USV

Your Reliable Healthcare Partner

UDAPA*-S

Dapagliflozin 10 mg + Sitagliptin 100 mg Tablets

PRODUCT MONOGRAPH

Crest

TOWARDS MAKING India A DIABETES CARE CAPITAL OF THE WORLD

Content

Overview

The global prevalence of type 2 diabetes mellitus (T2DM) is estimated to be 537 million and is expected to rise to 783 million by 2045 [1]. In India, 74 million people were estimated to have diabetes in 2021, and by 2045, that number is expected to reach over 124 million [2]. The goal of treatment in T2DM is to prevent diabetic complications by measuring glycated haemoglobin (HbA1c) as a measure of glycemic control and lowering blood glucose by a combination of lifestyle changes and drug therapy [3]. It is recommended to add T2DM treatments sequentially, moving from monotherapy to combination therapy to manage hyperglycemia and associated complications [4,5].

There are single-pill combinations for both more recent drugs like sodium-glucose cotransporter 2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors, as well as more traditional ones like sulfonylureas and thiazolidinediones, metformin, or metformin extended-release [6]. According to the comorbidities and physiological state of the patients, different combination approaches have been tried; however, established therapies comprising metformin, sulphonylureas, or thiazolidinediones have some undesirable properties, including the risk of hypoglycemia and weight gain, indicating the need for newer agents with more favorable safety profiles that can be used in combination therapy. One of the choices is to use the most recent class of glucose-lowering medications, SGLT2 inhibitors and DPP-4 inhibitors [6-8]. The synergistic methods used by DPP-4 inhibitors and SGLT2 inhibitors to lower blood sugar levels include facilitating insulin production and the promotion of urine glucose excretion. Since these agents have different mechanisms of action, it is unlikely that their safety profiles will deteriorate [9,10].

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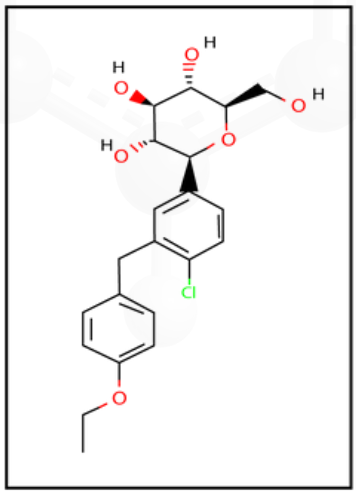
Science of dapagliflozin

INTRODUCTION

Dapagliflozin is a selective and reversible inhibitor of SGLT2 [1]. It belongs to a class of hypoglycemic agents associated with potent cardiovascular benefits, [2] which provides an insulin-independent mechanism to reduce blood glucose by increasing urinary glucose excretion, an exception to other glucose-lowering agents. [3].

CHEMICAL STRUCTURE



PHARMACOKINETIC PROPERTIES

Parameters	Dapagliflozin
Administration route	Oral
Inhibitor of the SGLT2 transporter	Reversible
Time to peak concentration (Tmax)	1h
Bioavailability	78%
Metabolism	By UGT1A9 producing inactive glucuronidated metabolites, mostly dapagliflozin-3-O-glucuronide
Half-life	12.9 hours
Peak plasma concentration	2h

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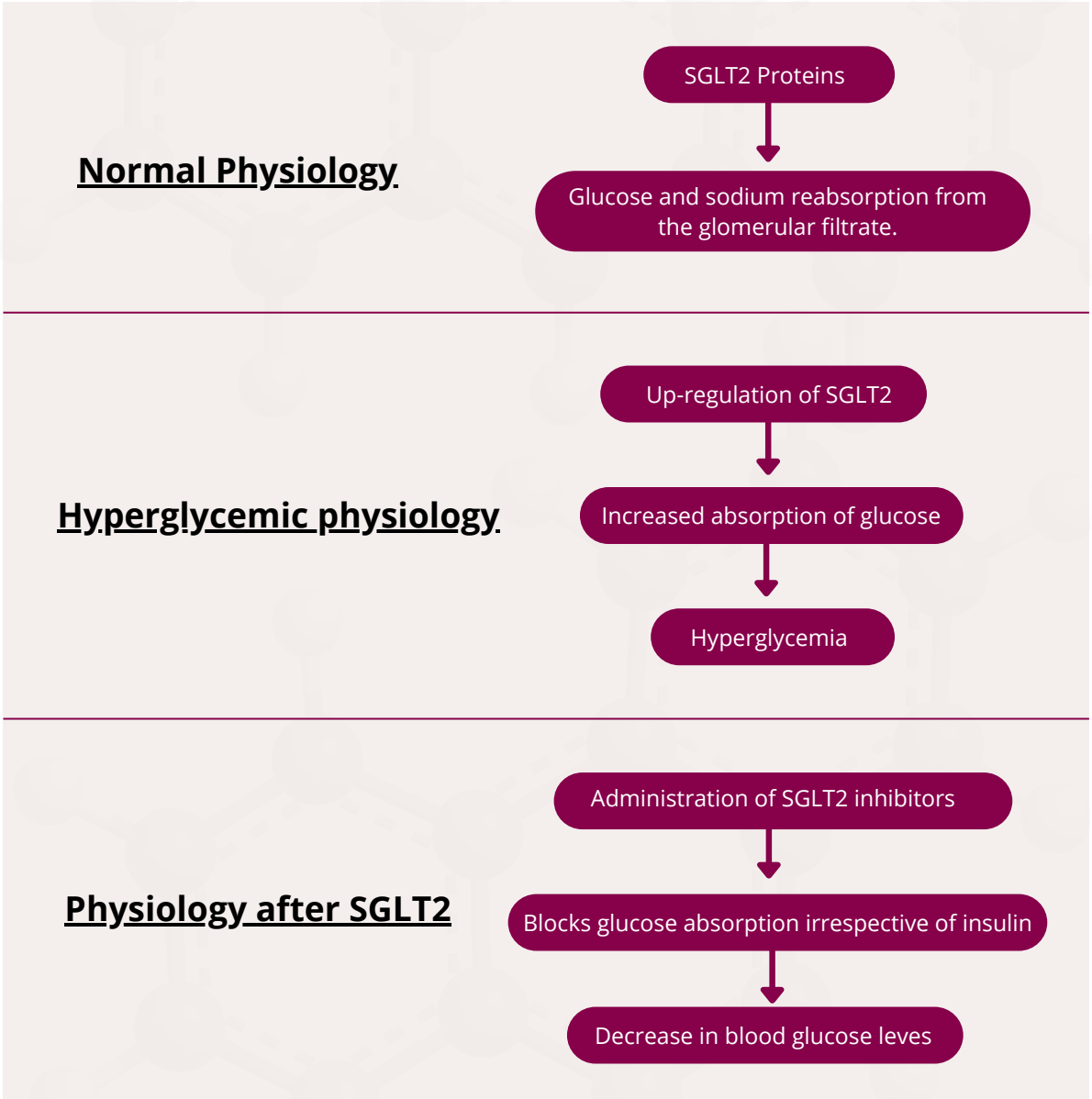
MECHANISM OF ACTION

- Approximately 180 g of glucose is physiologically filtered and subsequently reabsorbed each day, the majority of which happens via SGLT2 and the remainder via SGLT1. As a result, healthy people do not excrete glucose in their urine. Sodium-Glucose Co-Transporter-2 inhibitors prevent glucose absorption, and the resulting glycosuria of about 80 g per day lowers blood sugar in a way that does not require insulin **(Figure 1)** [4].

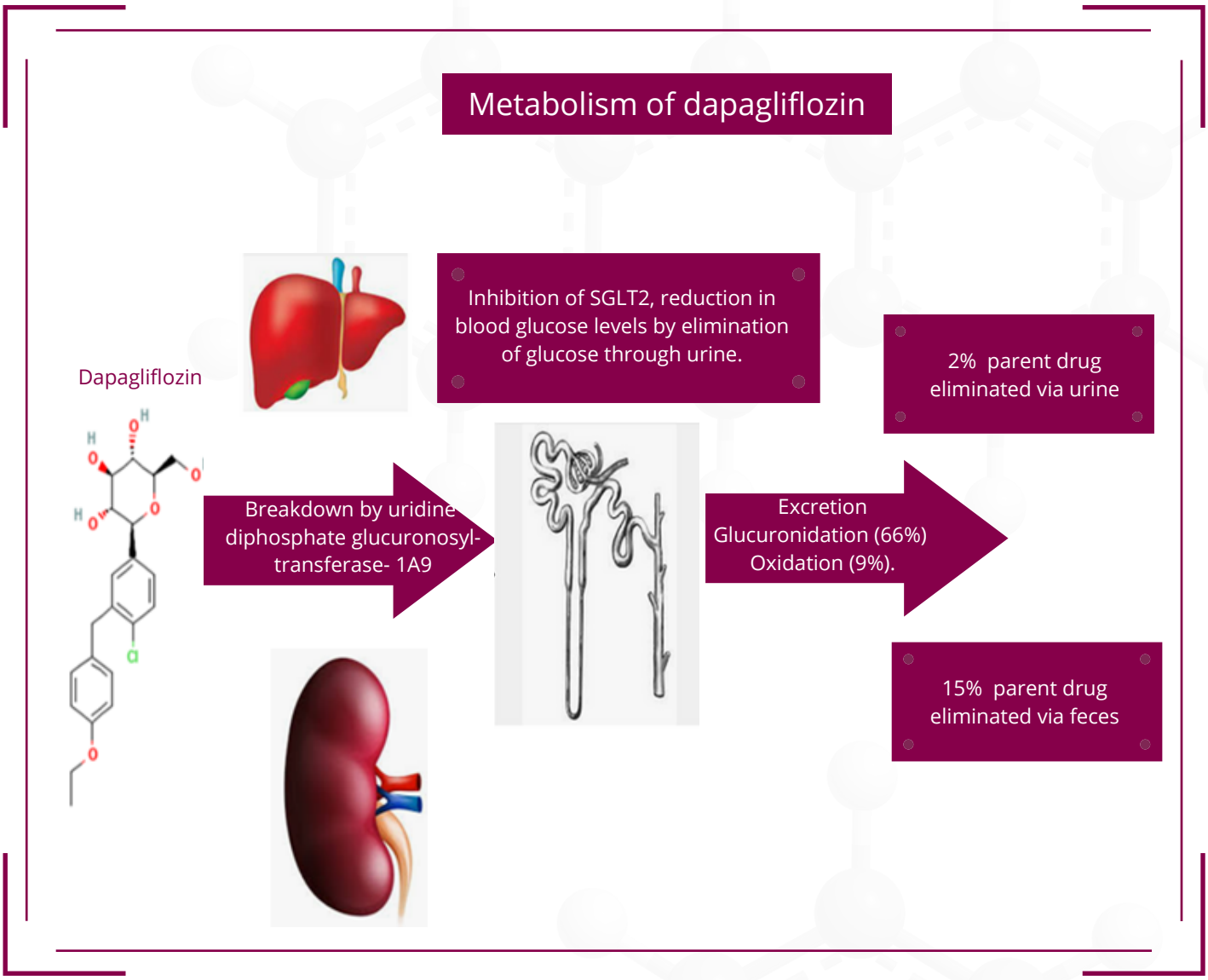
Figure 1: Dapagliflozin mechanism of action



