetes mellitus (T2DM)?

A. Combination therapy to address multiple pathophysiological mechanisms of hyperglycemia in order to achieve glycemic control

B. Additional treatments that provide both glycemic and non-glycemic benefits, as the control of diabetes comorbidities is needed in most of the patients

C. Reducing the occurrence of hypoglycaemia or weight gain

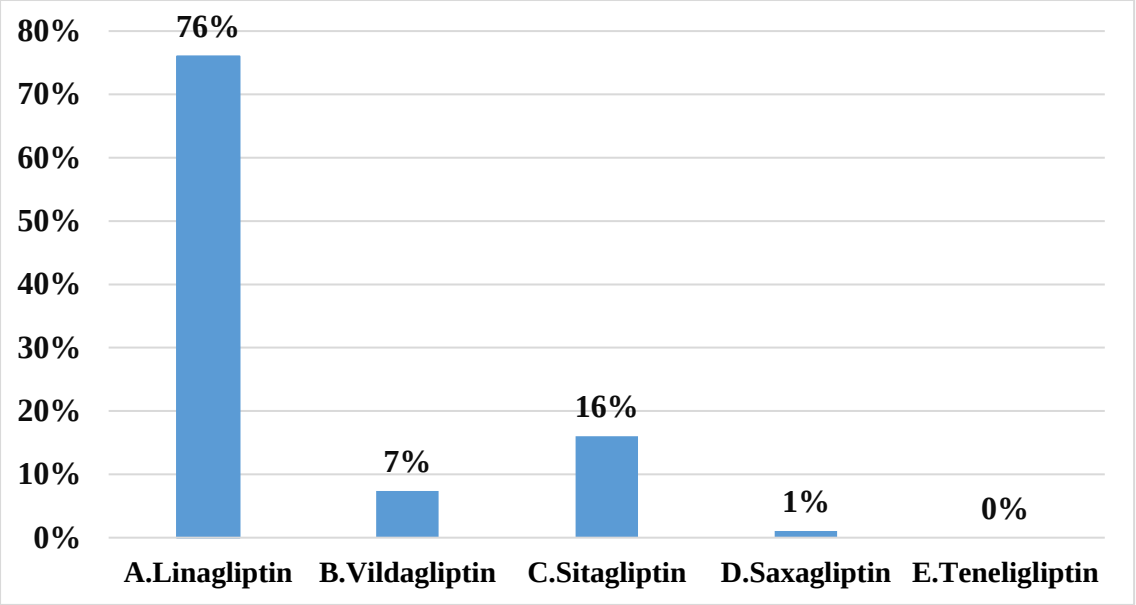
D. Treatment regimens which focuses on reduction of cardiovascular risk



As per 48% of doctors, combination therapy to address multiple pathophysiological mechanisms of hyperglycemia in order to achieve glycemic control is the unmet medical need in patients with type 2 diabetes mellitus (T2DM).

2) Which is the most preferred Dipeptidyl peptidase 4 (DPP-4) inhibitor in your current clinical practice?

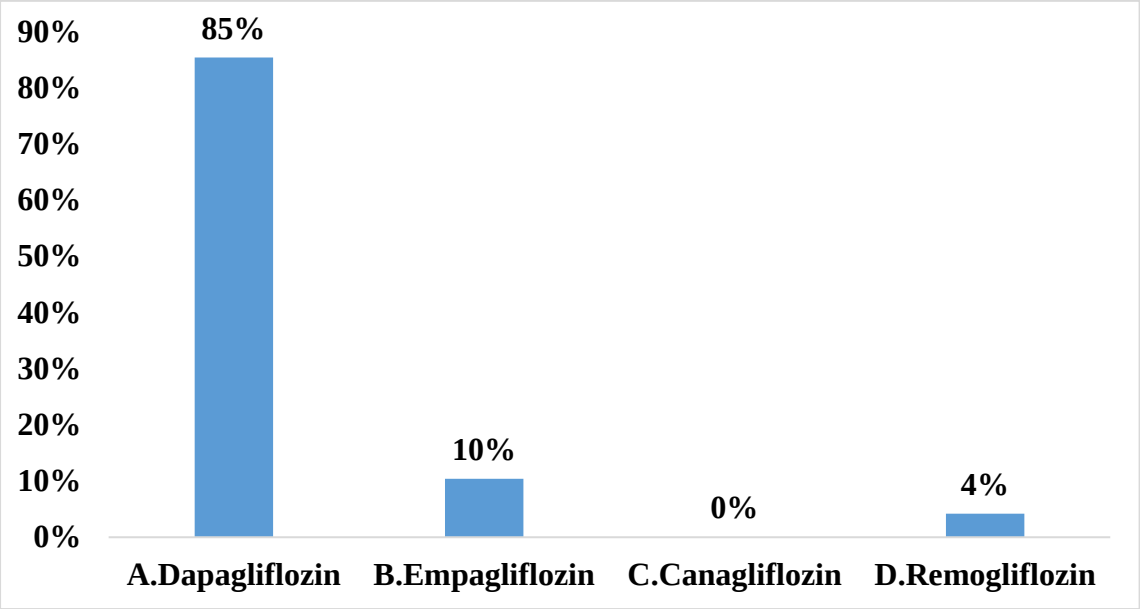
A. Linagliptin
B. Vildagliptin
C. Sitagliptin
D. Saxagliptin
E. Teneligliptin



