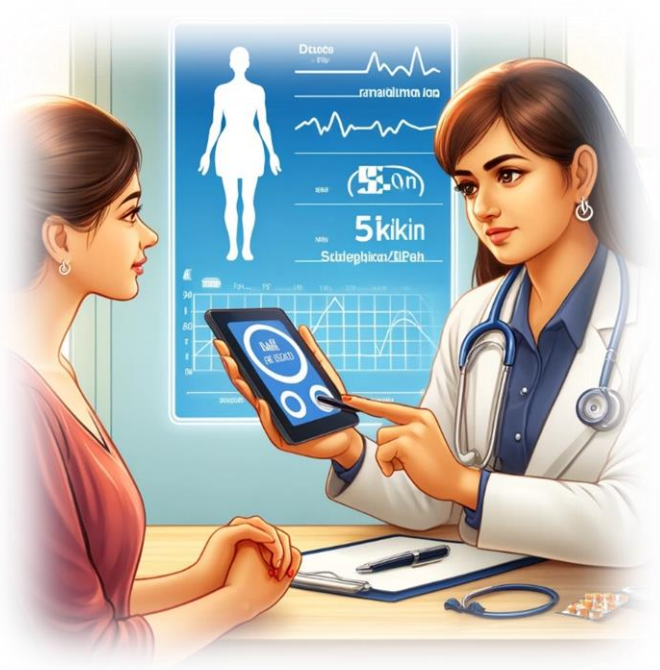


To Understand the Therapeutic Usage of Dapagliflozin + Sitagliptin + Metformin Combination In Indian Patient Population During Real-Life Clinical Scenario

CONTENTS

Background and Objective of the Survey

Background

India is grappling with a severe epidemic of type 2 diabetes, which poses a significant challenge in managing this chronic condition effectively. The increasing prevalence not only emphasizes the need for effective therapeutic strategies but also the necessity for innovative treatment combinations that can address various aspects of the disease. Metformin, long established as the cornerstone of type 2 diabetes management, is favored for its ability to lower blood glucose levels and its beneficial effects on weight and cardiovascular risk. However, many patients eventually require additional pharmacotherapy to maintain glycemic control due to the progressive nature of diabetes.

In this context, combining Dapagliflozin and Sitagliptin with Metformin offers a comprehensive approach. Dapagliflozin, an SGLT2 inhibitor, prevents glucose reabsorption in the kidneys, promoting glycosuria, which lowers blood glucose levels and provides cardiovascular and renal benefits essential given the high risk of heart and kidney diseases associated with diabetes. Sitagliptin, a DPP-4 inhibitor, increases incretin levels which inhibit glucagon release, thereby increasing insulin secretion, decreasing gastric emptying, and reducing blood glucose levels.

The combination of Dapagliflozin, Sitagliptin, and Metformin in a single treatment regimen is designed to provide a comprehensive approach to the management of type 2 diabetes. Each of these medications targets different mechanisms involved in glucose control, offering a synergistic effect to improve glycemic control.

Metformin: It decreases hepatic glucose production and intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Sitagliptin: As a DPP-4 inhibitor, it works by increasing the levels of incretin hormones, which increase insulin synthesis and release from pancreatic beta cells and decrease glucagon levels in the circulation.

Dapagliflozin: An SGLT2 inhibitor, it works by preventing glucose reabsorption in the kidney, leading to the excretion of glucose through urine.

Clinical Benefits:

Enhanced Glycemic Control: The combined action on different physiological pathways helps in more effective control of blood sugar levels than any single therapy alone.

Reduced Glucose Toxicity: By lowering blood glucose levels, this combination helps in reducing the glucotoxic effects that exacerbate insulin resistance and beta-cell dysfunction.

Cardiovascular Benefits: Dapagliflozin has shown potential benefits in reducing hospitalization for heart failure and cardiovascular death, which are critical considerations for diabetic patients who are at increased risk of cardiovascular diseases.

Practical Considerations:

Convenience: Combining these three drugs can reduce the pill burden compared to taking each medication separately, potentially improving adherence to treatment.

Side Effects: Each component has its side effects; when combined, they need to be monitored closely by healthcare providers. For instance, dapagliflozin may increase the risk of urinary tract infections, while sitagliptin has been associated with a risk of pancreatic inflammation, and metformin often causes gastrointestinal upset.

Patient Selection: This combination might not be suitable for all patients, such as those with severe renal impairment, and it's essential to tailor diabetes treatment based on individual patient needs and health conditions.

The use of a combination therapy involving Dapagliflozin, Sitagliptin, and Metformin offers a powerful tool in the management of type 2 diabetes, particularly for patients who may not have achieved optimal glycemic control with monotherapy or dual therapy.

Objective

The primary objective of this study is to investigate the real-world effectiveness and safety of the triple combination therapy of Dapagliflozin, Sitagliptin, and Metformin in the Indian diabetic population. This includes an evaluation of:

- **Efficacy:** How effectively does this combination control glycemic levels and what impact does it have on long-term blood sugar control metrics like HbA1c levels

- **Safety and Tolerability:** The common side effects and safety concerns associated with the triple therapy and how tolerable it is for the average patient

- **Cardiovascular and Renal Outcomes:** Considering the individual benefits of Dapagliflozin and Metformin on heart and kidney health, does this combination further enhance protective effects against diabetes-related complications

- **Patient Adherence and Satisfaction:** Whether the combination therapy is conducive to high adherence rates and the factors that influence patient satisfaction and continued use of this therapy

By addressing these points, the study aims to provide a comprehensive analysis of the triple combination therapy's role in effectively managing type 2 diabetes in an Indian setting, potentially guiding treatment practices and policy-making in healthcare.

Methodology of the Survey

A survey was conducted to understand the current Opinion **on "To understand the therapeutic usage of Dapagliflozin + Sitagliptin + Metformin combination in Indian patient population during real-life clinical scenario**" and to understand the market better and offer better services to improve the patient outcome. 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 literature search:

- **Combination Therapy for Type 2 Diabetes: Dapagliflozin Plus Metformin**

- **Fixed-Dose Combination of Dapagliflozin + Sitagliptin + Metformin in Patients with Type 2 Diabetes Poorly Controlled with Metformin: Phase 3, Randomized Comparison with Dual Combinations**

Step 2:
A survey questionnaire was prepared based on the literature search. The survey form was shared through digital medium with 150 doctors across India.

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

Literature Review

Combination Therapy for Type 2 Diabetes: Dapagliflozin Plus Metformin

Type 2 diabetes (T2D) is recognized as a complex, progressive disorder characterized by chronic high blood sugar levels and involves multiple biological pathways. These include reduced insulin production by the pancreas, increased resistance to insulin in the body, disrupted fat metabolism, enhanced glucose production by the liver, deficits in gastrointestinal hormones, and alterations in kidney glucose processing and hormone regulation by alpha cells[1][2]. Lifestyle factors such as obesity, poor diet, alcohol consumption, and smoking significantly contribute to the increase in T2D incidence[3]. Importantly, each 1% rise in HbA1c, a measure of long-term glucose control, is associated with a 30% higher risk of general mortality and a 40% increase in cardiovascular-related death[4]. Therefore, maintaining blood sugar levels is crucial, particularly for diabetic individuals at risk of heart disease[5][6].

Metformin is the preferred initial treatment for T2D, especially beneficial for those who are overweight, due to its ability to decrease hepatic glucose production and enhance insulin sensitivity[7][8][9][10]. The integration of metformin with other antidiabetic drugs like dapagliflozin, an SGLT2 inhibitor, which promotes glucose excretion in urine, offers enhanced glycemic control. This combination has been shown to significantly reduce HbA1c and fasting plasma glucose levels more effectively than either drug alone, underscoring the synergy of their mechanisms[11][12-15].

Combination therapies also reduce the dosage requirements for each drug, minimizing potential side effects and enhancing patient adherence to treatment[16]. Fixed-dose formulations can further simplify medication regimens, decrease pill burden, and potentially reduce healthcare costs, as demonstrated in a systematic review which found fixed-dose combinations to be more cost-effective than multiple-pill regimens[17]. This review highlights the importance of evaluating the combined use of dapagliflozin and metformin for their potential to significantly improve treatment outcomes in T2D management.

Body of review

- **Overview of the market**

In the management of new-onset type 2 diabetes, the integration of metformin with lifestyle modifications is highly advocated by major diabetes associations[8]. Following the initiation of such foundational therapy, the evaluation of additional antidiabetic medications becomes crucial to tailor treatments based on their impacts on blood glucose levels, body weight, and overall safety profiles. The options include a variety of agents

like insulin, sulfonylureas, thiazolidinediones, SGLT2 inhibitors, DPP-4 inhibitors, and GLP-1 receptor agonists.

The reality, however, is that achieving optimal glycemic control often remains elusive with monotherapy alone for most patients[2]. This necessitates the adoption of combination therapies that employ drugs with different mechanisms of action, a strategy essential for effective diabetes management[18]. Among the various agents, dapagliflozin stands out. It not only enhances glycemic control but also promotes weight loss and reduces blood pressure, offering added benefits for patients with concurrent obesity or cardiovascular concerns[11].