Adapted from: Nicholson MK et al. Expert Opin Pharmacother. 2021;22(17):2303-10.

- Hepatic and renal impairment had a similar impact on metabolism, increasing exposure overall by 67% and 87%, respectively. This suggests that both the liver and the kidneys' enzymes are involved in the metabolism of dapagliflozin (Figure 2) [5,6].

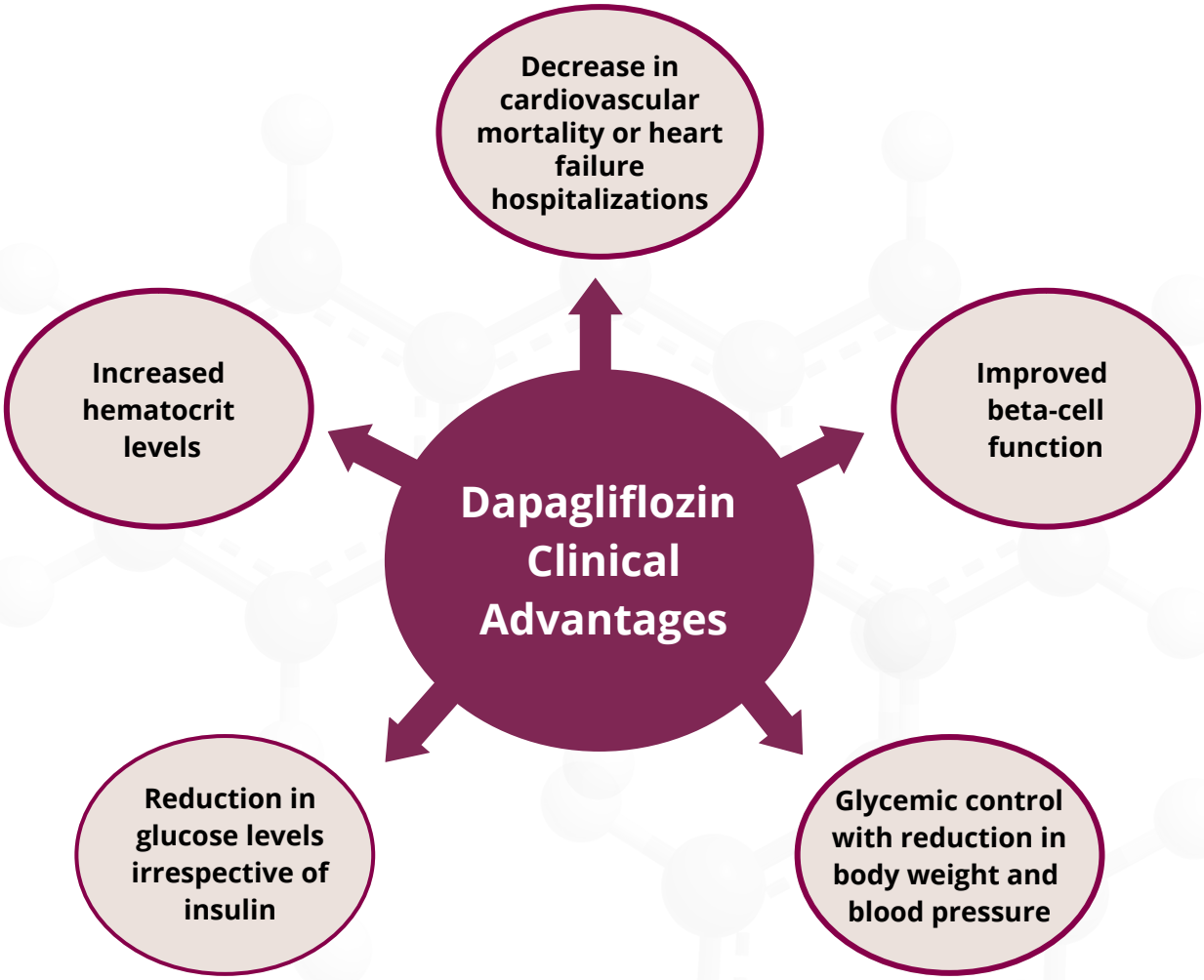
Figure 2: Metabolism of dapagliflozin



Adapted from: 1) Kalra S. Diabetes Ther. 2014;5(2):355–66. 2) U.S. Food and Drug Administration, AstraZeneca Pharmaceuticals LP. FORXIGA. Dapagliflozin [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202293s022lbl.pdf. Accessed on 01 July, 2022.

Clinical advantages of dapagliflozin in diabetes population with and without complications

Figure 3: Clinical benefits of dapagliflozin [7-11]



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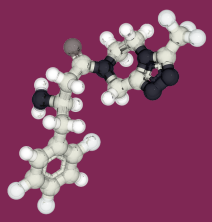
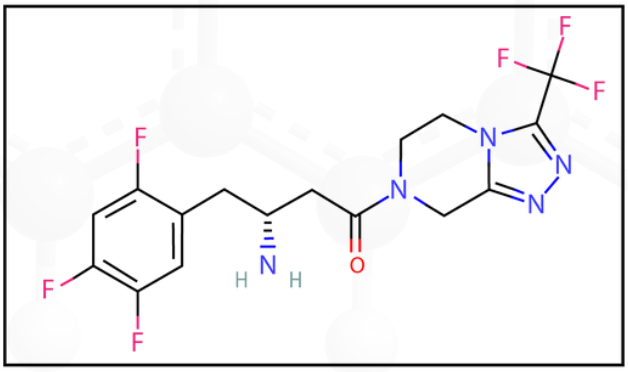


Science of Sitagliptin

INTRODUCTION

A novel family of glucose-lowering drugs called DPP-4 inhibitors have been shown to reduce blood glucose levels by inhibiting DPP-4 [1] and enhance pancreatic β-cells activity in T2DM [2]. The first DPP-4 inhibitor to get commercial approval was sitagliptin in 2006 [3,4].

CHEMICAL STRUCTURE



PHARMACOKINETICS OF SITAGLIPTIN

Parameters	Dapagliflozin
Administration route	Oral
Bioavailability	87%
Metabolism	The metabolic pathways are mediated mainly by cytochrome p450(CYP)3A4 and to a lesser extent by CYP2C8.
Half-life	12.4 hours
Peak plasma concentration	2h

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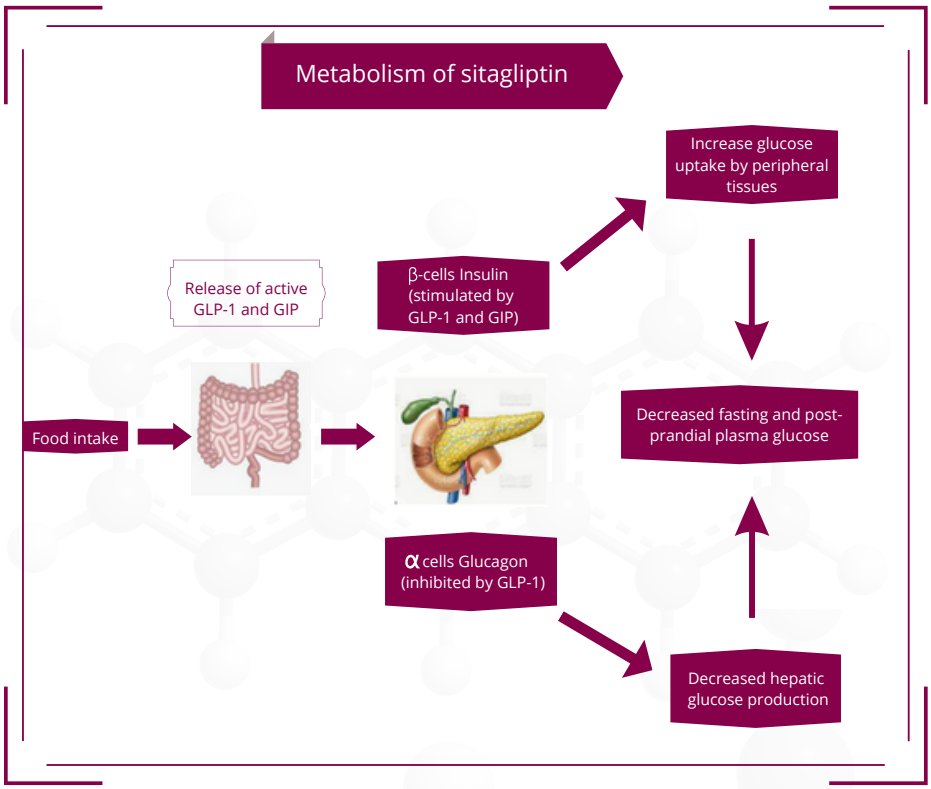
MECHANISM OF ACTION [5-7]

- DPP-4 inhibitors improve glycemic regulation in patients by raising insulin secretion, improving insulin sensitivity to glucose, and lowering glucagon secretion (Figure 4) [6,7].