According to majority of doctors, Linagliptinis the most preferred dipeptidyl peptidase 4 (dpp-4) inhibitor in their current clinical practice.

3) Which is the most preferred Sodium glucose co-transporter-2 (SGLT-2) inhibitor in your current clinical practice?

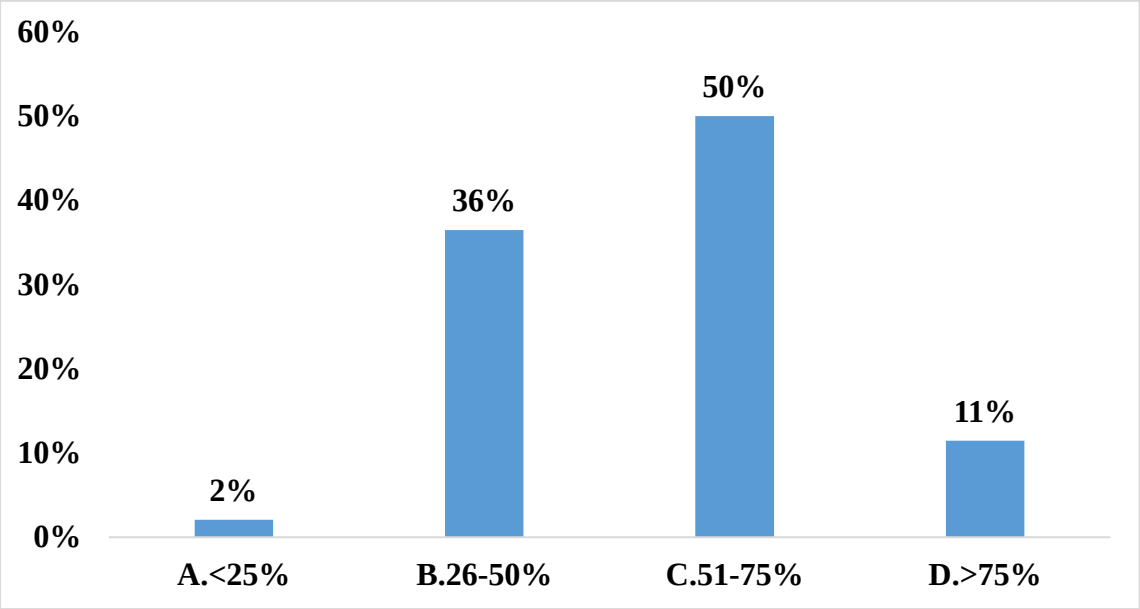
A. Dapagliflozin
B. Empagliflozin
C. Canagliflozin
D. Remogliflozin



As per majority of doctors, dapagliflozin is the most preferred sodium glucose co-transporter-2 (sglt-2) inhibitor in their current clinical practice.

4) In your clinical practice how often do you find the need to initiate therapy for T2DM with a combination?