Metformin continues to be revered as a cornerstone in T2D treatment due to its efficacy in lowering blood glucose without significantly increasing hypoglycemia risk, alongside a modest reduction in weight. When used in conjunction with dapagliflozin, this combination is particularly potent, presenting a viable option for enhancing therapeutic outcomes and patient compliance. This synergistic approach not only targets multiple pathophysiological pathways but also mitigates the risk and intensity of diabetes-related complications.

Introduction to the compound

➢ SGLT2 inhibitors

SGLT2 inhibitors are a class of drugs that target glucose transport proteins in the kidneys and gastrointestinal tract to manage glucose levels in patients with type 2 diabetes (T2D). These proteins, particularly sodium-glucose co-transporter 2 (SGLT2), play a crucial role in reabsorbing glucose from the glomerular filtrate back into the bloodstream. In T2D, the functionality of these transporters is often enhanced, leading to abnormal glucose reabsorption and elevated blood sugar levels[15][19][20][21].

By inhibiting SGLT2, these drugs reduce glucose reabsorption in the kidney, thereby promoting glucose excretion through urine and lowering plasma glucose levels. The effectiveness of SGLT2 inhibitors is closely linked to kidney function and plasma glucose concentrations, as their glucose-lowering action is proportional to the amount of glucose filtered by the kidneys[22].

These inhibitors also offer additional health benefits, such as weight loss through caloric loss via glucose excretion and reductions in blood pressure due to osmotic diuresis and natriuresis. Unlike many other diabetes medications, the mechanism of SGLT2 inhibitors does not depend on insulin secretion, which minimizes the risk of hypoglycemia[11][23].

Current SGLT2 inhibitors available or in development include dapagliflozin, canagliflozin, ipragliflozin, empagliflozin, and ertugliflozin. Dapagliflozin, in particular, has been approved in several regions, including the United States and European countries, due to its efficacy and safety profile.

➢ Dapagliflozin

The standard initial dose of dapagliflozin is recommended at 5 mg once daily, which can be adjusted up to 10 mg based on patient needs and response[26]. When used as a sole treatment, dapagliflozin has been shown to decrease HbA1c levels by 0.6–0.9% over periods ranging from 24 to 52 weeks[11][13-15]. When combined with metformin, this regimen not only further reduces HbA1c but also allows for lower doses of both medications, enhancing tolerance and minimizing side effects. Clinical trials have documented reductions in fasting plasma glucose (FPG) by 0.8–1.5 mmol/L and postprandial glucose by 2.4–2.9 mmol/L[12][27]. Additionally, dapagliflozin often results in weight loss and can lower blood pressure, particularly systolic pressure[11][15][27][28].

It is particularly effective in older T2D patients with cardiovascular conditions, showing significant improvements in HbA1c, body weight, and systolic blood pressure compared to placebo[29]. However, it is crucial to monitor kidney function before and during treatment with dapagliflozin, especially since it should be discontinued if the estimated glomerular filtration rate (eGFR) falls persistently below 60 mL/min/1.73 m^2[26].

Common side effects include genital and urinary tract infections, which are more frequently observed with dapagliflozin than with some other diabetic treatments like glipizide[13]. These side effects are attributable to the drug's mechanism of increasing glucose excretion in urine. The drug also shows a low risk of hypoglycemia when used alone or in combination with other antidiabetic agents[12][27]. Furthermore, dapagliflozin can influence lipid profiles, with some trials noting variable effects on cholesterol and triglyceride levels [30].

➢ Biguanide

Biguanides, specifically recognized for their role in the treatment of Type 2 diabetes (T2D), began to see clinical use in the late 1950s. They effectively enhance peripheral glucose uptake, inhibit gluconeogenesis, and increase glycolysis without stimulating insulin secretion[31]. Unlike sulfonylureas that can increase insulin output, biguanides do not affect insulin levels directly. Their usage ranges from monotherapy to combination therapies with other antidiabetic drugs. However, some biguanide derivatives like phenformin and buformin were removed from the market due to severe side effects such as lactic acidosis. Currently, metformin stands out as the most widely used biguanide due to its safety profile

Metformin is the cornerstone of T2D management, particularly effective in obese patients, as it reduces hepatic glucose production by activating AMP-activated protein kinase and enhances insulin sensitivity[7][8][10]. It also promotes weight loss, which is

Table 1. Pharmacokinetic features of dapagliflozin and metformin.

Dose	Dapagliflozin 10 mg/d	Metformin 500, 850 mg
Absorption	~78% absorbed C_{max} 158 ng/ml AUC 628 ng h/ml T_{max} < 2 h	50 ~ 60% absorbed C_{max} < 5 ug/ml Steady state plasma concentration <1 ug/ml T_{max} 2.5 h
Distribution	Protein bound 91% Vd 118L	Protein bound negligible Vd 63-276 l
Metabolism	Extensively metabolished Metabolic enzyme UGT1A9	Unchanged in the urine No metabolites
Elimination	$T_{1/2}$ 12.9 h ~15% urine unchanged	Renal clearance >400 ml/min $T_{1/2}$ 6.5 h

advantageous compared to insulin and sulfonylureas that may cause weight gain and increased hypoglycemia risk[32].

As T2D progresses, the efficacy of metformin alone may diminish, necessitating the addition of other drugs like sulfonylureas or insulin to achieve glucose control[1]. These combinations, however, can lead to adverse effects like weight gain and insulin resistance. Therefore, combining metformin with non-insulin-dependent mechanisms like SGLT2 inhibitors (such as dapagliflozin) can enhance therapeutic outcomes while mitigating these risks[12][13].

Xigduo XR is one such combination product that includes dapagliflozin and metformin in a fixed-dose formulation, leveraging their complementary actions to maintain glucose homeostasis in T2D patients. Dapagliflozin works by blocking glucose reabsorption in the kidneys, enhancing urinary glucose excretion independent of insulin[33]. Metformin supports this by inhibiting hepatic glucose production and improving glucose uptake in peripheral tissues[34][35]. This combination not only improves glycemic control but also supports better patient compliance and treatment outcomes[12][14][15].

Clinical efficacy

Clinical efficacy studies have robustly supported the use of the combination of dapagliflozin and metformin in managing Type 2 diabetes (T2D), demonstrating significant improvements in both glycemic control and body weight management[39][40][43][13].

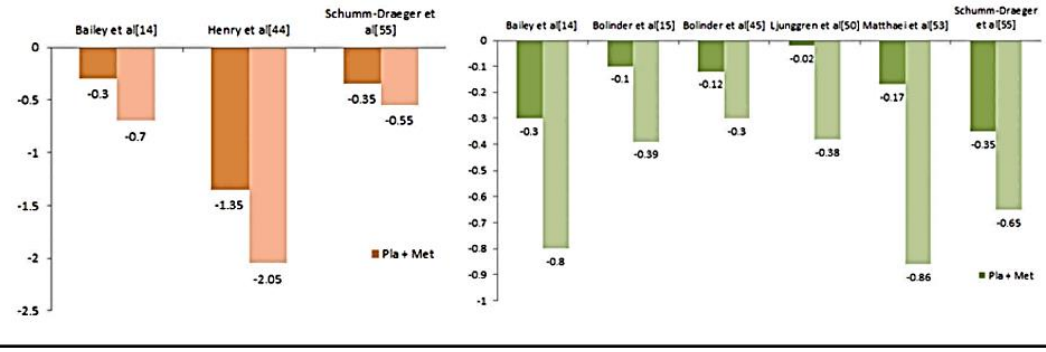


Figure 1. Reduction in HbA_{1c} with combination treatment (Dapagliflozin 5 and 10 mg).

➢ Glycemic Control

In various clinical trials, the combination of dapagliflozin and metformin has consistently shown to be more effective than either drug alone in reducing HbA1c and fasting plasma glucose (FPG). The superior efficacy of this combination therapy was evident, with a higher proportion of patients achieving an HbA1c of less than 7% compared to monotherapy groups. For instance, in a 24-week study, the addition of dapagliflozin to patients already on metformin resulted in a greater reduction in HbA1c compared to placebo groups[40]. Further trials reinforced these findings, highlighting the sustained and significant decreases in both HbA1c and FPG levels, which surpassed results seen with metformin alone[12].

In another detailed 24-week phase 3 trial, different doses of dapagliflozin added to metformin showed a progressive and sustained reduction in HbA1c levels, surpassing those of the placebo group, which demonstrated the dose-dependent efficacy of dapagliflozin when used in combination with metformin[12].

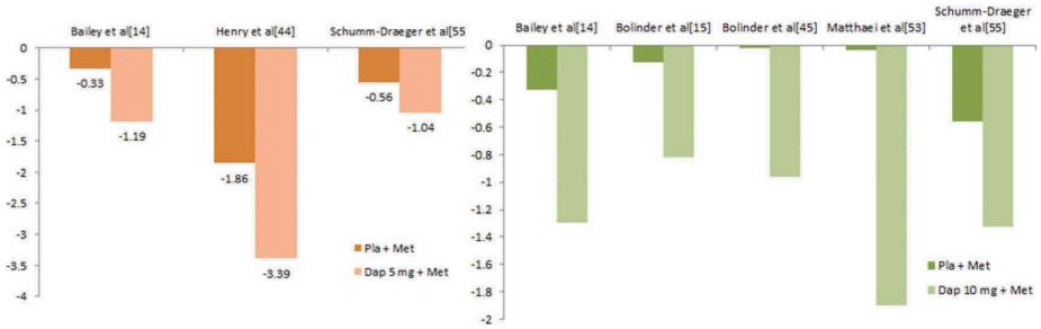


Figure 2. Reduction in FPG with combination treatment (Dapagliflozin 5 and 10 mg).