Figure 4: Mechanism of sitagliptin

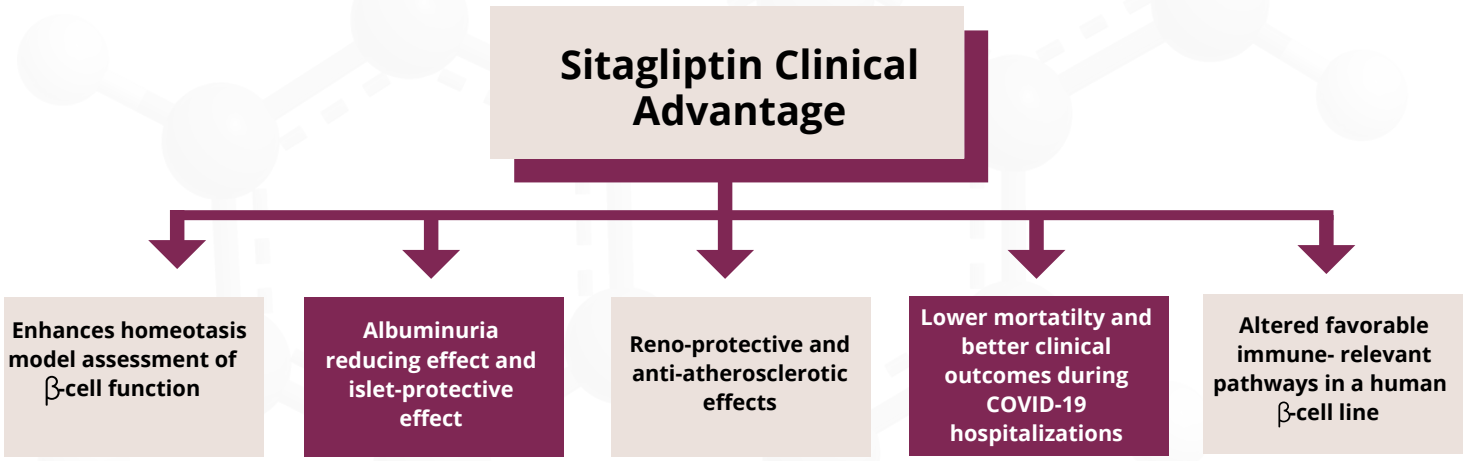


Abbreviations: GLP-1; glucagon-like peptide 1, GIP; gastric inhibitory polypeptide

Adapted from Gallwitz B. Front Endocrinol (Lausanne). 2019;10:389

Clinical advantages of sitagliptin in the diabetes population

Figure 5: Clinical benefits of sitagliptin [8-16]



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Indications, Dosage, Administration and Contraindication

Figure 6: Indications, dosage, administration and contraindication of dapagliflozin [1]

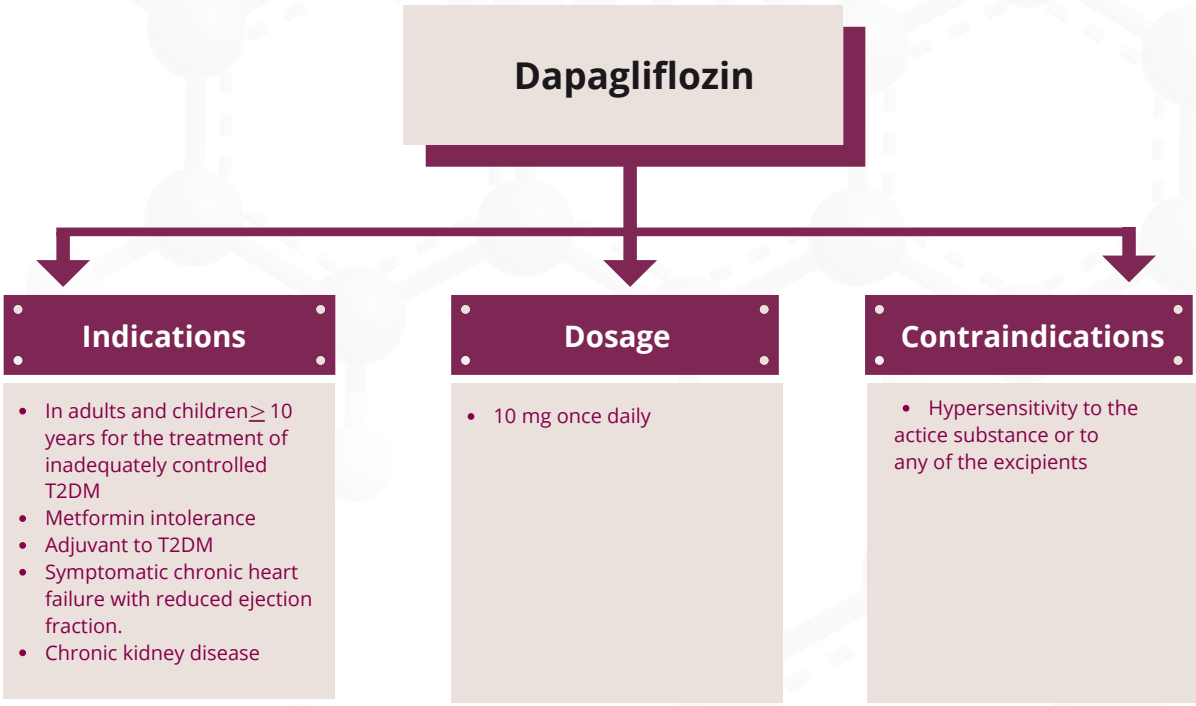
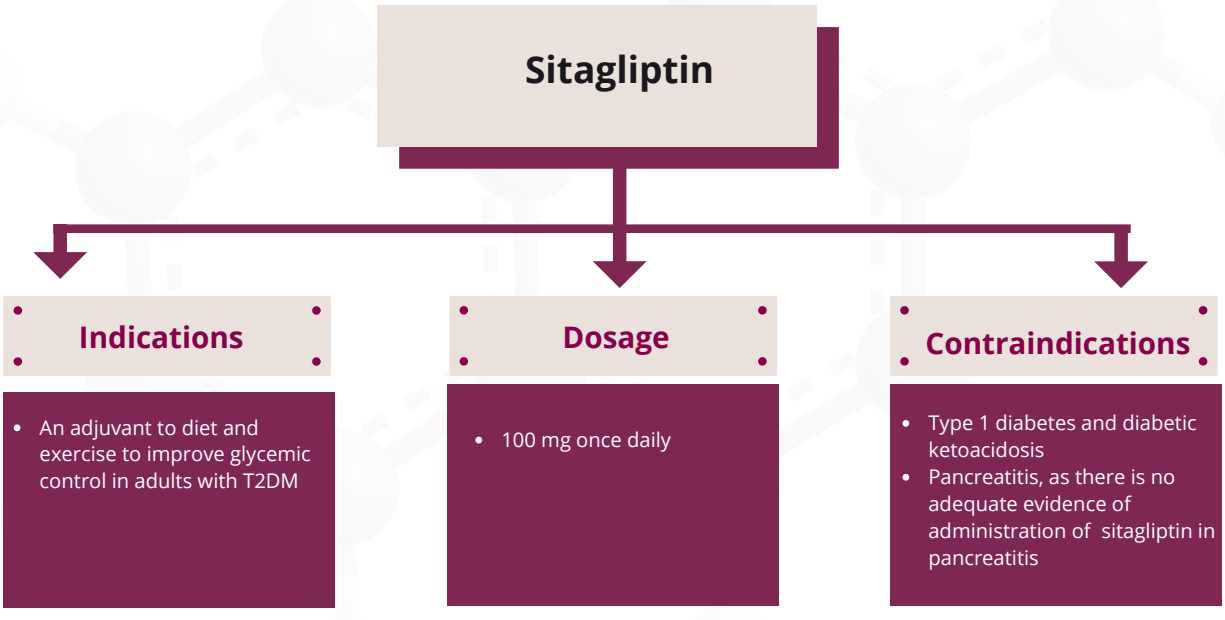


Figure 7: Indications, dosage, administration and contraindication of sitagliptin [2]



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Rationale for Add-on Therapy or Combination Therapy [1]

The four pressing unmet needs in the management of T2DM include:

- The requirement for a combinatorial approach to target several pathophysiological processes of hyperglycemia to achieve robust glycemic control is one of the four urgent unmet needs in the management of T2DM.
- The need for additional drugs that offer glycemic and non-glycemic advantages, particularly given that most patients' diabetic comorbidities control is subpar.
- Lowering the incidences of hypoglycemia or weight gain, as these side effects of conventional antidiabetic medications lower the morale of both the patient and the treating physician.
- An oral treatment choice that not simply meets the pressing requirements moreover works with the patients' willingness to comply.

Combination therapy with two drugs may aid patients in reaching their target HbA1c more rapidly than monotherapy, in addition to lowering pill burden and enhancing compliance.

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UDAPA-S

Sodium-Glucose Cotransporter 2 And Dipeptidyl Peptidase-4 Inhibition: A perfect combination with the Synergistic Mechanism of Action

- An appealing strategy for the management of T2DM is the combination of SGLT2 inhibitors, which encourages glycosuria and improves glucose tolerance without the need for insulin, and a DPP-4 inhibitor. This incretin-based therapy addresses islet dysfunction (Figure 8) [1,2].