A. <25%
B. 26-50%
C. 51-75%
D. >75%



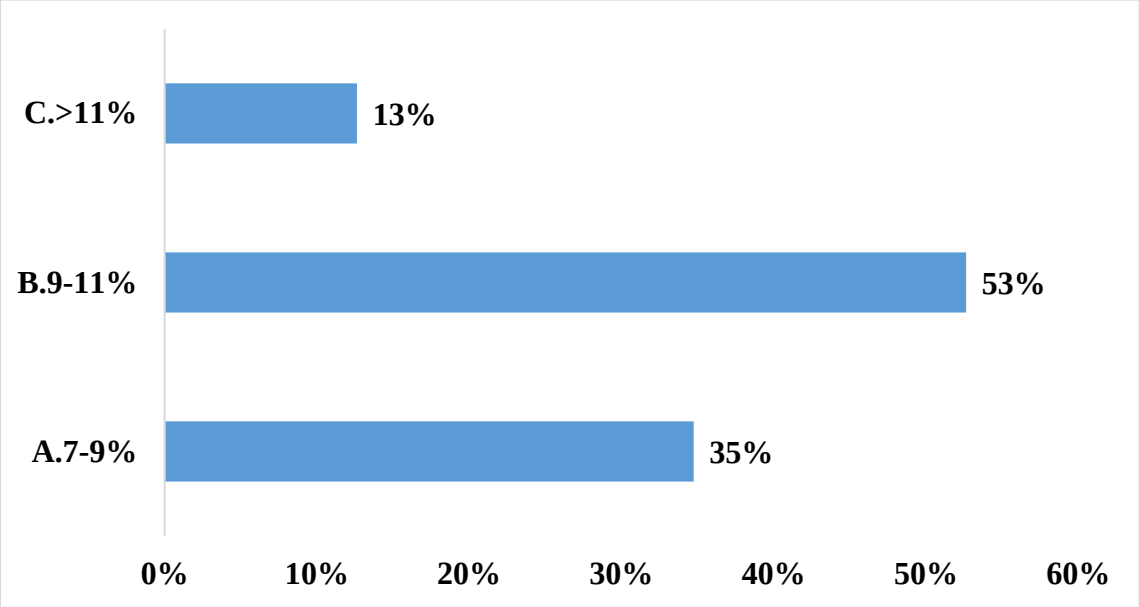
As per 50% of doctors, 51-75% is often needed to initiate therapy for T2DM with a combination in their clinical practice.

5) At what HbA1c level would you consider initiating a dual combination therapy for T2DM?

A. 7-9%

B. 9-11%

C. >11%

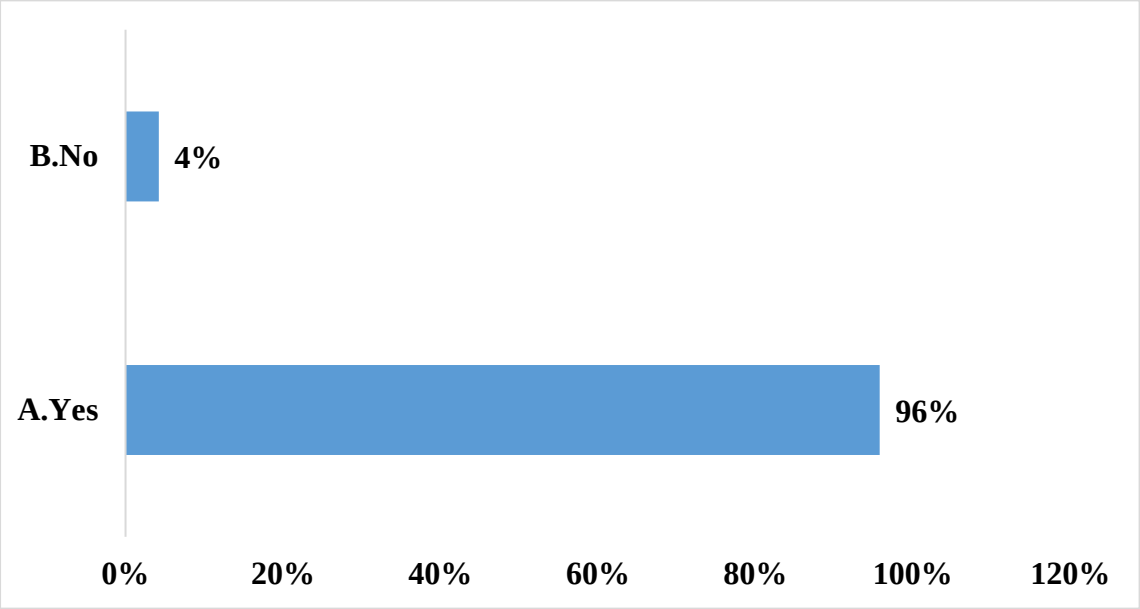


According 53% of doctors, 9-11% is the hba1c level they would consider initiating a dual combination therapy for T2DM.

6) Do you have a clinical experience of concomitantly prescribing a Linagliptin plus Dapagliflozin combination therapy?