➢ Body Weight

The advantage of using dapagliflozin, particularly in combination with metformin, extends beyond glycemic control to also include weight management — a critical aspect of T2D management. Unlike other antidiabetic agents such as sulfonylureas and

thiazolidinediones, which may cause weight gain, dapagliflozin has been shown to induce weight loss. This is attributed to its mechanism of inducing glucosuria-induced osmotic diuresis and caloric loss[15][13][45]. Long-term studies over 52 and 104 weeks have confirmed significant weight reduction in patients treated with dapagliflozin compared to those treated with glipizide, where the latter group actually gained weight[13].

Moreover, a comprehensive study by Schumm-Draeger et al. found that dapagliflozin treatment resulted in considerable reductions in total body fat mass alongside overall weight loss[45]. This dual effect of glycemic control and weight management underscores the therapeutic potential of dapagliflozin, especially when used in conjunction with metformin.

- **Blood pressure**

Numerous studies have established that hypertension significantly increases cardiovascular risk among individuals with diabetes[47]. Utilizing antidiabetic medications that also lower blood pressure can therefore mitigate this risk. Although the exact mechanism by which dapagliflozin reduces blood pressure is not fully understood, it is hypothesized to be related to its effects on osmotic diuresis and sodium loss. Research conducted by Nauck et al.[13] observed that the combination of dapagliflozin and metformin notably decreased systolic blood pressure compared to the combination of glipizide and metformin, with reductions noted as -3.9 mmHg (95% CI: −6.1, −1.7). This antihypertensive benefit of dapagliflozin has been corroborated by various other clinical trials[12][43], indicating its potential utility in managing both blood glucose and blood pressure in diabetic patients.

- **Safety and tolerability**

The combination of dapagliflozin and metformin has been studied extensively for safety and tolerability, with results indicating that this combination does not introduce new safety concerns beyond those observed with either agent alone[36]. Common side effects reported include urinary or genital infections, diarrhea, headache, and nausea, with urinary and genital infections being the most frequently observed adverse reactions[38]. These infections are typically related to the mechanism of dapagliflozin, which promotes glucosuria.

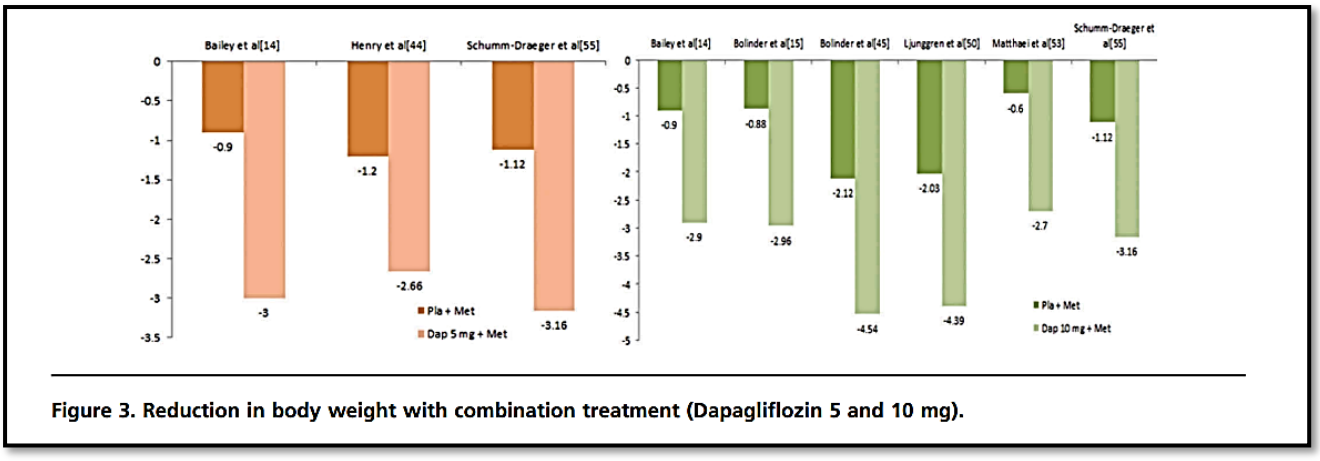


Figure 3. Reduction in body weight with combination treatment (Dapagliflozin 5 and 10 mg).

One of the notable benefits of dapagliflozin, particularly in comparison to traditional antidiabetic medications like sulfonylureas, is its low risk of inducing hypoglycemia. This is because its glucose-lowering action does not depend on insulin. In studies comparing dapagliflozin with glipizide, a significant reduction in hypoglycemia incidents was observed with dapagliflozin use (3.5% vs 40.8%, $P < 0.0001$)[13]. Additionally, despite the higher incidence of genital infections with dapagliflozin plus metformin compared to glipizide plus metformin, these side effects rarely led to discontinuation of the study[13].

Furthermore, the cardiovascular effects of SGLT-2 inhibitors like dapagliflozin are under thorough investigation due to their potential benefits. One of the significant ongoing trials is the DECLARE-TIMI58, which aims to enroll over 17,000 participants to explore the cardiovascular outcomes associated with dapagliflozin[48]. This trial is particularly focused on assessing whether dapagliflozin can provide cardiovascular advantages while addressing other safety-related concerns.

Conclusion

Given the combined effects on glucose lowering, the co-administration of dapagliflozin and metformin presents a compelling option for patients whose blood sugar levels are not adequately controlled by metformin alone. This therapeutic strategy benefits from the complementary actions of both drugs—dapagliflozin increases glucose excretion in the urine, while metformin reduces glucose production in the liver and enhances insulin sensitivity. Importantly, this combination therapy is associated with a low risk of causing hypoglycemia, enhancing its suitability for long-term management of type 2 diabetes.

References:

1.American Diabetes Association. Standards of medical care in diabetes-2015. Diabetes Care. 2015;38(Suppl. 1):S1–S49.

2. Defronzo RA. Banting lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58:773–795.

3. Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375:2215–2222.

4. Khaw K-T, Wareham N, Luben R, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). BMJ. 2001;322:15–18.

5. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med. 1993;329:304–309.

6. Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a metaanalysis of randomised controlled trials. Lancet. 2009;373:1765–1772.

7. Ismail-Beigi F. Glycemic management of type 2 diabetes mellitus. N Engl J Med. 2012;366:1319–1327.

8. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015;38:140–149.

9. Hundal RS, Krssak M, Dufour S, et al. Mechanism by which metformin reduces glucose production in type 2 diabetes. Diabetes. 2000;49:2063–2069.

10. Bailey CJ, Turner RC. Metformin. N Engl J Med. 1996;334:574–579.

11. Katsiki N, Papanas N, Mikhailidis DP. Dapagliflozin: more than just another oral glucose-lowering agent? Expert Opin Investig Drugs. 2010;19:1581–1589.

12. Bailey CJ, Gross JL, Pieters A, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet. 2010;375:2223–2233. Nauck MA, Del PS, Meier JJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care. ;34:2015–2022. • Clinical trial on combination therapy of dapagliflozin and metformin.

14. Bailey CJ, Gross JL, Hennicken D, et al. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC
Med. 2013;11:43. • Clinical trial on combination therapy of dapagliflozin and metformin.

15. Bolinder J, Ljunggren O, Kullberg J, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. J Clin Endocrinol Metab. 2012;97:1020–1031. • Clinical trial on combination therapy of dapagliflozin and metformin.

16. Bailey CJ, Day C. Fixed-dose single tablet antidiabetic combinations. Diabetes Obes Metab. 2009;11:527–533.

17. Hutchins V, Zhang B, Fleurence RL, et al. A systematic review of adherence, treatment satisfaction and costs, in fixed-dose combination regimens in type 2 diabetes. Curr Med Res Opin. 2011;27:1157–1168.

18. Hanefeld M, Bornstein SR, Barthel A. Modern medical treatment of type 2 diabetes. Dtsch Med Wochenschr. 2014;139:2494–2497.

19. Vallon V, Platt KA, Cunard R, et al. SGLT2 mediates glucose reabsorption in the early proximal tubule. J Am Soc Nephrol. 2011;22:104–112.

20. Abdul-Ghani MA, DeFronzo RA. Inhibition of renal glucose reabsorption: a novel strategy for achieving glucose control in type 2 diabetes mellitus. Endocr Pract. 2008;14:782–790.

21. Wright EM. Renal Na(+)-glucose cotransporters. Am J Physiol Renal Physiol. 2001;280:10–18.

22. Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabet Med. 2010;27:136–142.

23. List JF, Whaley JM. Glucose dynamics and mechanistic implications of SGLT2 inhibitors in animals and humans. Kidney Int Suppl. 2011;120:S20–S27.