- To treat hyperglycemia in T2DM, various pharmaceutical strategies are used. Due to their synergistic mechanisms of action, combining an SGLT2 inhibitor, also known as gliflozin and a DPP-4 inhibitor, also known as gliptin, seems to be a promising approach (Figure 9) [2].

Figure 8: Mechanism of action of the dual therapy [1,2]

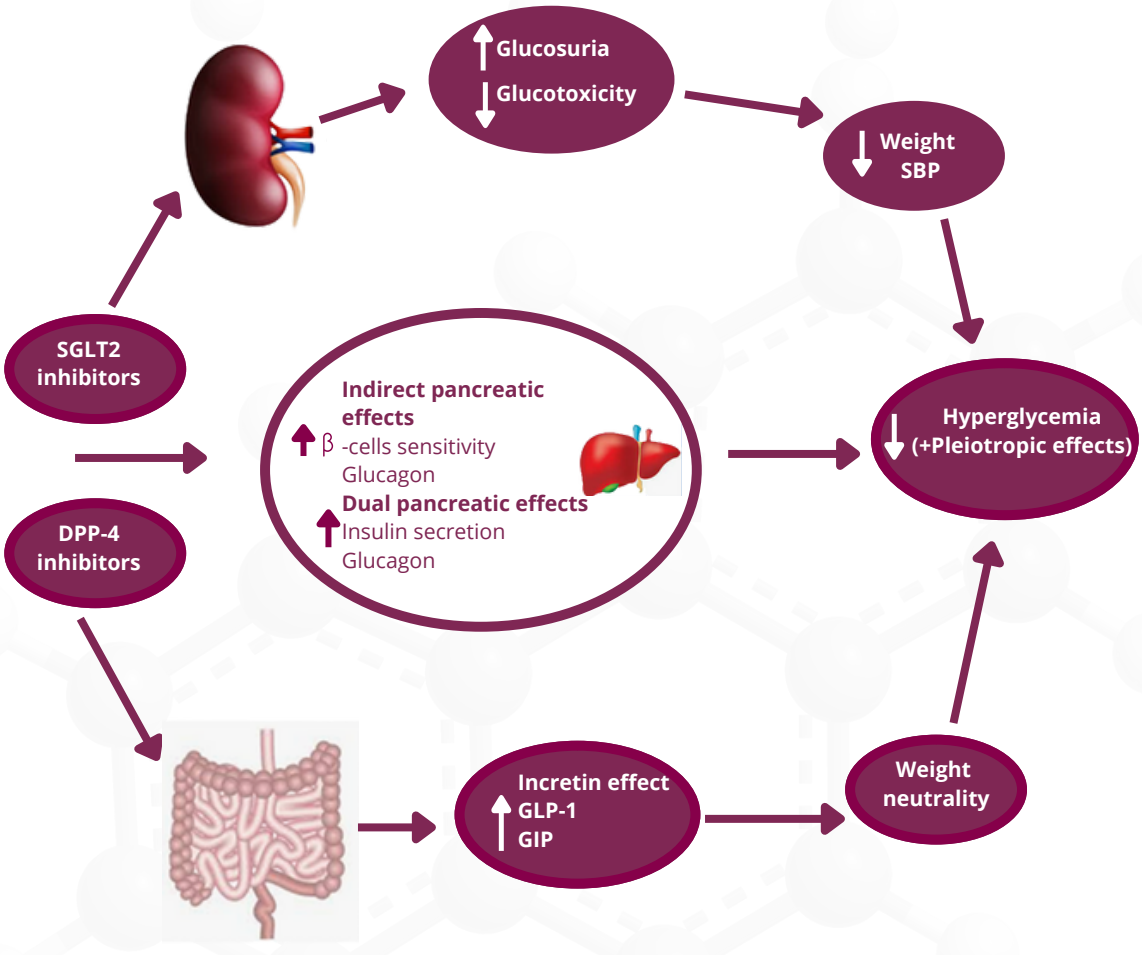

Figure 9: The dynamic duo of SGLT-2 inhibitor and DPP-4 inhibitor [4-11]

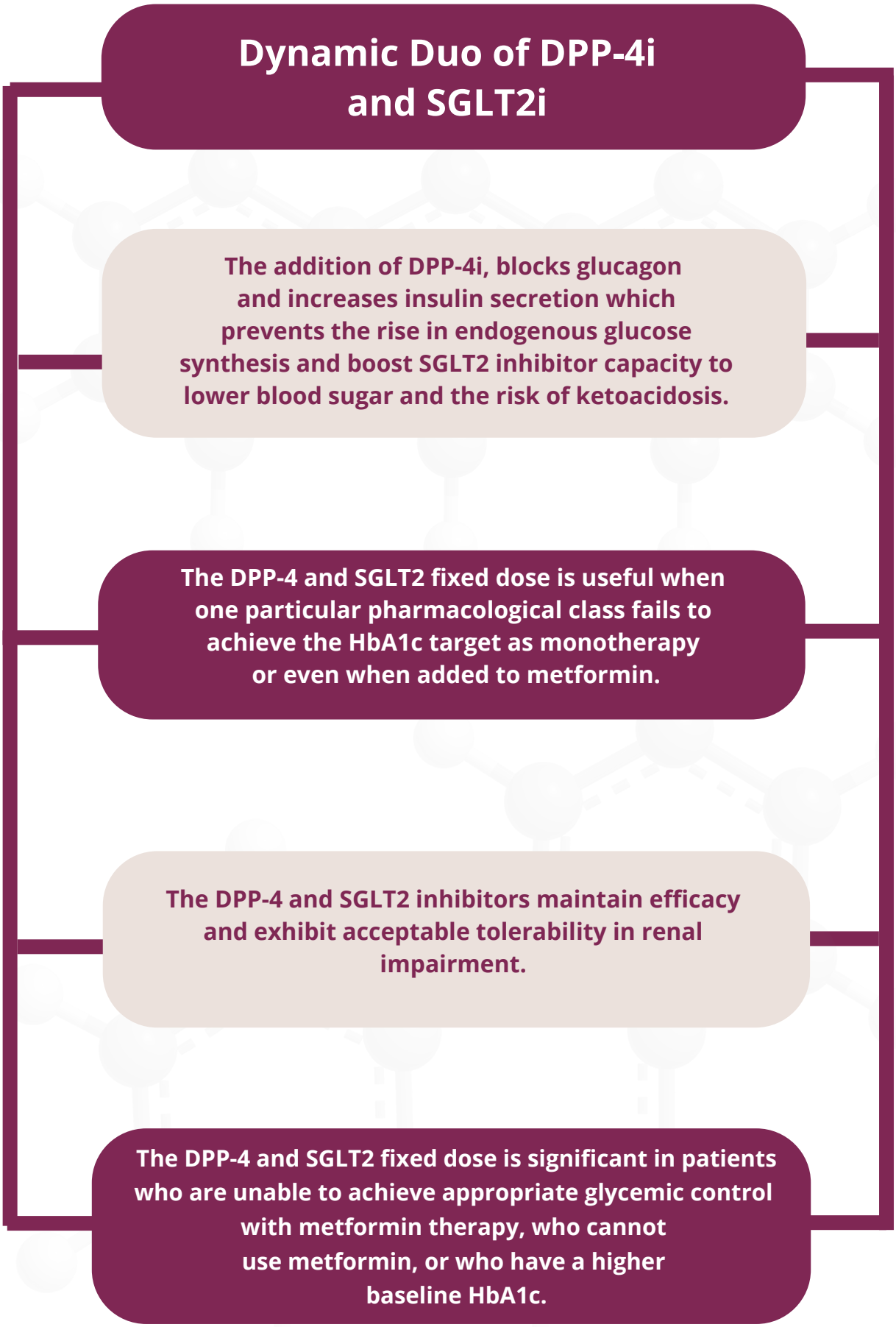

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Table 1: Non-glycemic mechanisms of SGLT2 inhibitors [12] and DPP-4 inhibitors [13,14]

Non-glycemic mechanism of SGLT2 inhibitors and DPP-4 inhibitors

	SGLT2 inhibitors	DPP-4 inhibitors
Renal effects	• Reduction in albuminuria • Reduction in tubular inflammation due to lower RAAS activation • Reduction in intraglomerular pressure and tabular hypertrophy	• Inhibit glomerulosclerosis,fibrosis and albuminuria. • Decrease NaHCO3 reabsorption in renal promixal tubule by inhibiting Na+/H+ exchanger type 3 activity.
Cardio-vascular effects	• Weight loss • BP reduction • Decrease in epicardial fat thickness • Favorable effect in lipid profile • Lesser urges of insulin secondary to hypoglycemia as the glycemic actions of the class are non insulin dependent.	• Reduce infarct size after myocardial ischemia/reperfusion injury. • Decrease cardiac fibrosis in uremic cardiomyopathy model • Potentially attenuate cardiac remodelling

Although the desired beneficial effect of this combination has not yet been established, this combination can aid early treatment intensification by: 1) good tolerability 2) a low risk of hypoglycemia 3) a potential for weight loss 4) a minimal treatment burden

- With promising efficacy evidence on one SGLT2 inhibitor and consistent cardiovascular safety data for the DPP-4 inhibitor family, this combination has the prospect of cardiovascular benefits [15].

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Clinical Evidence
Dapagliflozin 10 mg

A strong wall of evidence, including multiple phase 3 RCTs with dapagliflozin as monotherapy and combination therapy, have demonstrated its efficacy in improving glycemic control and reducing body weight and BP in a broad spectrum of patients with T2DM, including those with high baseline HbA1c (≥ 9%) and the elderly (aged ≥ 65 years) [1,2]. Furthermore, the efficacy and safety of dapagliflozin have been explored in special populations, including patients with chronic kidney disease (CKD) stage 3A, hypertension or CVD [3-7]. Three vital clinical trials assessing the efficacy and safety of dapagliflozin include DECLARE TIMI (Thrombolysis in Myocardial Infarction) 58, DAPA-HF, and DAPA-CKD.

a) DECLARE TIMI (Thrombolysis in Myocardial Infarction) 58 [8]

DECLARE TIMI 58

AIM

To investigate the cardiovascular safety and renal outcomes of dapagliflozin in T2DM.