A. Yes

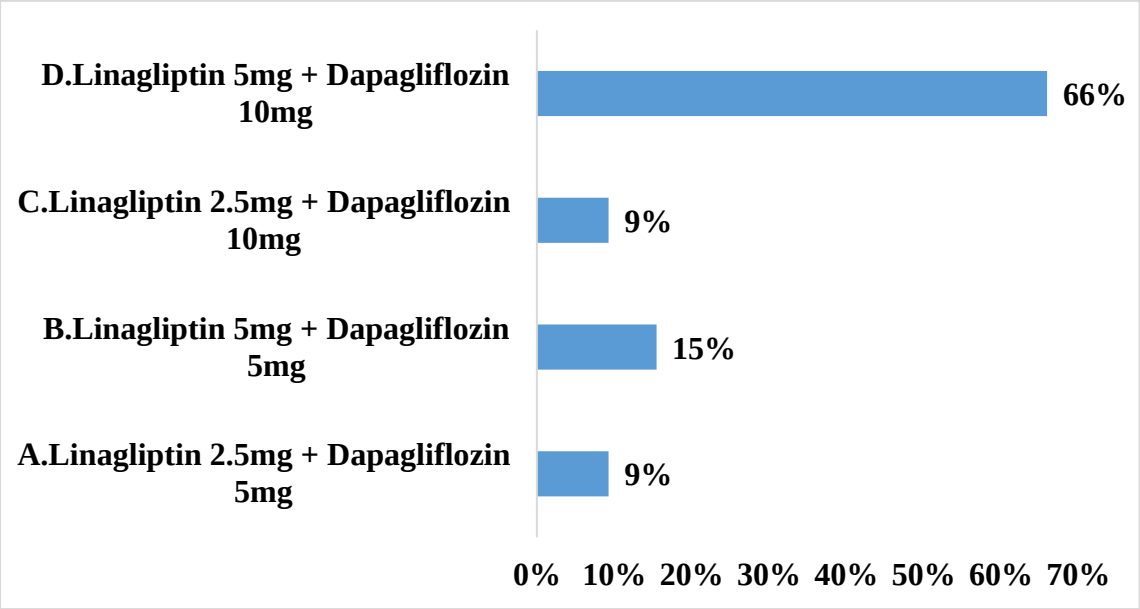
B. No



According to majority of doctors, 96%, they do have a clinical experience of concomitantly prescribing a linagliptin plus dapagliflozin combination therapy**.**

7) In your opinion, what would be the ideal dose for Linagliptin and Dapagliflozin fixed drug combination?

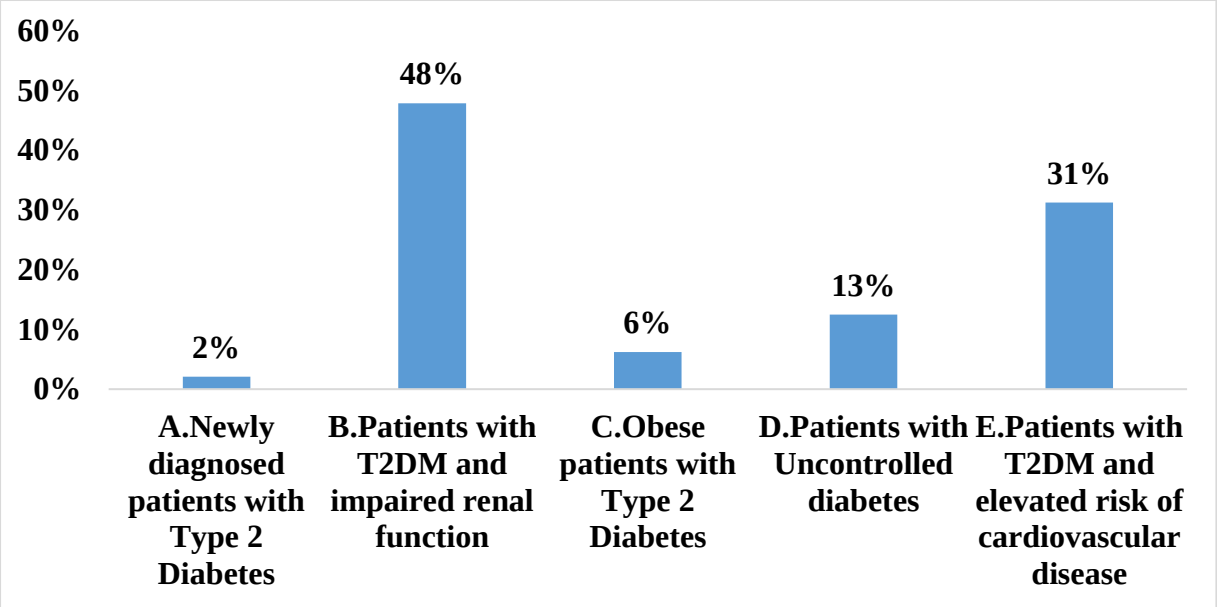
A. Linagliptin 2.5mg + Dapagliflozin 5mg
B. Linagliptin 5mg + Dapagliflozin 5mg
C. Linagliptin 2.5mg + Dapagliflozin 10mg
D. Linagliptin 5mg + Dapagliflozin 10mg



As per majority of doctors, linagliptin 5mg + dapagliflozin 10mg would be the ideal dose for linagliptin and dapagliflozin fixed drug combination.