24. European Commission, Public Health. Community register of medicinal products for human use. Invokana [Internet]. 2013 [cited 2013 Dec 3]. Available from: http://ec.europa.eu/health/documents/com munity-register/html/h884. htm#EndOfPage

25. US Food and Drug Administration. FDA news release: FDA approves Farxiga to treat type 2 diabetes [Internet]. 2014 [cited 2014 Sept 2]. Available from: http:// www.fda.gov/NewsEvents/Newsroom/ PressAnnouncements/ucm380829.htm

26. Farxiga® (dapagliflozin). Full prescribing information. Princeton (NJ): Bristol- Myers Squibb; 2014.

27. Rosenstock J, Vico M, Wei L, et al. Effects of dapagliflozin, a sodium-glucose cotransporter- 2 inhibitor, on hemoglobin A1c, body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care. 2012;35:1473–1478.

28. Zhang L, Feng Y, List J, et al. Dapagliflozin treatment in patients with different stages of type 2 diabetes mellitus: effects on glycaemic control and body weight. Diabetes Obes Metab. 2010;12:510–516.

29. Leiter LA, Cefalu WT, de Bruin TW,et al. Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: a 24-week, multicenter, randomized, double- blind, placebo-controlled study with a 28-week extension. J Am Geriatr Soc. 2014;62:1252–1262.

30. Matthaei S, Bowering K, Rohwedder K, et al. Dapagliflozin improves glycemic control and reduces body weight as addon therapy to metformin plus sulfonylurea: A 24-week randomized, doubleblind clinical trial. Diabetes Care. 2015;38:365–372. • Clinical trial on combination therapy of dapagliflozin and metformin.

31. Schafer G. On the mechanism of action of hypoglycemia-producing biguanides. A reevaluation and a molecular theory. Biochem Pharmacol. 1976;25:2005–2014.

32. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352:854–865.

33. Plosker GL. Dapagliflozin: a review of its use in type 2 diabetes mellitus. Drugs. 2012;72:2289–2312.

34. Mannucci E, Ognibene A, Cremasco F, et al. Effect of metformin on glucagonlike peptide 1 (GLP-1) and leptin levels in obese nondiabetic subjects. Diabetes Care. 2001;24:489–494.

35. Giannarelli R, Aragona M, Coppelli A, et al. Reducing insulin resistance with metformin: the evidence today. Diabetes Metab. 2003;29:S28–S35.

36. Chang M, Liu X, Cui D, et al. Bioequivalence, food effect, and steadystate assessment of dapagliflozin/metformin extended-release fixed-dose combination tablets relative to single-component dapagliflozin and metformin extendedrelease tablets in healthy subjects. Clin Ther. 2015;37:1517–1528.

37. Kasichayanula S, Liu X, Shyu WC, et al. Lack of pharmacokinetic interaction between dapagliflozin, a novel sodiumglucose transporter 2 inhibitor, and metformin, pioglitazone, glimepiride or sitagliptin in healthy subjects. Diabetes Obes Metab. 2011;13:47–54.

38. AstraZeneca. Xigduo(dapagliflozin/metformin filmcoated tablets): US prescribing information [Internet]. 2015. Available from: http://www.accessdata.fda.gov/drug satfda_docs/label/2014/205649s000lbl.pdf

39. Henry RR, Murray AV, Marmolejo MH, et al. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. Int J Clin Pract. 2012;66:446–456. • Clinical trial on combination therapy of dapagliflozin and metformin.

40. Bolinder J, Ljunggren Ö, Johansson L, et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. Diabetes Obes Metab. 2014;16:159–169. • Clinical trial on combination therapy of dapagliflozin and metformin.

41. Ljunggren Ö, Bolinder J, Johansson L, et al. Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin. Diabetes Obes Metab. 2012;14:990–999.Clinical trial on combination therapy of dapagliflozin and metformin.

42. Jabbour SA, Hardy E, Sugg J, et al. Dapagliflozin is effective as add-on therapy

to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes Care. 2014;37:740–750. • Clinical trial on combination therapy of dapagliflozin and metformin.

43. Rosenstock J, Hansen L, Zee P, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. Diabetes Care. 2015;38:376–383. • Clinical trial on combination therapy of dapagliflozin and metformin.

44. Del Prato S, Nauck M, Durán-Garcia S, et al. Long-term glycaemic response and tolerability of dapagliflozin versus a sulphonylurea as add-on therapy to metformin in patients with type 2 diabetes: 4-year data. Diabetes Obes Metab. 2015;17:581–590. • Clinical trial on combination therapy of dapagliflozin and metformin.

45. Schumm-Draeger PM, Burgess L, Korányi L, et al. Twice-daily dapagliflozin coadministered with metformin in type 2 diabetes: a 16-week randomized, placebocontrolled clinical trial. Diabetes Obes Metab. 2015;17:42–51. • Clinical trial on combination therapy of dapagliflozin and metformin.

46. Derosa G, Maffioli P. Effects of thiazolidinediones and sulfonylureas in patients with diabetes. Diabetes Technol Ther. 2010;12:491–501.

47. Lorber D. Importance of cardiovascular disease risk management in patients with type 2 diabetes mellitus. Diabetes Metab Syndr Obes. 2014;7:169–183.

48. AstraZeneca. Multicenter trial to evaluate the effect of dapagliflozin on the incidence of cardiovascular events (clinicaltrials.gov identifier: NCT01730534) [Internet]. 2012 [cited 2015 Sep 14]. Available from: https://clinicaltrials.gov/ct2/show/ NCT01730534?term= NCT01730534&rank=1.

49. Chaplin S, McCourt C, Joseph F. Xigduo: dapagliflozin plus metformin for T2DM. Prescriber. 2014;25:36–38.

50. Lambers Heerspink HJ, de Zeeuw D, Wie L, et al. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. Diabetes Obes Metab. 2013;15:853–862.

51. Ho PM, Rumsfeld JS, Masoudi FA, et al. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. Arch Intern Med. 2006;166:1836–1841.

52. Zinman B. Initial combination therapy for type 2 diabetes mellitus: is it ready for prime time? Am J Med. 2011;124: S19–S34.

53. Fu AZ, Qiu Y, Davies MJ, et al. Treatment intensification in patients with type 2 diabetes who failed metformin monotherapy. Diabetes Obes Metab. 2011;13:765–769.

54. Engel SS, Seck TL, Golm GT, et al. Assessment of AACE/ACE recommendations for initial dual antihyperglycemic therapy using the fixed-dose combination of sitagliptin and metformin versus metformin. Endocr Pract. 2013;19:751–757.

55. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. Diabetes Care. 2012;35:2650–2664.

56. American Diabetes Association. Diabetes statistics [Internet]. [cited 2014 Apr 10]. Available from: http://www.diabetes.org/ diabetes-basics/statistics/?loc=superfooter.

57. Freeman JS, Gross B. Potential drug interactions associated with treatments for type 2 diabetes and its comorbidities: a clinical pharmacology review. Expert Rev Clin Pharmacol. 2012;5:31–42.

Fixed-Dose Combination of Dapagliflozin + Sitagliptin + Metformin in Patients with Type 2 Diabetes Poorly Controlled with Metformin: Phase 3, Randomized Comparison with Dual Combinations

Introduction

This study assesses the efficacy and safety of a fixed-dose combination (FDC) therapy comprising dapagliflozin, sitagliptin, and metformin extended-release (ER), comparing it against dual therapy combinations of sitagliptin plus metformin sustained-release (SR) and dapagliflozin plus metformin ER in type 2 diabetes patients inadequately controlled with metformin alone.

Methods

Employing a phase 3, randomized, open-label, active-controlled design, this study included adult patients with type 2 diabetes characterized by a glycated hemoglobin (HbA1c) between 8% (64 mmol/mol) and 11% (97 mmol/mol). Participants were assigned in a 1:1:1 ratio to three treatment groups: FDC of dapagliflozin, sitagliptin, and metformin ER; co-administration of sitagliptin and metformin SR; and FDC of dapagliflozin and metformin ER. The primary endpoint was the mean change in HbA1c from baseline to week 16.

Results

Each treatment group started with a similar average HbA1c around 9% (75 mmol/mol). By week 16, the triple drug combination showed a significantly greater reduction in HbA1c compared to both dual therapy groups. Additional benefits included significant improvements in both postprandial and fasting blood glucose levels when compared to one or both dual therapy groups. The proportion of patients achieving an HbA1c of less than 7.0% was also notably higher in the triple therapy group. All treatments were well-tolerated among participants.

Conclusion

The triple combination of dapagliflozin, sitagliptin, and metformin ER was more effective in improving glycemic control compared to the two dual therapy combinations in patients with type 2 diabetes poorly controlled with metformin alone. The study supports the use of this triple FDC for achieving better clinical outcomes in diabetes management without significant safety concerns.

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) In your clinical practise, what is the usual range of HbA1c in majority of T2DM patients?

A. 7-9%

B. 9-11%

C. >11%

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

A. Dapagliflozin

B. Empagliflozin

C. Canagliflozin

D. Remogliflozin

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

A. Sitagliptin

B. Linagliptin

C. Vildagliptin

D. Saxagliptin

E. Teneligliptin

5) In your practise how often do you initiate therapy for T2DM with a combination?

A. <25%

B. 26-50%

C. 51-75%

D. >75%

6) In your clinical practise, what percentage of your T2DM patients are controlled on a dual combination therapy?

A. <25%

B. 26-50%

C. 51-75%

D. >75%

7) Do you concomitantly use Dapagliflozin + Sitagliptin + Metformin?