DESIGN

Double-blind, placebo-controlled, multinational RCT
17,160 patients were recruited from 882 sites over 33 countries

SELECTION

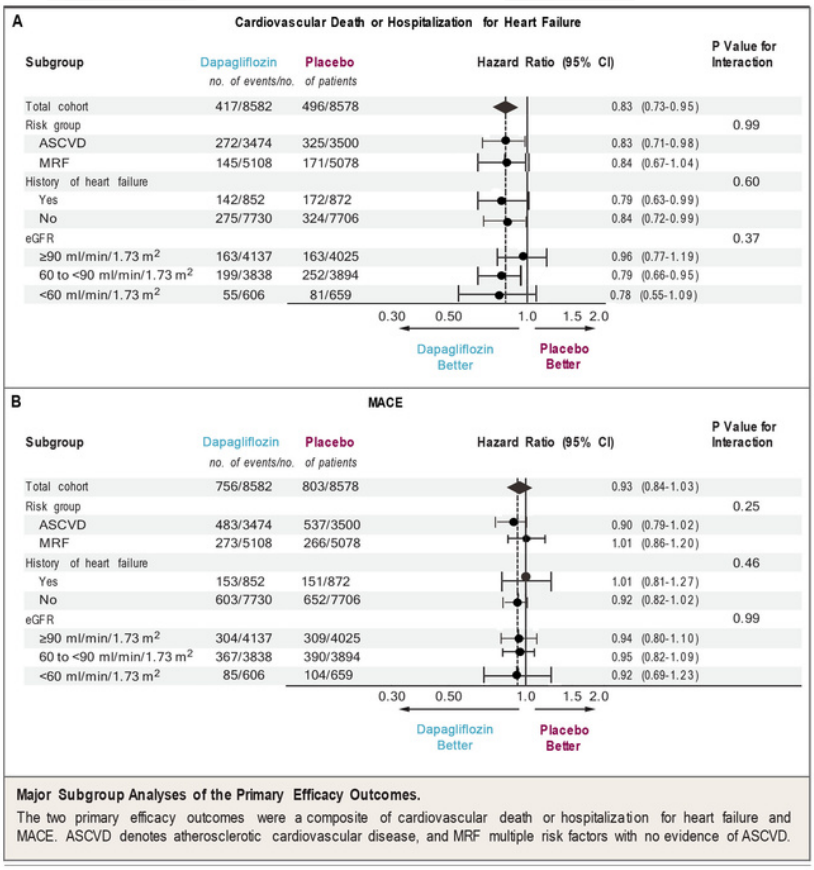
Patients with T2DM plus either established atherosclerotic cardiovascular disease (aCVD;40.6%), or risk factors for CVD (59.4%)

DOSAGE

Dapagliflozin 10mg once daily or placebo in addition to other antihyperglycemic agents.

KEY OBSERVATIONS

- Lower HbA1c throughout the trial (mean absolute difference 0.42%, 95% CI 0.4-0.45)
- Significant weight reduction (1.8kg, 95% CI 1.7-2.0)
- A small reduction in both systolic and diastolic blood pressure (2.7mmHg, 95% CI 2.4-3; 0.7mmHg, 95% CI 0.6-0.9, respectively)
- A lower rate of the composite outcome 'cardiovascular death and HHF' (hazard ratio 0.83; 4.9% vs 5.8%)

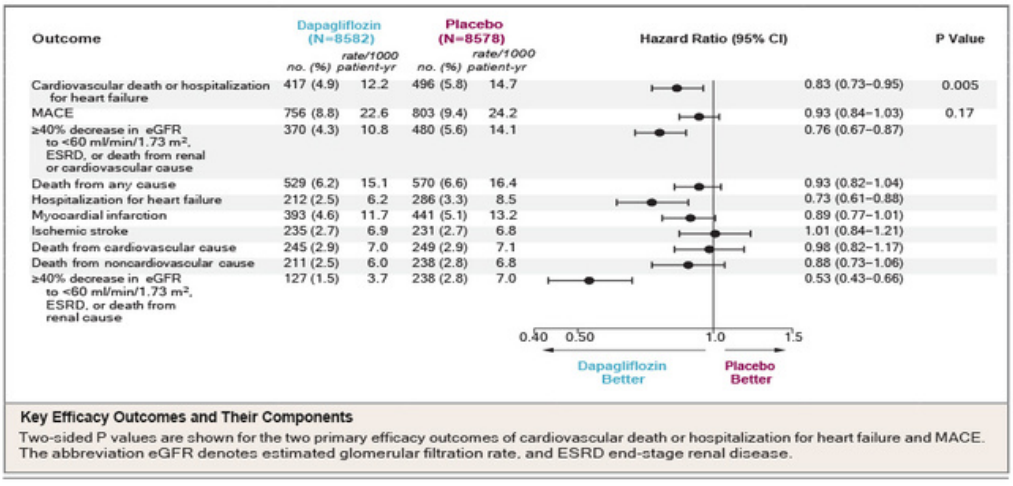


Major Subgroup Analyses of the Primary Efficacy Outcomes.
The two primary efficacy outcomes were a composite of cardiovascular death or hospitalization for heart failure and MACE. ASCVD denotes atherosclerotic cardiovascular disease, and MRF multiple risk factors with no evidence of ASCVD.

KEY LEARNING

In patients with T2DM who had or were at risk for atherosclerotic cardiovascular disease, treatment with dapagliflozin did not result in a higher or non-inferior of MACE than placebo but did result in a lower rate of CV death or HHF, a finding that reflects a lower rate of hospitalization for HF. Additionally, dapagliflozin reduces the likelihood of progression of renal disease (lower incidences of the renal composite outcomes).

DAPAGLIFLOZIN TYPE 2 DIABETES



Key Efficacy Outcomes and Their Components
Two-sided P values are shown for the two primary efficacy outcomes of cardiovascular death or hospitalization for heart failure and MACE. The abbreviation eGFR denotes estimated glomerular filtration rate, and ESRD end-stage renal disease.

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b) DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure): Important study - the first to show the benefits of an SGLT2 inhibitor in HF in people with and without T2DM [9].

DAPA - HF

AIM

To explore the effects of dapagliflozin in patients with HF regardless of whether or not they also had a diagnosis of T2DM.

DESIGN

RCT involving 4744 patients.

SELECTION

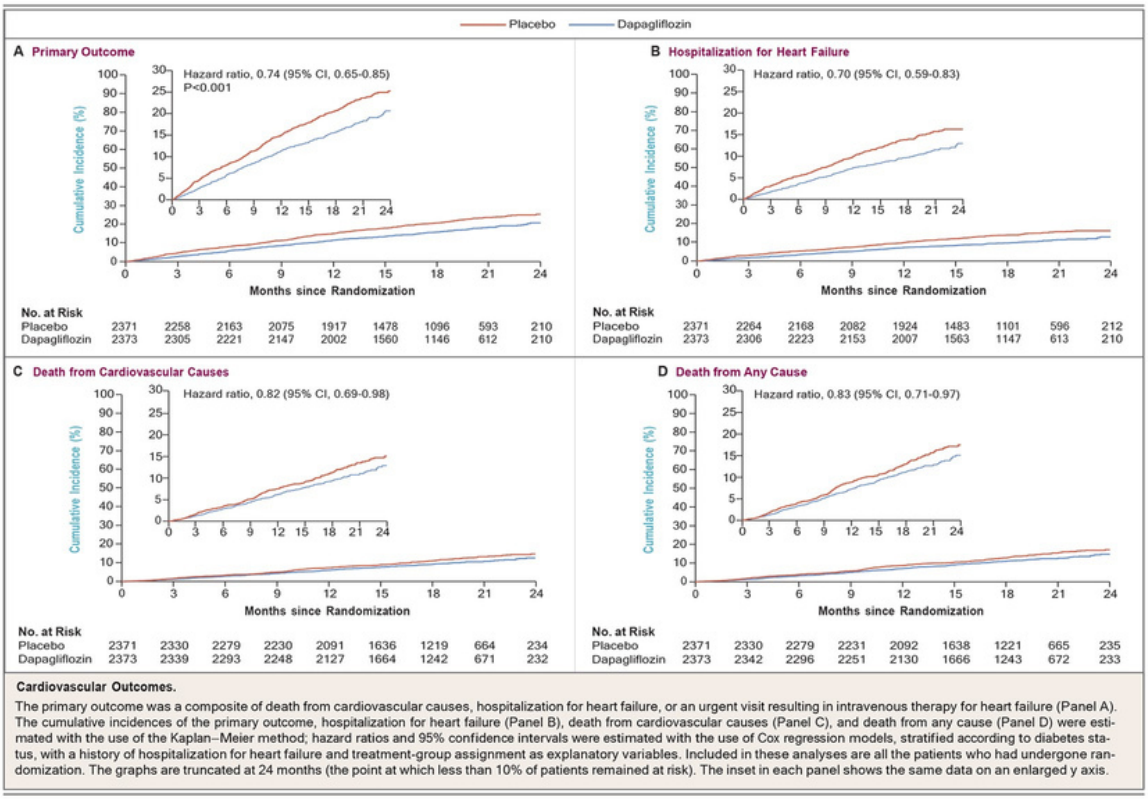
Eligible patients were those with with both New York Heart Association Class II,III , or IV HF and an ejection fraction $\leq$ 40% (i.e. HFrEF).

DOSAGE

Dapagliflozin 10 mg once daily or placebo in addition to standard recommended therapy for HF.