8) In which patient population would the combination Linagliptin and Dapagliflozin be preferred?

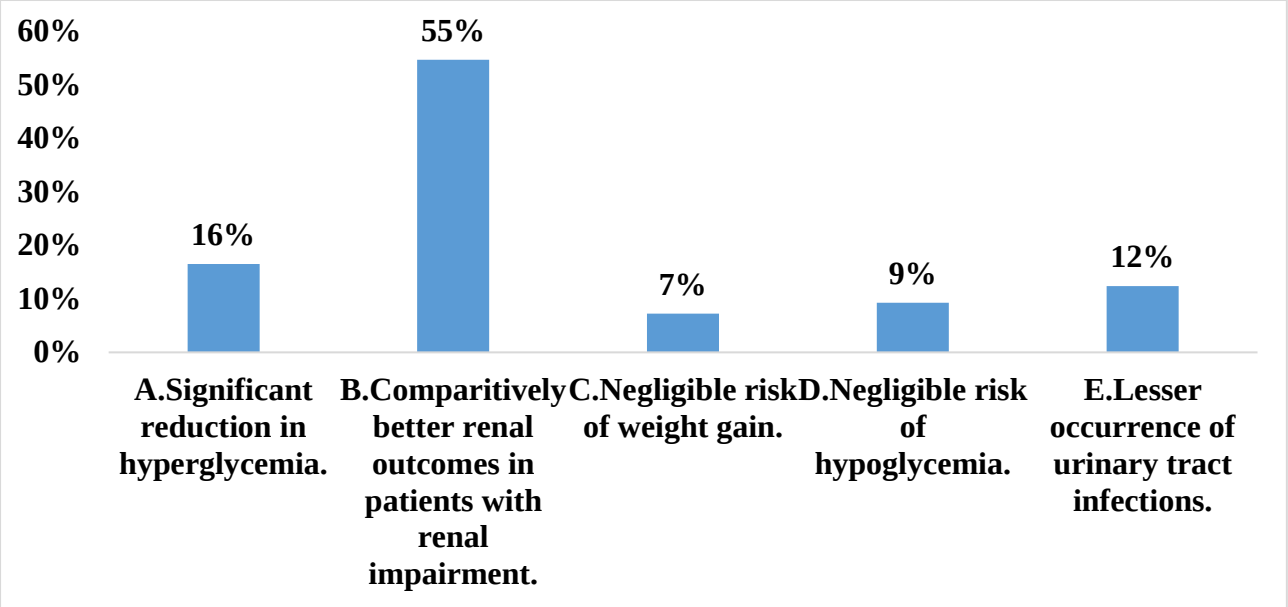
A. Newly diagnosed patients with Type 2 Diabetes
B. Patients with T2DM and impaired renal function
C. Obese patients with Type 2 Diabetes
D. Patients with Uncontrolled diabetes
E. Patients with T2DM and elevated risk of cardiovascular disease



As per 48% of doctors, the combination of linagliptin and dapagliflozin will be preferred in patients with T2DM and impaired renal function.

9) Which of the clinical advantage do you perceive with the usage of Combination of Linagliptin and Dapagliflozin:

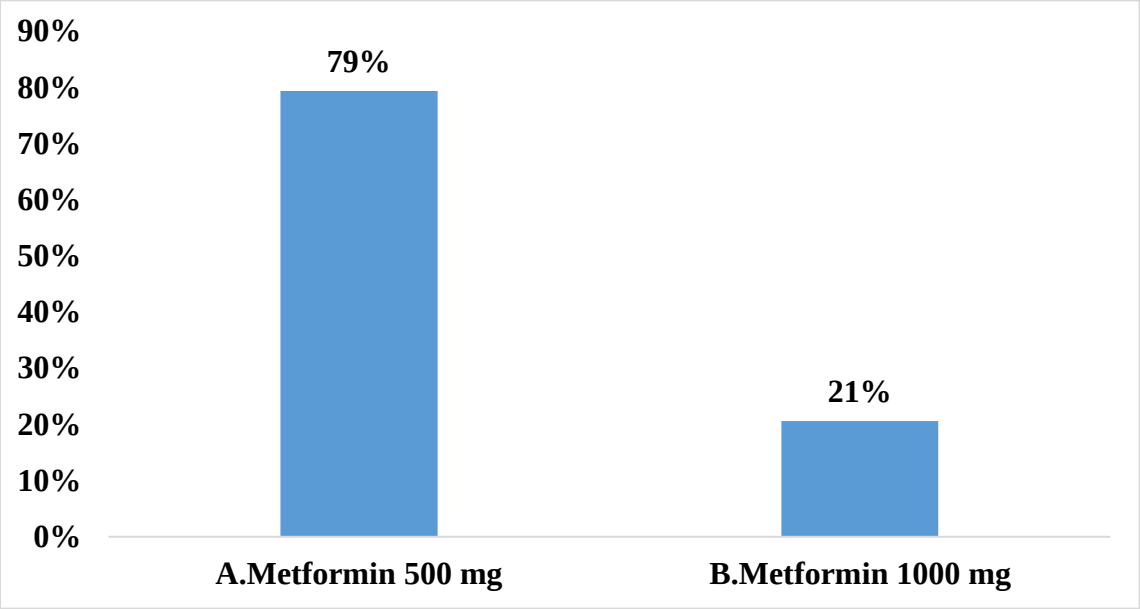
A. Significant reduction in hyperglycemia.
B. Comparitively better renal outcomes in patients with renal impairment.
C. Negligible risk of weight gain.
D. Negligible risk of hypoglycemia.
E. Lesser occurrence of urinary tract infections.