A. Yes

B. No

8) What percentage of T2DM patients require triple drug therapy with Dapagliflozin + Sitagliptin + Metformin in your clinical practice?

A. <10%

B. 10-20%

C. 20-50%

D. >50%

9) In which patient population the combination Dapagliflozin + Sitagliptin + Metformin be preferred?

A. Obese patients with Type 2 Diabetes

B. Patients with Uncontrolled diabetes

C. Patients with T2DM and elevated risk of cardiovascular disease

10) What is the clinical advantage with the usage of the combination of Dapagliflozin + Sitagliptin + Metformin?

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.

11) As per your opinion, what is the average duration for of Dapagliflozin + Sitagliptin + Metformin Therapy in T2DM patient?

A. <6 months

B. 6 months to 1 year

C. >1 year to 5 years

D. Life-long

12) In your opinion, how is the long-term safety profile of Dapagliflozin + Sitagliptin + Metformin?

A. Excellent

B. Very Good

C. Good

D. Poor

13) In which age group is the combination of Dapagliflozin + Sitagliptin + Metformin preferred?

A. 20-40 years old

B. 40-60 years old

C. >60 years old

SURVEY FINDINGS

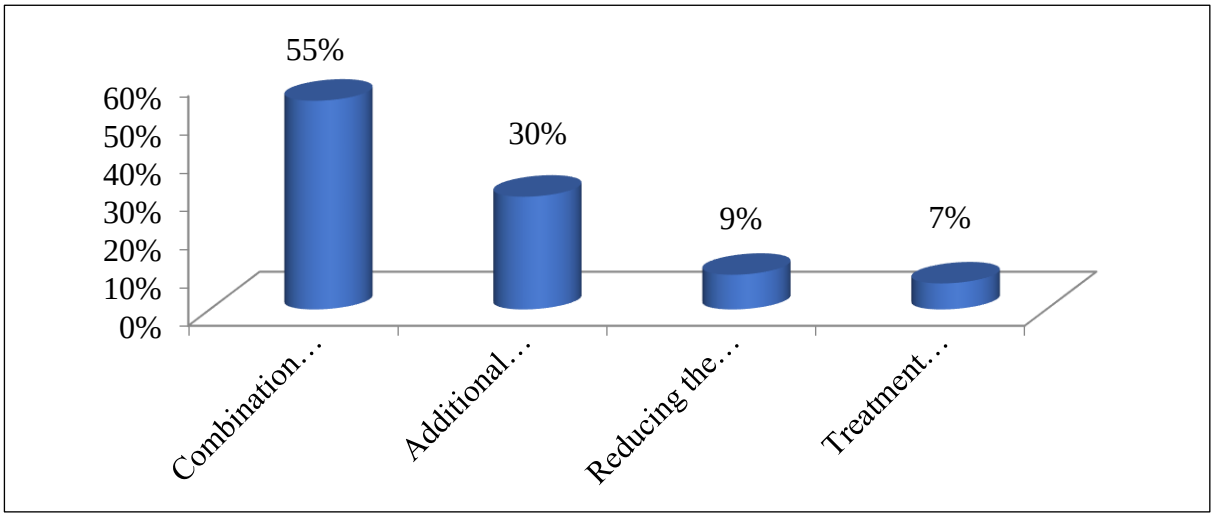
1) As per your opinion, which is the unmet medical need in patients with type 2 diabetes mellitus (T2DM)?

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



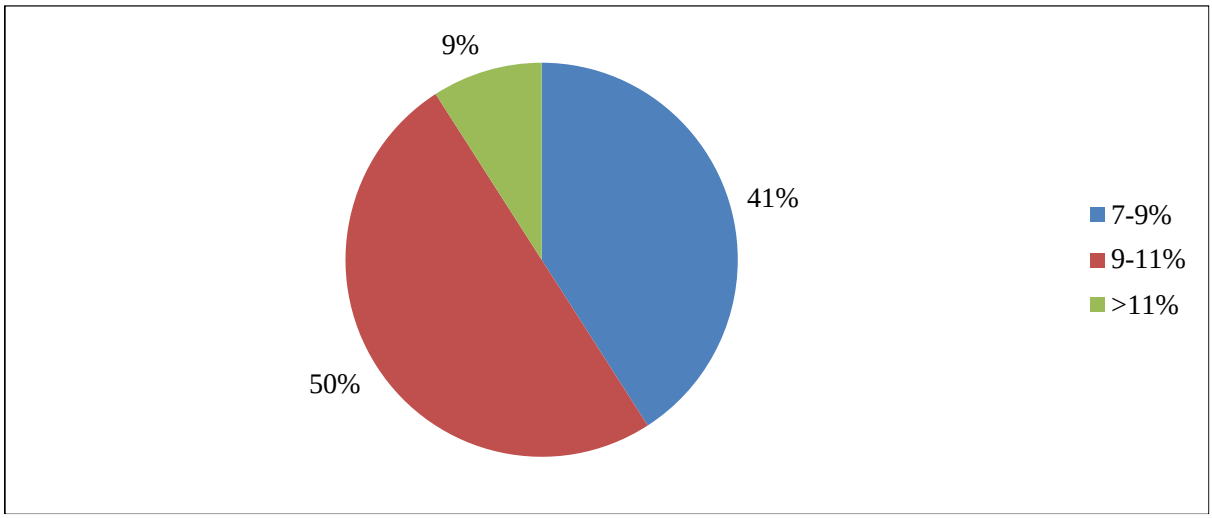
55% of respondents indicated that the most significant unmet medical need in patients with T2DM is combination therapy targeting multiple pathophysiological mechanisms of hyperglycemia to achieve glycemic control.

2) In your clinical practise, what is the usual range of HbA1c in majority of T2DM patients?

A. 7-9%

B. 9-11%

C. >11%



50% of respondents reported observing a typical range of HbA1c between 9-11% in the majority of T2DM patients.

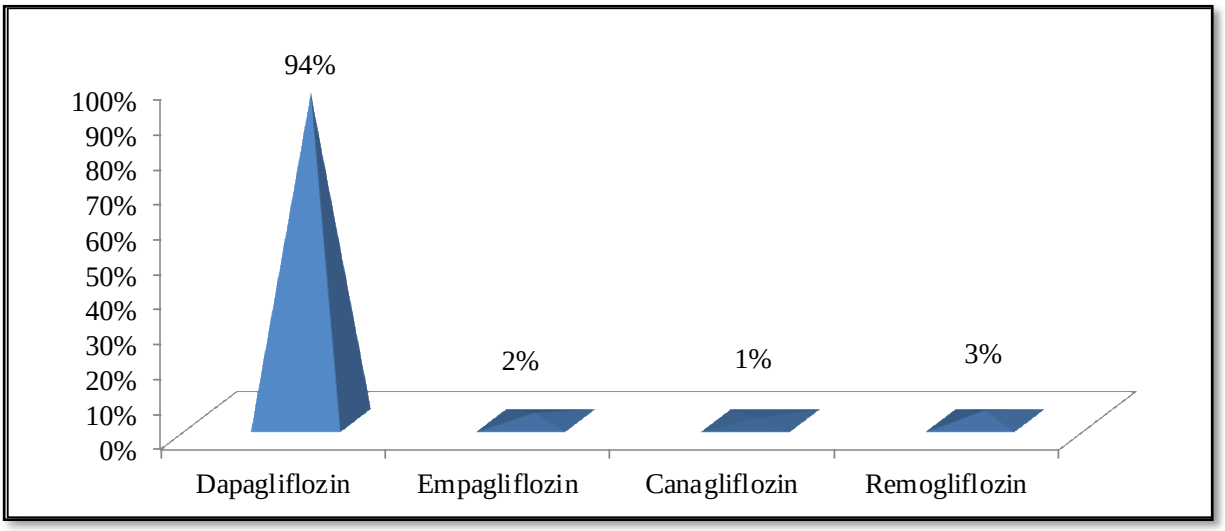
3) Which is the preferred Sodium glucose co-transporter-2 (SGLT-2) inhibitor in your practice?

A. Dapagliflozin

B. Empagliflozin

C. Canagliflozin

D. Remogliflozin



In the practice, the preferred Sodium glucose co-transporter-2 (SGLT-2) inhibitor is dapagliflozin, as reported by 94% of doctors.