KEY OBSERVATIONS

Composite outcomes	Dapagliflozin	Placebo	HR (95% CI); p
At least one composite event	386/2373 (16.3%)	502/2371 (21.2%)	0.70 (0.65-0.85); <0.001
First episode of worsening HF (either hospitalization with or urgent IV treatment of HF	237 (10%)	326 (13.7%)	0.70 (0.59-0.83)
CV death	227 (9.6%)	273 (11.5%)	0.82 (0.71-0.97)
All-cause death	226 (11.6%)	329 (13.9%)	0.83 (0.71-0.97)



Cardiovascular Outcomes.

The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, or an urgent visit resulting in intravenous therapy for heart failure (Panel A). The cumulative incidences of the primary outcome, hospitalization for heart failure (Panel B), death from cardiovascular causes (Panel C), and death from any cause (Panel D) were estimated with the use of the Kaplan–Meier method; hazard ratios and 95% confidence intervals were estimated with the use of Cox regression models, stratified according to diabetes status, with a history of hospitalization for heart failure and treatment-group assignment as explanatory variables. Included in these analyses are all the patients who had undergone randomization. The graphs are truncated at 24 months (the point at which less than 10% of patients remained at risk). The inset in each panel shows the same data on an enlarged y axis.

KEY LEARNING

Among patients with HFrEF, the risk of worsening HF or death from cardiovascular causes was lower among those who received dapagliflozin than placebo, regardless of the presence or absence of diabetes. DAPA-HF further supports the conclusion that patients with a greater degree of renal disease may benefit more from SGLT2 inhibitors with regard to mortality.

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c) DAPA-CKD (Dapagliflozin And Prevention of Adverse outcomes in chronic kidney disease): An important study that shows the benefits of dapagliflozin in slowing CKD progression in people with and without T2DM [10].

DAPA - CKD

AIM

To assess the efficacy and safety of dapagliflozin in CKD patients with and without a T2DM diagnosis.

DESIGN

4304 patients from 386 sites in 21 countries were recruited.

SELECTION

Eligible patients were those with an eGFR of 25-75 ml/min/1.73m^2 and a urinary albumin-creatinine ratio (ACR) of 200-5000 mg/g.

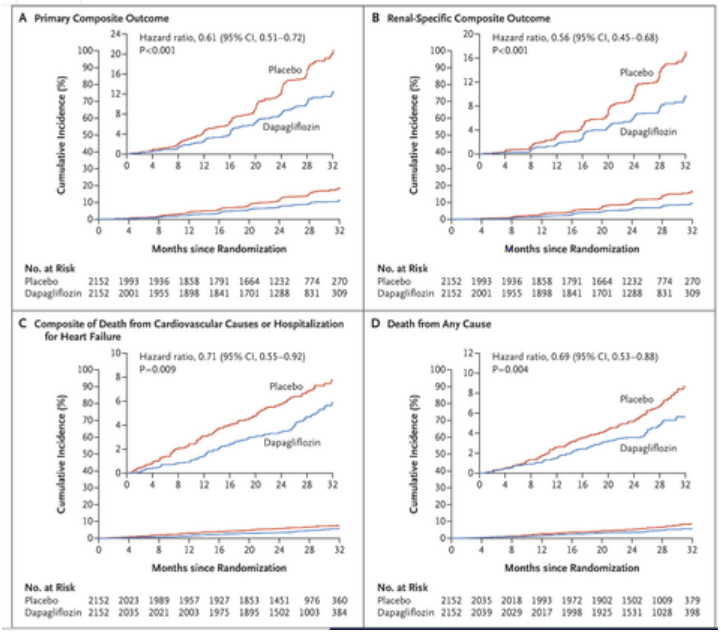
DOSAGE

Dapagliflozin 10 mg OD or placebo, with groups stratified by T2DM diagnosis and urinary ACR $\leq$1000 or >1000.

KEY OBSERVATIONS

- Patients in the dapagliflozin group had a lower risk of the composite outcome (HR 0.56, 95% CI 0.45-0.68, P<0.001), as well as a smaller mean annual decrease in eGFR than the placebo group (difference of 1.92 ml/min/1.73 m^2/year, 95% CI, 1.61 to 2.24).

- A lower risk of CV death or HF in the dapagliflozin group (HR 0.71, 95% CI, 0.55-0.92; P=0.009), as well as a lower risk of all-cause death (HR, 0.69; 95% CI, 0.53 to 0.88; P=0.004).



KEY LEARNING

Among patients with CKD, regardless of the presence or absence of diabetes, the risk of a composite outcome, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo. Dapagliflozin had a lower risk of death from cardiovascular causes or HHF and had longer survival.

KEY INSIGHTS FROM DAPAGLIFLOZIN TRIALS

- With the findings of the DAPA-HF trial, dapagliflozin has evolved from simply being an oral antihyperglycemic agent to a therapy for HF.
- Considering the cardiovascular benefits, dapagliflozin demonstrated greater protection against HF as compared to less dramatic effects on secondary outcomes such as MACE.
- DAPA-HF and DAPA-CKD have provided evidence that dapagliflozin has both cardio and reno protective effects, and may reduce the risk of all-cause death in patients with HF or impaired renal function.
- Since these effects of dapagliflozin are seen in patients both with and without T2DM, it is likely that they are mediated through mechanisms independent of the hypoglycemic properties of SGLT2 inhibitors.

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UDAPA-S

Clinical Evidence
Sitagliptin

CompoSIT –I study

a) Continuing sitagliptin when initiating insulin therapy in subjects with T2DM: Learnings from CompoSIT-I [1]

AIM

To compare the effects of continuing versus discontinuing sitagliptin when initiating and intensively titrating insulin glargine.

DESIGN

Double-blind, placebo-controlled, multinational RCT
Conducted at 149 sites in 22 countries

SELECTION

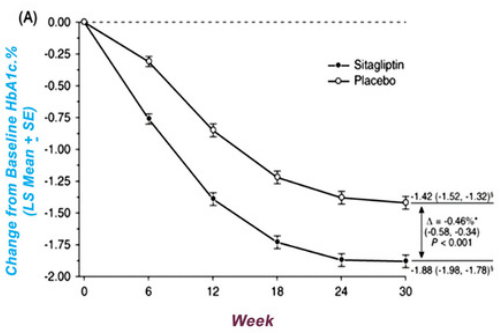
Patients with inadequately controlled type 2 diabetes taking metformin in dual combination therapy with sitagliptin and initiating insulin treatment.

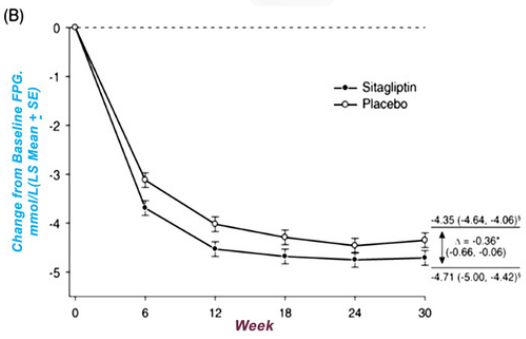
DOSAGE

Continuing sitagliptin (n=373) and discontinuing sitagliptin (n=370)

KEY OBSERVATIONS

- Continuing treatment with sitagliptin resulted in greater blood glucose reduction at week 30 compared to discontinuing sitagliptin.
- LS mean changes from baseline HbA1C of -1.88% with sitagliptin and -1.42% with placebo (P<0.001).
- 54% of patients who continued treatment with sitagliptin (n=202) achieved the ADA target HbA1C goal of <7.0%, compared to 35% of patients who were taking insulin alone (n=131) (P<0.001).





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KEY LEARNING

When initiating insulin therapy, continuation of sitagliptin, compared with discontinuation, resulted in a clinically meaningful greater reduction in HbA1c without an increase in hypoglycemia indicating the significant glycemic benefits of continuing sitagliptin in these settings.

CompoSIT –R study

b) Sitagliptin improved glycemic control to a greater extent than dapagliflozin: Learnings from the CompoSIT-R study [2]

AIM

To compare the efficacy and safety of the sitagliptin with dapagliflozin in patients with T2DM and mild renal insufficiency.

DESIGN

Double-blind, active comparator-controlled, parallel-group multinational RCT

SELECTION

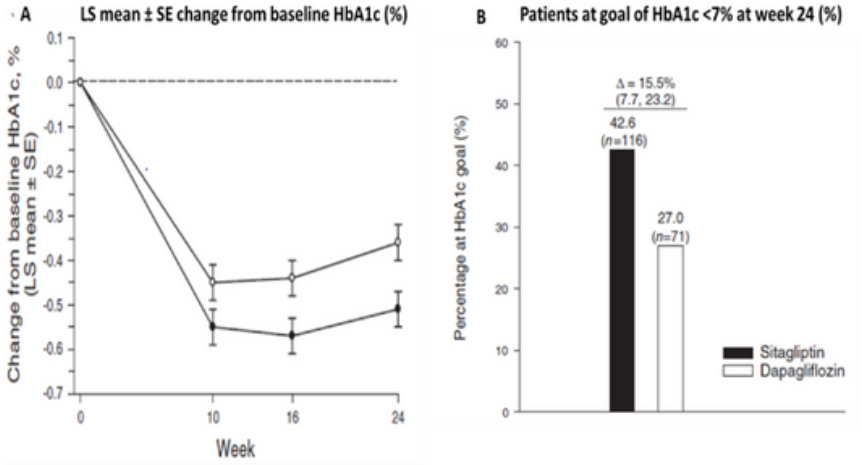
Patients wih HbA1c ≥7.0 ≤ 9.5 % (≥53 to ≤80 mmol/mol) and estimated glomerular flitration rate ≥60 to <90mL/min/1.73m^2 on metformin (≥1500 mg/d) ± sulfonylurea

DOSAGE

Sitagliptin 100 mg (n=307) or dapagliflozin 5 mg titrated to 10 mg (n=306) once daily for 24 weeks.