According to 55% of doctors, the clinical advantage perceived with the usage of combination of linagliptin and dapagliflozin has comparatively better renal outcomes in patients with renal impairment.

10) In your opinion, what would be the preferred dose of Metformin to be added to a combination of Linagliptin and Dapagliflozin?

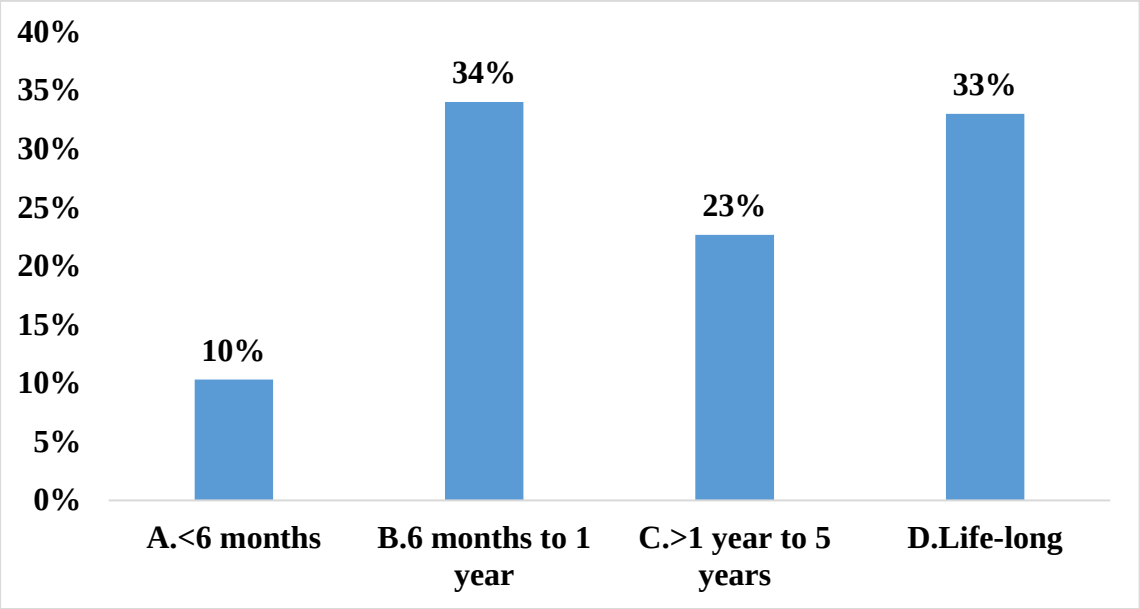
A. Metformin 500 mg
B. Metformin 1000 mg



According to majority of doctors, 79%, metformin 500 mg would be the preferred dose of metformin to be added to a combination of linagliptin and dapagliflozin.

11) As per your opinion, what can be the average duration for Linagliptin + Dapagliflozin + Metformin Therapy in patient with T2DM?