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

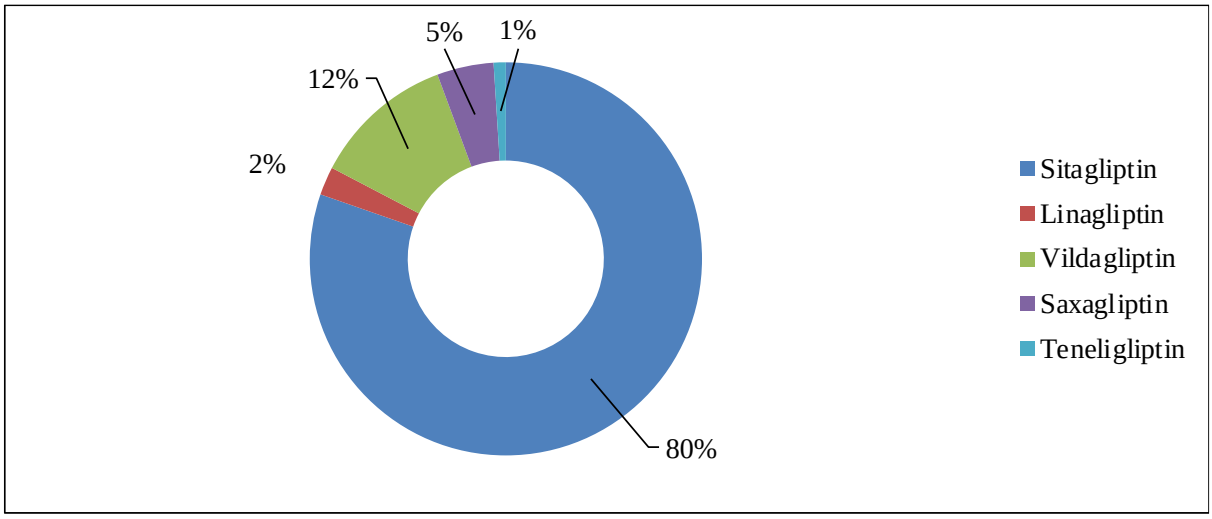
A. Sitagliptin

B. Linagliptin

C. Vildagliptin

D. Saxagliptin

E. Teneligliptin



In current clinical practice, the preferred Dipeptidyl peptidase 4 (DPP-4) inhibitor is sitagliptin, chosen by 80% of practitioners.

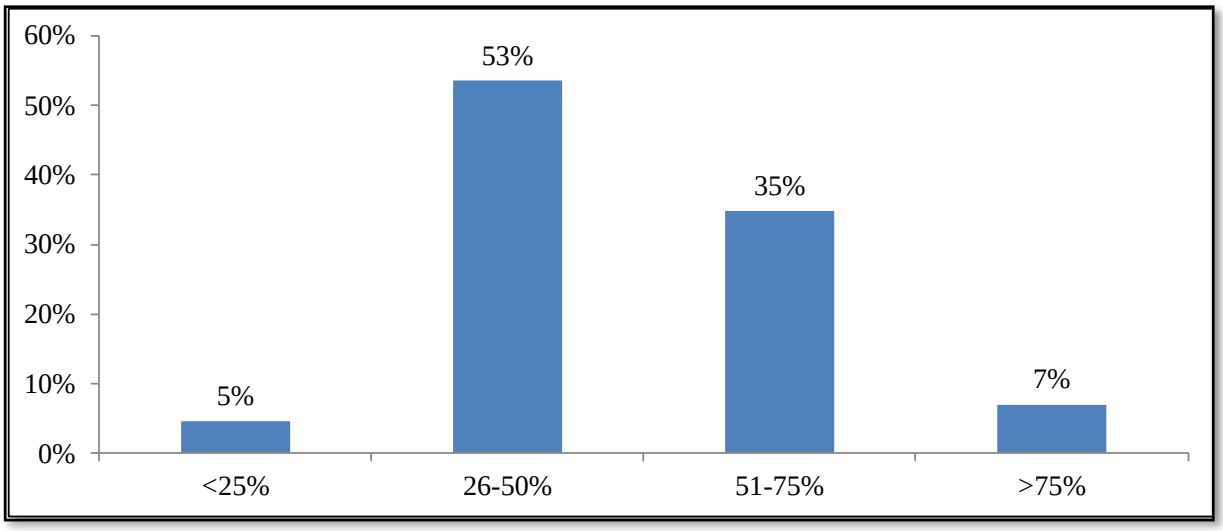
5) In your practise how often do you initiate therapy for T2DM with a combination?

A. <25%

B. 26-50%

C. 51-75%

D. >75%



In practice, therapy initiation for type 2 diabetes mellitus (T2DM) with a combination approach is initiated in 26-50% of cases.

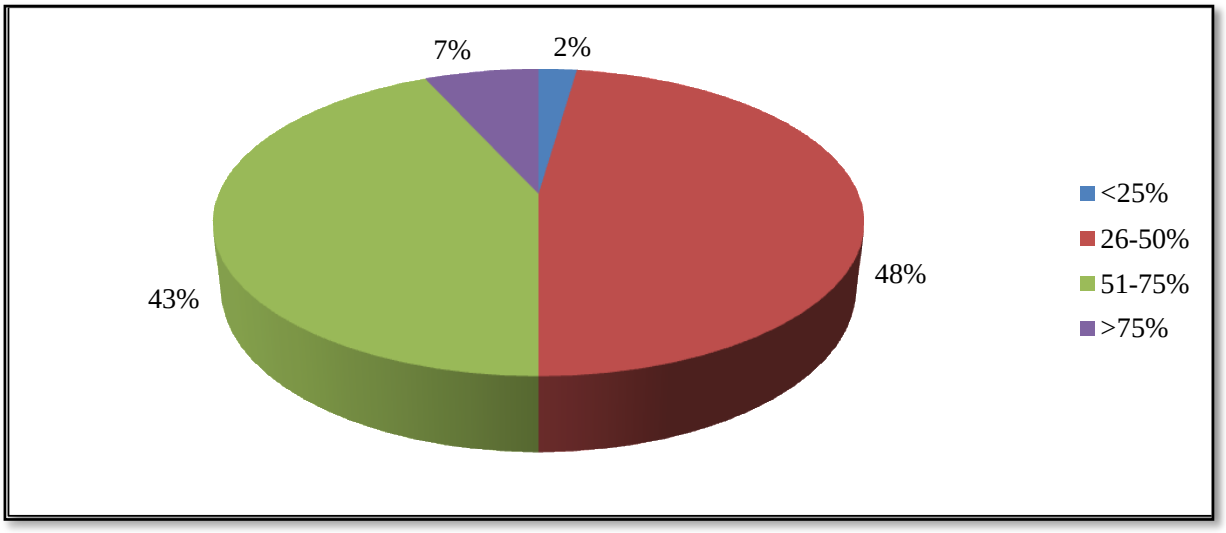
6) In your clinical practise, what percentage of your T2DM patients are controlled on a dual combination therapy?

A. <25%

B. 26-50%

C. 51-75%

D. >75%

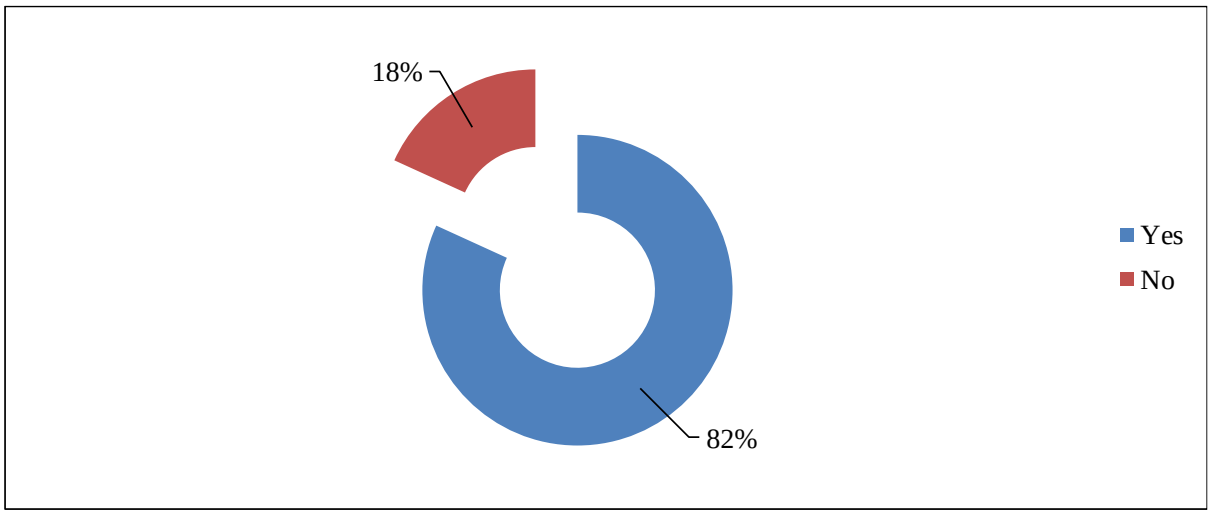


In our clinical practice, approximately 26-50% of our T2DM patients achieve control on a dual combination therapy.

7) Do you concomitantly use Dapagliflozin + Sitagliptin + Metformin?

A. Yes

B. No



Concomitant use of Dapagliflozin + Sitagliptin + Metformin is employed by 82% of practitioners.