KEY OBSERVATIONS

- The least squares (LS) mean change from baseline in HbA1c was significantly greater with sitagliptin 100 mg compared with dapagliflozin (P=0.006).Sitagliptin was non-inferior to Dapagliflozin.
- In both treatment groups, a near-maximum reduction in HbA1c was observed by week 10 and improved glycemic efficacy continued through the end of treatment.
- At week 24, the between group difference (sitagliptin-dapagliflozin) in patients (95%CI) with HbA1c<7.0% was 15.5% (7.7, 23.2).



KEY LEARNING

In patients with T2DM, mild renal insufficiency and inadequate glycemic control on metformin ± sulfonylurea, treatment with sitagliptin compared with dapagliflozin demonstrated greater glycemic efficacy, a greater percentage of patients at glycemic goal, and a good safety profile.

KEY INSIGHTS FROM SITAGLIPTIN TRIALS

- Sitagliptin treatment continuation was associated with the clinically meaningful glycemic benefits during insulin initiation in patients with T2DM.

- Sitagliptin improved glycemic outcomes to a greater extent than dapagliflozin in patients with T2DM and mild renal insufficiency.

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UDAPA*-S

Real World Evidence

Dapagliflozin 10 mg [1-3]

Real World Evidence Dapagliflozin

Real world SGLT 2 inhibitor use was assosiated with:

- A lower rate of HHF(HR 0.61, 95% CI 0.51-0.73, P<0.001)
- A lower risk of death overall (HR 0.49, 95% CI 0.41-0.57, P<0.001)

In concordance with the conclusions of DECLARE and DAPA- HF

CVD- REAL Study

Real world SGLT 2 inhibitor use was assosiated with:

- All-cause death(HR 0.51, 95% CI 0.37-0.70, P<0.001)
- HHF(HR 0.64, 95% CI 0.50-0.82, P=0.001
- MI (HR 0.81, 95% CI 0.74-0.88, P<0.001),and
- Stroke (HR 0.68, 95% CI 0.55-0.84, p<0.001).

CVD- REAL 2 (Stroke and Mi)

Real world SGLT 2 inhibitor use was associated with:

- a reduction in the rate of eGFR decline (1.53 mL/min/1.73 m^2/year, 95% CI 1.34-1.72, p<0.0001)

CVD- REAL 3 (Renel progression)

Sitagliptin 100 mg [4-6]

Real world Evidence sitagliptin

- An improvement in metabolic control (A significant improvement in HbA1c[p<0.01] and the rapid reduction in HbA1c [median HbA1c after 4-6 months: 7.5%} and continued at longer follow-up).
- A reduction in CV risk.
- No relevant adverse events.

PERsistent Sitagliptin Treatment & Outcomes (PERS&O) study in T2DM Patients

- HbA1c level reduction of 0.9% at 3, 6, and 9 months and of 0.8% at 12 months.
- The proportion of patients attaining the goal of HbA1c level< 7.0% doubled at different time points after treatment with sitagliptin

Realworld effectiveness of sitagliptin as add-on therapy in pateints with T2DM

- Sitagliptin produces a significant reduction of 0.8% in the mean HbA1c value, 3 to 6 months after use.
- However this reduction in HbA1c was lesser 7 to 12 month later (0.6%) but still similar to that reported in clinical trials

Sitagliptin: Is it Effective in routine clinical practice

KEY LEARNING

- This real-world evidence support **cardio-protective** and **reno-protective** findings associated with dapagliflozin use seen in experimental trials.
- Patients with T2D treated with sitagliptin achieved **an improvement in metabolic control and a reduction in CV risk.**
- A meaningful **clinical improvement in glycemic control.**

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UDAPA-S

Insights into the safety of Dapagliflozin and Sitagliptin

Dapagliflozin

- Dapagliflozin use is associated with a slightly higher risk of genitourinary infection. This might be attributable to the increased glucosuria from SGLT2 inhibitors [1]. However, various RCTs have reported inconsistent observations concerning urinary tract infections.

- Observations from a pooled analysis which included 12 clinical efficacy studies demonstrated that compared to patients treated with placebo, a relatively higher proportion of patients treated with dapagliflozin 10 mg (6.5%) had UTI symptoms; however, these symptoms were of mild to moderate intensity and patients recovered fast with available treatment [2].

- In real-world clinical settings, the risk of UTIs associated with SGLT2 inhibitor use is similar to the risk associated with using other second-line antidiabetic drug classes [3].

- Patients with T2DM are inherently susceptible to acquiring UTIs, with an elevated risk of about 60% [4]. The DECLARE and DAPA-HF studies showed fewer UTI occurrences among those taking dapagliflozin [5,6].

- This conclusion was corroborated by the DECLARE study, which found that dapagliflozin increased the likelihood of genital infections relative to placebo (HR 8.36, 95 % Ci 4.19-16.68) [7]. These infections were rapidly managed but seldom resulted in discontinuing medicine or study.

- The risk of more serious complications such as diabetic ketoacidosis (DKA) is rare. Results from DECLARE showed that DKA was more likely to occur in those in the dapagliflozin group compared to the control (0.3% vs 0.1%, HR 2.18, 95% CI 1.10–4.30). This occurred in 27 T2DM patients, of which 22 were also receiving insulin, thus putting them at greater risk.

Sitagliptin

- Pooled analysis of the safety and tolerability of sitagliptin across a large number of patients demonstrated that sitagliptin is generally well tolerated up to 2 years of duration and has comparable safety and tolerability profile with the other available treatment options [7,8].

- Furthermore, the incidence rate of hypoglycemia was lower in sitagliptin-treated patients compared to the non-sitagliptin treatment group [7].

- Among specific adverse events, incidence rates of hypoglycemia were similar to placebo when sitagliptin was used as a single agent or initial combination therapy with metformin or pioglitazone or as add-on therapy to metformin or a thiazolidinedione. However, it was high in the sitagliptin group when sitagliptin was used in combination with sulfonylurea or insulin [7].

- The overall incidence of gastrointestinal events was also comparable between the sitagliptin and non-sitagliptin treatment groups; a slight increase in the incidence of constipation was observed in the sitagliptin group [7].

- There were no reports of association of greater risk of major adverse cardiovascular events with sitagliptin treatment.

- Therefore, a vigilant assessment of the safety and tolerability profile of specific sitagliptin-based treatment options is necessary for clinicians before prescribing these medicines to their patients.

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Benefits of Combination Therapy

Dual or triple combination therapy

- If monotherapy fails to achieve glycemic control, dual therapy is advised; if dual therapy is ineffective at lowering the target glycated haemoglobin (HbA1c), triple therapy should be considered.
- One of the choices is to use the newest kinds of glucose-lowering medications, SGLT2 and DPP-4 inhibitors.
- When sitagliptin, with or without metformin, is not sufficient to control T2DM in a patient, dapagliflozin add-on therapy offers significant clinical benefits and is well tolerated [1,2,3].
- According to the findings of this study with a 24-week extension period, once-daily treatment with dapagliflozin 10 mg, in dual combination with sitagliptin, or triple combination with sitagliptin plus metformin, was well tolerated and led to clinically significant reductions in glycemic parameters and body weight that were maintained for 48 weeks of treatment [4].
- Dapagliflozin 10 mg was evaluated in a randomised controlled trial (RCT) as adjunctive therapy to sitagliptin 100 mg with or without metformin in patients with inadequately controlled T2DM. A significant reduction in HbA1c and body weight and an additional therapeutic benefit were seen after 24 weeks of dapagliflozin add-on therapy [4].
- Dapagliflozin significantly lowered HbA1c when administered with sitagliptin either by itself or in combination with metformin. Fewer patients receiving dapagliflozin needed to be evacuated or discontinued as they weren't achieving their glycemic objectives, and the benefits for body weight and glycemic control that were evident at week 24 remained through week 48 [4].
- While metformin is typically the first-line drug used to treat hyperglycemia in T2DM, patients with mild renal insufficiency frequently receive additional treatments to help them regulate their blood sugar levels, such as oral SU, DPP-4 inhibitors, or SGLT-2 inhibitors [5].
- In the Indian population, an SGLT2i 1 DPP4i FDC is a suitable option for various reasons (Figure 1) [6].

REFERENCES

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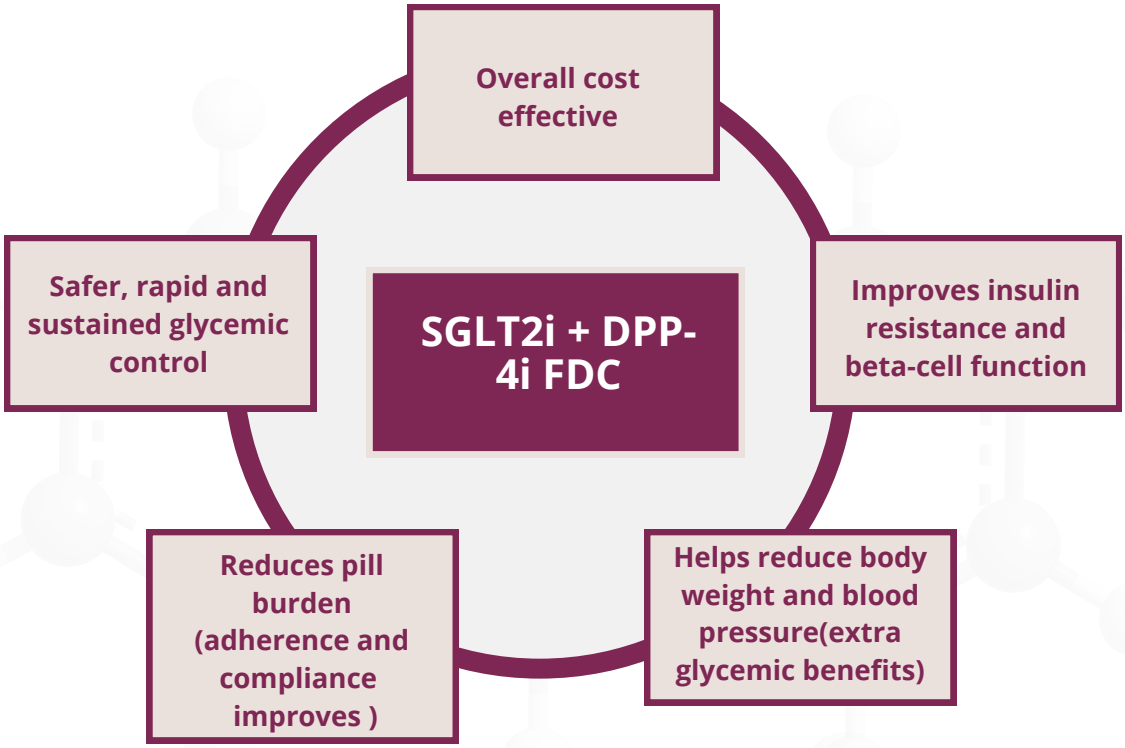
Figure 1: SGLT2 inhibitor plus DPP-4 inhibitor FDC: Suitable option for Indian T2DM patients