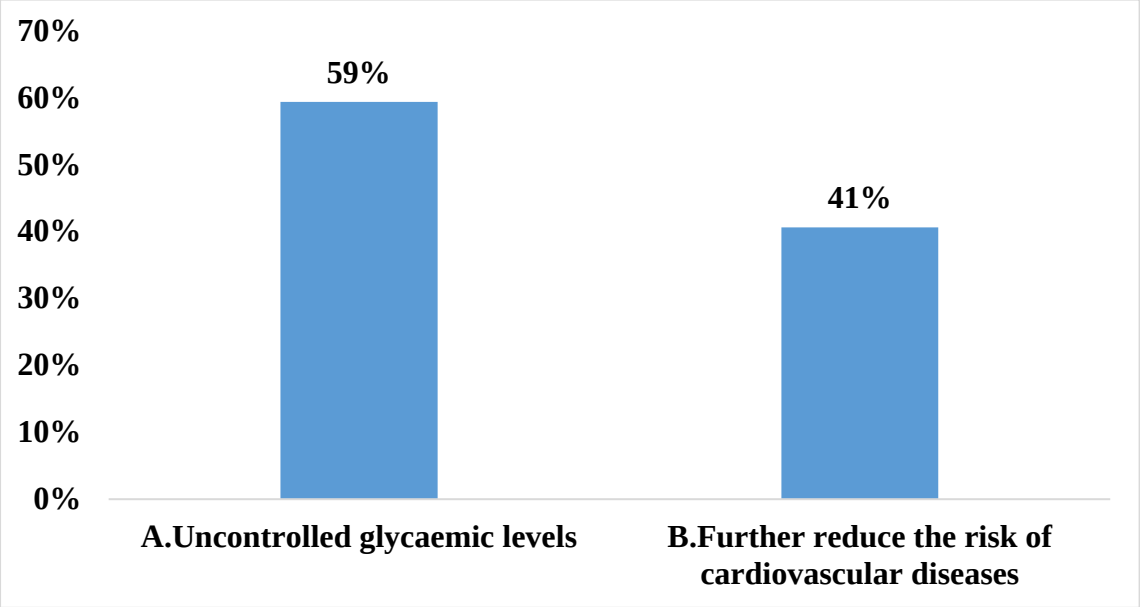
A. <6 months
B. 6 months to 1 year
C. >1 year to 5 years
D. Life-long



According to 34% of doctors, 6 months to 1 year can be the average duration for linagliptin + dapagliflozin + metformin therapy in patient with T2DM. While as per 33% of doctors, life-long can be the average duration for linagliptin + dapagliflozin + metformin therapy in patient with T2DM.

12) In your clinical practice, when do you consider to escalate the dose of Dapagliflozin and Metformin for a patient with T2DM already on a lower strength fixed drug combination of Linagliptin + Dapagliflozin + Metformin?

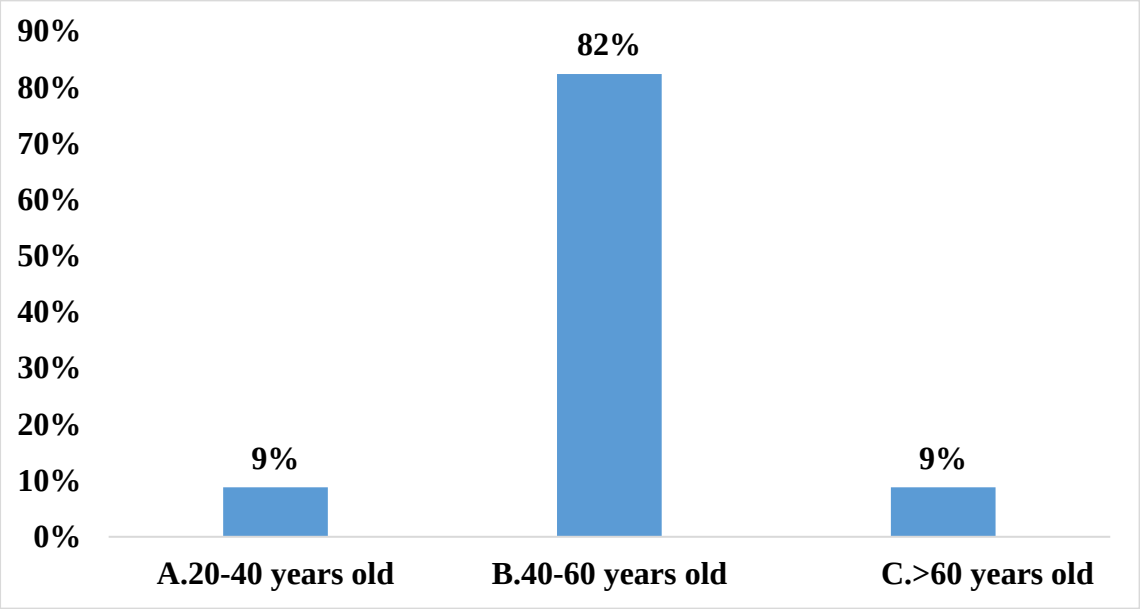
A. Uncontrolled glycaemic levels
B. Further reduce the risk of cardiovascular diseases



As per 59% of doctors, uncontrolled glycaemic levels can be considered to escalate the dose of dapagliflozin and metformin for a patient with T2DM already on a lower strength fixed drug combination of linagliptin + dapagliflozin + metformin.