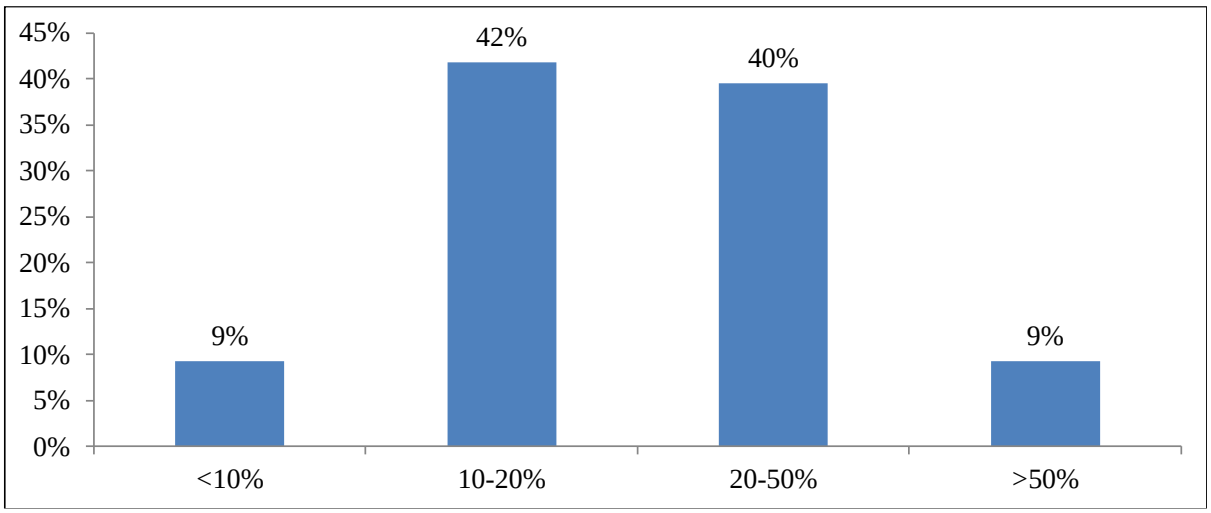
8) What percentage of T2DM patients require triple drug therapy with Dapagliflozin + Sitagliptin + Metformin in your clinical practise?

A. <10%

B. 10-20%

C. 20-50%

D. >50%



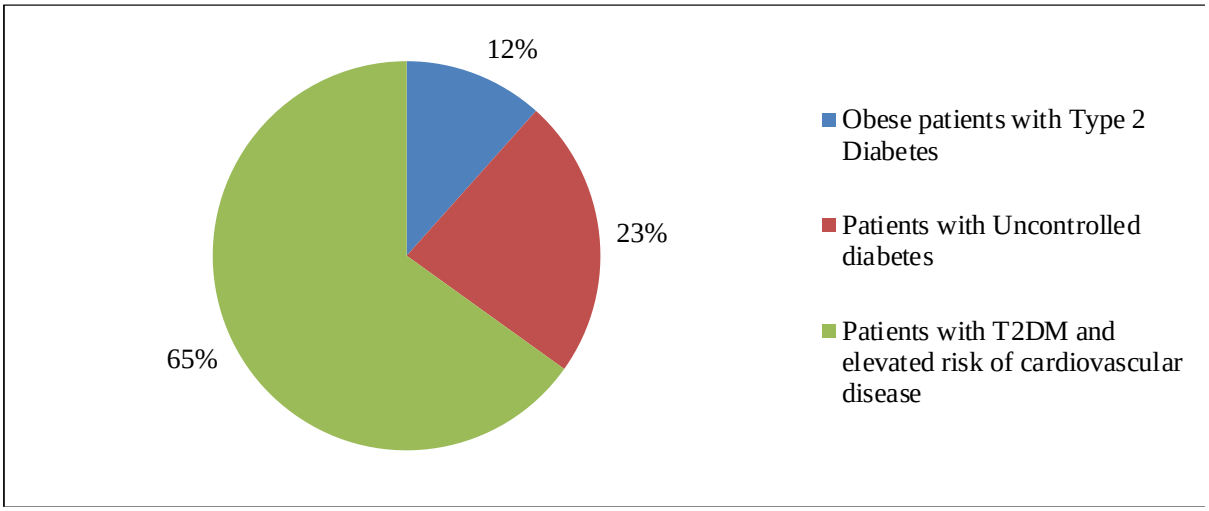
In the clinical practice, approximately 10-20% of T2DM patients require triple drug therapy with Dapagliflozin + Sitagliptin + Metformin.

9) In which patient population the combination Dapagliflozin + Sitagliptin + Metformin be preferred?

A. Obese patients with Type 2 Diabetes

B. Patients with Uncontrolled diabetes

C. Patients with T2DM and elevated risk of cardiovascular disease



The combination of Dapagliflozin + Sitagliptin + Metformin is preferred in patients with type 2 diabetes mellitus (T2DM) and an elevated risk of cardiovascular disease, as indicated by 65% of respondents.

10) What is the clinical advantage with the usage of the combination of Dapagliflozin + Sitagliptin + Metformin?

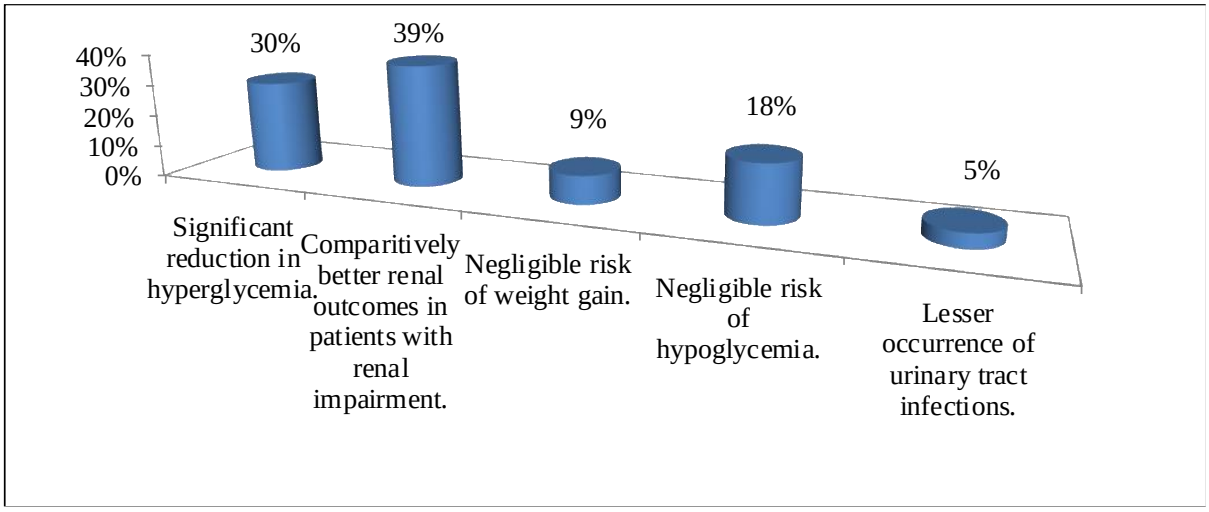
A. Significant reduction in hyperglycemia.

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.



The clinical advantage of using the combination of Dapagliflozin + Sitagliptin + Metformin is the comparatively better renal outcomes in patients with renal impairment, as chosen by 39% of respondents.

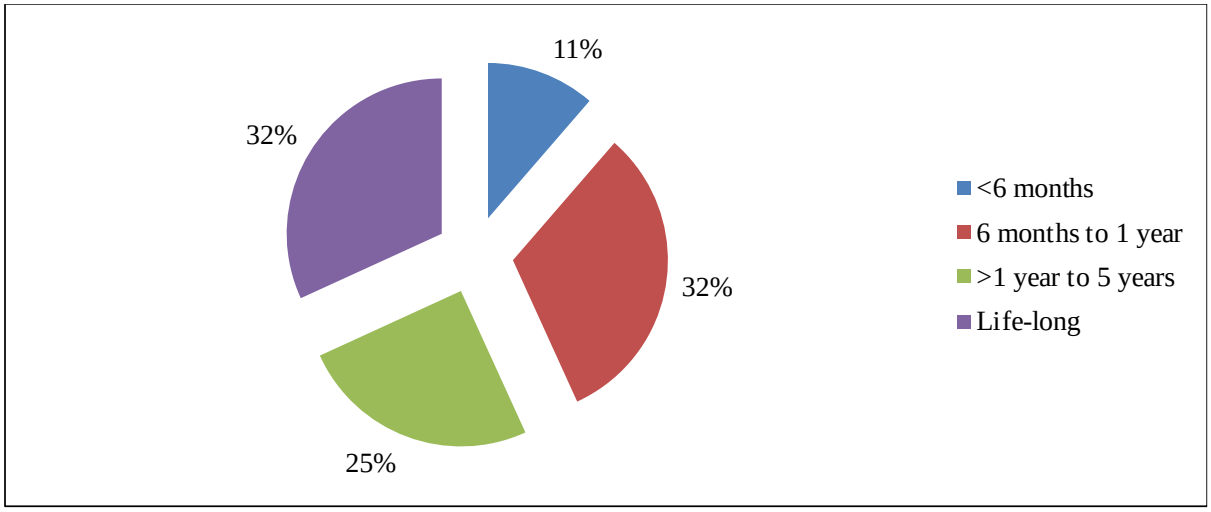
11) As per your opinion, what is the average duration for of Dapagliflozin + Sitagliptin + Metformin Therapy in T2DM patient?