Adapted from: Chadha M et al. Diabetes Ther. 2022 May;13(5):1097-1114.

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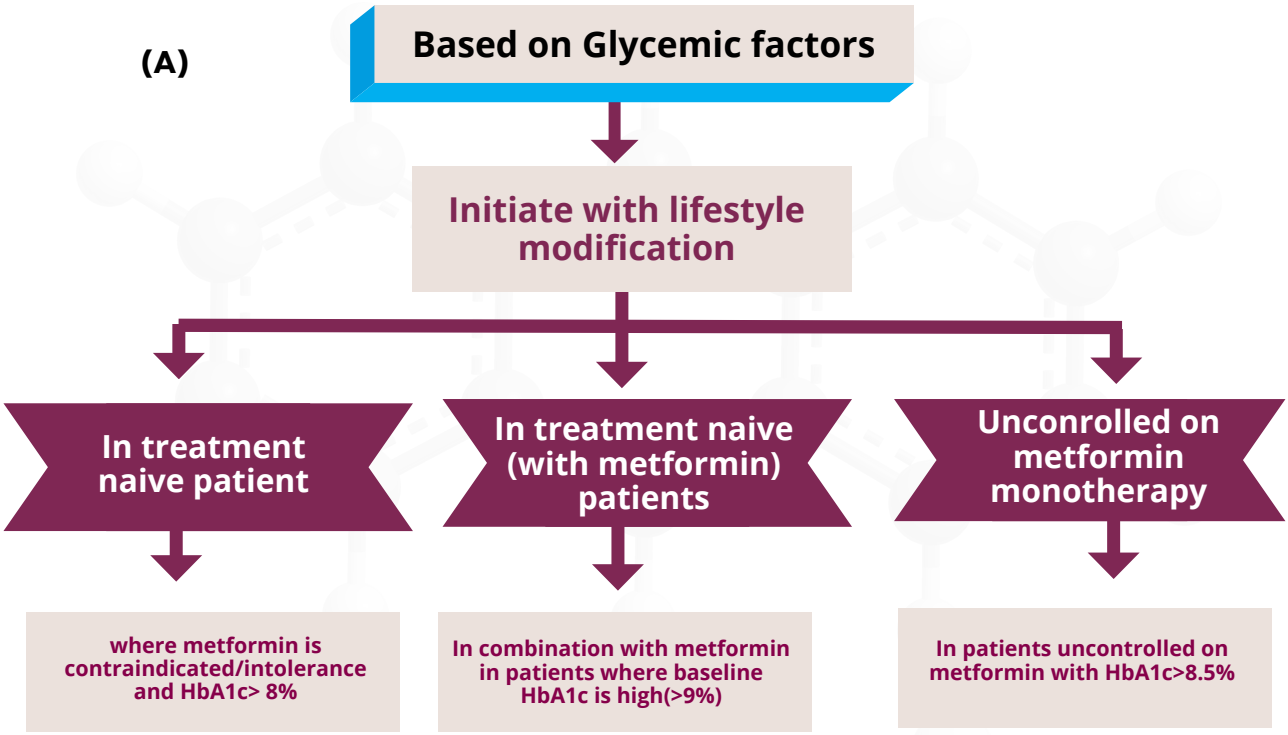
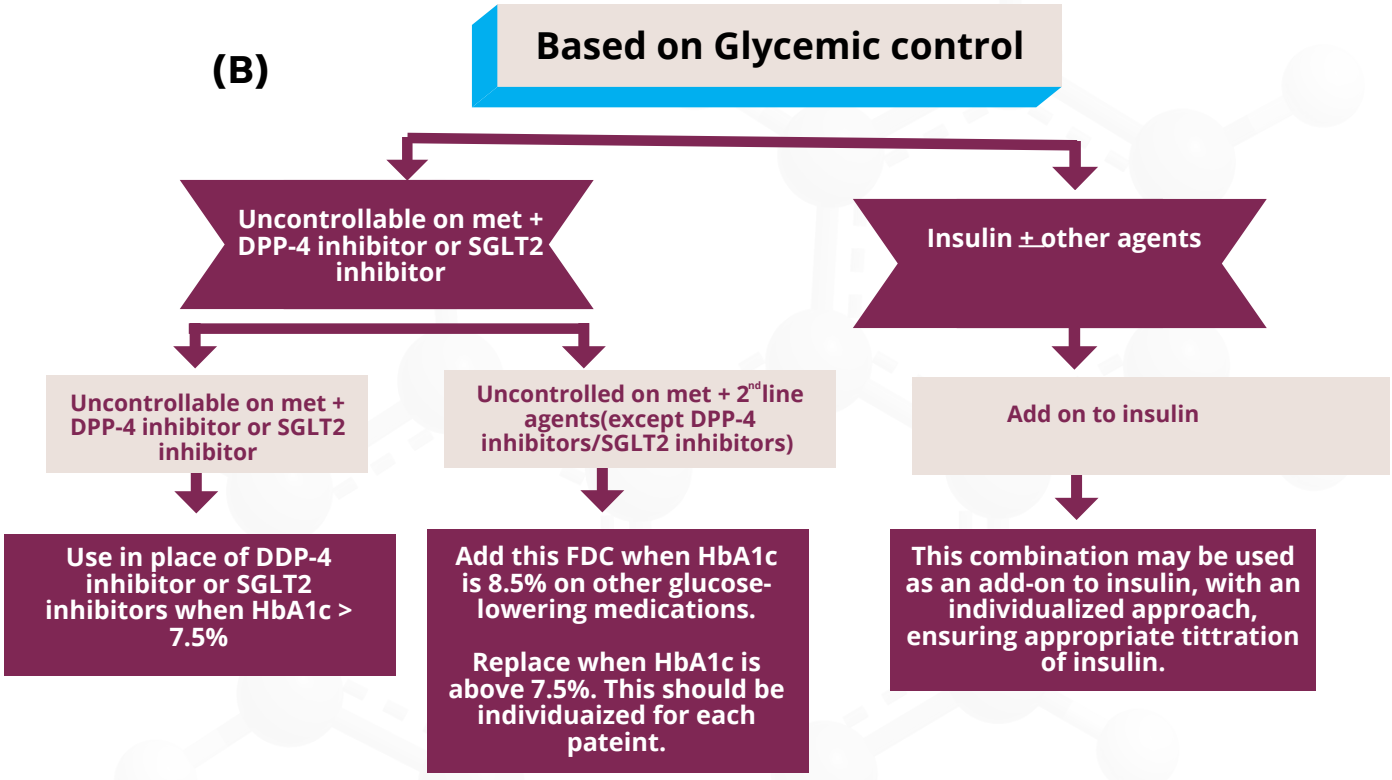
Clinical Decision-making Algorithm for the appropriate use of the SGLT-2 Inhibitors and DPP-4 inhibitors FDCs in T2DM management



Abbreviations: HbA1c; haemoglobin A1c



Abbreviations: HbA1c; haemoglobin A1c

UDAPA-S

(C)

Based on CV risk, including heart failure

SGLT2 inhibitors

SGLT2 inhibitors with proven CV and HF benefits are preferred agents in cases with cardiovascular disease including heart failure.

DPP-4 inhibitors

DPP-4 inhibitors with proven CV and HF safety such as linagliptin and sitagliptin have shown a favorable safety profile including no increased risk of hospitalizations due to heart failure in their CVOTs.

This combination may be preffered over other conventional therapies (those with no CV benefit) in cases of established CV disease and / or heart failure.

Abbreviations: CV; cardiovascular, CVOTs; cardiovascular outcome trials

(D)

Based on Chronic kidney Diseases

SGLT2 inhibitors

- SGLT2 inhibitors can only be used when eGFR>45ml/min/m2.
- SGLT2 inhibitors with positive outcomes CVOTs should be preferred in kidney disease.

DPP-4 inhibitors

- DPP-4 inhibitors with proven kidney safety should be preferred in kidney disease.

This combination may be preferred over other conventional glucose-lowering therapies in diabetes with CKD (when eGFR>45ml/min)

Abbreviations: CVOTs; cardiovascular outcome trials, eGFR; estimated glomerular filtration rate

(E)

Based on promoting weight loss or preventing hypoglycemia

SGLT2 inhibitors

- SGLT2 inhibitors promote weight loss.

DPP-4 inhibitors

- DPP-4 inhibitors are weight neutral

This combination may be preferred over other conventional therapies to promote weight loss with no increased risk of hypoglycemia in T2DM management .

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