13) In your opinion, in what age group can the combination of Linagliptin + Dapagliflozin+ Metformin be preferred?

A. 20-40 years old
B. 40-60 years old
C. >60 years old



As per majority of doctors, 82%, 40-60 years old age group can be preferred for the combination of linagliptin + dapagliflozin + metformin.

Summary

- As per 48% of doctors, combination therapy to address multiple pathophysiological mechanisms of hyperglycemia in order to achieve glycemic control is the unmet medical need in patients with type 2 diabetes mellitus (T2DM).
- According to majority of doctors, Linagliptinis the most preferred dipeptidyl peptidase 4 (dpp-4) inhibitor in their current clinical practice.
- As per majority of doctors, dapagliflozin is the most preferred sodium glucose co-transporter-2 (sglt-2) inhibitor in their current clinical practice.
- As per 50% of doctors, 51-75% is often needed to initiate therapy for T2DM with a combination in their clinical practice.
- According 53% of doctors, 9-11% is the hba1c level they would consider initiating a dual combination therapy for T2DM.
- According to majority of doctors, 96%, they do have a clinical experience of concomitantly prescribing a linagliptin plus dapagliflozin combination therapy**.**
- As per majority of doctors, linagliptin 5mg + dapagliflozin 10mg would be the ideal dose for linagliptin and dapagliflozin fixed drug combination.
- As per 48% of doctors, the combination of linagliptin and dapagliflozin will be preferred in patients with T2DM and impaired renal function.
- According to 55% of doctors, the clinical advantage perceived with the usage of combination of linagliptin and dapagliflozin has comparatively better renal outcomes in patients with renal impairment.
- According to majority of doctors, 79%, metformin 500 mg would be the preferred dose of metformin to be added to a combination of linagliptin and dapagliflozin.
- According to 34% of doctors, 6 months to 1 year can be the average duration for linagliptin + dapagliflozin + metformin therapy in patient with T2DM. While as per 33% of doctors, life-long can be the average duration for linagliptin + dapagliflozin + metformin therapy in patient with T2DM.

- As per 59% of doctors, uncontrolled glycaemic levels can be considered to escalate the dose of dapagliflozin and metformin for a patient with T2DM already on a lower strength fixed drug combination of linagliptin + dapagliflozin + metformin.
- As per majority of doctors, 82%, 40-60 years old age group can be preferred for the combination of linagliptin + dapagliflozin + metformin.

Consultant Opinion

Market Opportunities:

There is a significant market opportunity for pharmaceutical companies to develop combination therapies that target multiple pathophysiological mechanisms of hyperglycemia to achieve optimal glycemic control in patients with T2DM. Combination therapies, such as linagliptin plus dapagliflozin, address the unmet medical need for more effective treatment options.

Value for Healthcare Professionals:

Healthcare professionals should receive education and training on the optimal use of combination therapies, such as linagliptin plus dapagliflozin, in the management of T2DM. Continuing medical education programs can help ensure that healthcare professionals are knowledgeable about the benefits, dosing, and clinical considerations associated with these therapies.

Adverse Effect Management:

Healthcare professionals should closely monitor patients for potential adverse effects associated with combination therapy, such as renal impairment or hypoglycemia. Regular monitoring and patient education can help mitigate the risk of adverse events and improve patient safety.

Withdrawal Management:

Clear guidelines should be established for the duration and discontinuation of combination therapy in patients with T2DM. Healthcare professionals should tailor treatment plans based on individual patient factors, such as renal function and glycemic control, to optimize outcomes and minimize the risk of complications.

Market Positioning:

Pharmaceutical companies can capitalize on the clinical advantages of combination therapies, such as linagliptin plus dapagliflozin, by highlighting their efficacy in improving renal outcomes and glycemic control. Marketing strategies should emphasize the benefits of combination therapy compared to monotherapy or other treatment options, positioning these therapies as preferred choices for managing T2DM.

Personalized Treatment Decisions:

Healthcare professionals should consider individual patient factors, such as age, renal function, and glycemic control, when selecting the appropriate treatment regimen. Personalized treatment decisions can optimize outcomes and improve patient satisfaction by addressing the specific needs and preferences of each patient.

Improving Patient Outcomes:

Patient education is essential to ensure optimal outcomes with combination therapy for T2DM. Patients should be informed about the purpose of combination therapy, potential side effects, and the importance of adherence to prescribed regimens. Additionally, healthcare professionals should regularly assess patient response and adjust treatment plans as needed to achieve successful glycemic control and minimize complications.

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