A. <6 months

B. 6 months to 1 year

C. >1 year to 5 years

D. Life-long



Life-long therapy and therapy lasting from 6 months to 1 year were both selected by 32% of respondents for average duration for of Dapagliflozin + Sitagliptin + Metformin Therapy in T2DM patient

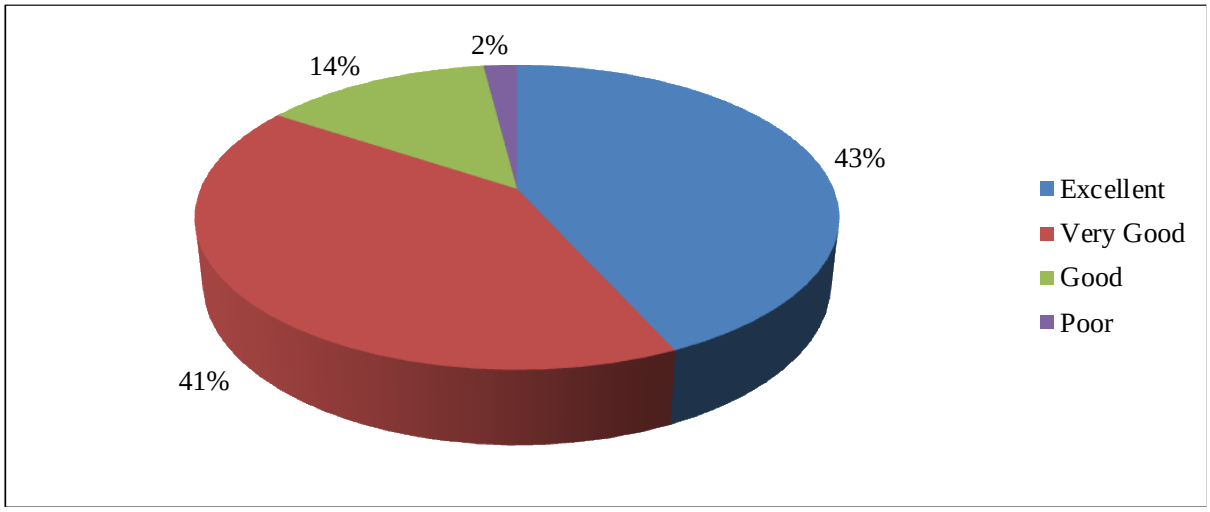
12) In your opinion, how is the long-term safety profile of Dapagliflozin + Sitagliptin + Metformin?

A. Excellent

B. Very Good

C. Good

D. Poor



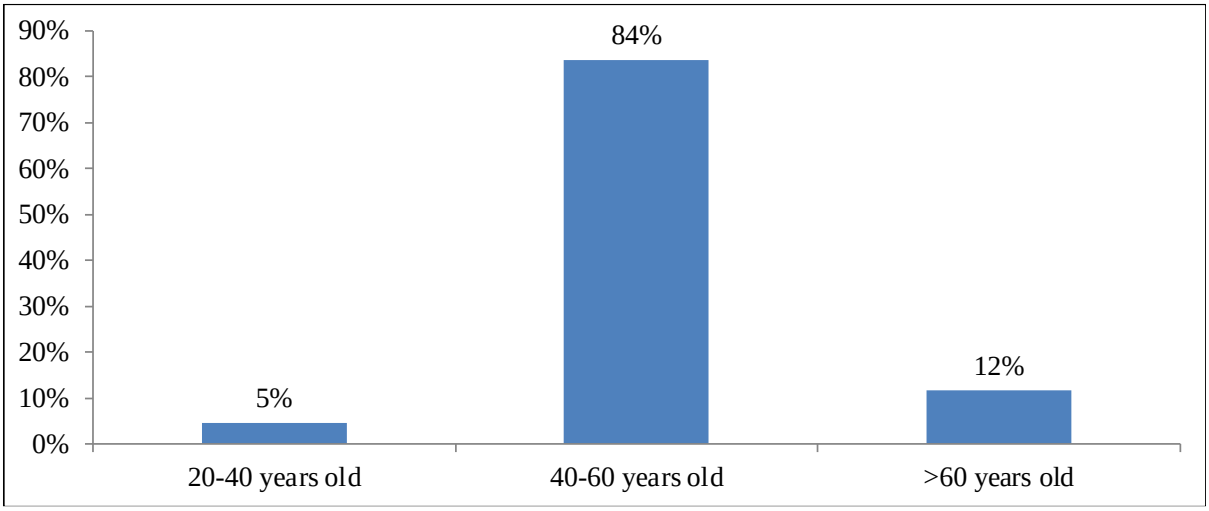
In my opinion, the long-term safety profile of Dapagliflozin + Sitagliptin + Metformin is excellent, as indicated by 43% of respondents.

13) In which age group is the combination of Dapagliflozin + Sitagliptin + Metformin preferred?

A. 20-40 years old

B. 40-60 years old

C. >60 years old



The combination of Dapagliflozin + Sitagliptin + Metformin is preferred in the age group of 40-60 years old, according to 84 % of respondents.

SUMMARY

1. 55% of respondents indicated that the most significant unmet medical need in patients with T2DM is combination therapy targeting multiple pathophysiological mechanisms of hyperglycaemia to achieve glycaemic control.

2. 50% of respondents reported observing a typical range of HbA1c between 9-11% in the majority of T2DM patients.

3. In the practice, the preferred Sodium glucose co-transporter-2 (SGLT-2) inhibitor is dapagliflozin, as reported by 94% of doctors.

4. In current clinical practice, the preferred Dipeptidyl peptidase 4 (DPP-4) inhibitor is sitagliptin, chosen by 80% of practitioners.

5. In practice, therapy initiation for type 2 diabetes mellitus (T2DM) with a combination approach is initiated in 26-50% of cases.

6. In our clinical practice, approximately 26-50% of our T2DM patients achieve control on a dual combination therapy.

7. Concomitant use of Dapagliflozin + Sitagliptin + Metformin is employed by 82% of practitioners.

8. In the clinical practice, approximately 10-20% of T2DM patients require triple drug therapy with Dapagliflozin + Sitagliptin + Metformin

9. The combination of Dapagliflozin + Sitagliptin + Metformin is preferred in patients with type 2 diabetes mellitus (T2DM) and an elevated risk of cardiovascular disease, as indicated by 65% of respondents.

10. The clinical advantage of using the combination of Dapagliflozin + Sitagliptin + Metformin is the comparatively better renal outcomes in patients with renal impairment, as chosen by 39% of respondents.

11. Life-long therapy and therapy lasting from 6 months to 1 year were both selected by 32% of respondents for average duration for of Dapagliflozin + Sitagliptin + Metformin Therapy in T2DM patient

12. In my opinion, the long-term safety profile of Dapagliflozin + Sitagliptin + Metformin is excellent, as indicated by 43% of respondents.

13. The combination of Dapagliflozin + Sitagliptin + Metformin is preferred in the age group of 40-60 years old, according to 84 % of respondents.

CONSULTING OPINION

Market Opportunities:

The therapeutic usage of Dapagliflozin + Sitagliptin + Metformin combination in the Indian healthcare landscape presents significant market opportunities. Emerging clinical evidence supports the synergistic effects of these three agents in managing type 2 diabetes, indicating a potential increase in demand for combination therapies.

Value for Healthcare Professionals:

Healthcare professionals in India can derive substantial value from the Dapagliflozin + Sitagliptin + Metformin combination therapy. The triple mechanism of action addresses multiple pathophysiological aspects of type 2 diabetes, offering a comprehensive approach to glycemic control. This combination provides healthcare professionals with a versatile tool for tailoring treatment strategies based on individual patient profiles, optimizing diabetes management in diverse patient populations.

Adverse Effect Management:

Effectively managing adverse effects is a crucial aspect of utilizing the Dapagliflozin + Sitagliptin + Metformin combination therapy in real-life clinical scenarios. Literature suggests that healthcare professionals should closely monitor patients for potential side effects such as urinary tract infections, genital mycotic infections, and gastrointestinal discomfort. Establishing a robust monitoring system and patient education can aid in early detection and management of adverse effects, ensuring the safety and tolerability of the treatment regimen.

Effective Management:

The combination of Dapagliflozin, Sitagliptin, and Metformin offers effective management of type 2 diabetes by addressing multiple underlying pathophysiological mechanisms. Healthcare professionals can leverage the complementary actions of these agents to achieve better glycemic control and reduce the risk of diabetes-related complications. Utilizing combination therapies may lead to enhanced efficacy compared to monotherapy, potentially reducing the need for additional medications and minimizing the risk of treatment-related complications.

Market Positioning:

Positioning the Dapagliflozin + Sitagliptin + Metformin combination therapy in the Indian diabetes market requires a strategic approach. Highlighting the synergistic benefits, safety profile, and potential to address unmet needs in diabetes management can enhance the market position of this triple therapy. Collaborative efforts between pharmaceutical companies, healthcare providers, and regulatory authorities are essential for successful market penetration and adoption of combination therapies in clinical practice.

Personalized Treatment Decisions:

The triple combination of Dapagliflozin, Sitagliptin, and Metformin allows healthcare professionals in India to make personalized treatment decisions based on individual patient characteristics and preferences. Factors such as age, comorbidities, and medication tolerance can be considered when tailoring treatment regimens, ensuring optimal outcomes and patient satisfaction. Personalized approaches contribute to improved treatment adherence and overall quality of care in the management of type 2 diabetes.

Improving Patient Outcomes:

Utilizing the Dapagliflozin + Sitagliptin + Metformin combination therapy in the Indian healthcare setting has the potential to significantly improve patient outcomes in type 2 diabetes management. By addressing multiple facets of diabetes pathology, this combination may lead to better glycemic control, reduced cardiovascular risks, and improved quality of life for patients. Monitoring and optimizing therapy in collaboration with healthcare providers can contribute to sustained positive outcomes and enhanced patient well-being.

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