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*In uncontrolled diabetes with comorbidities*

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1-10: References available on demand.

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## Notes



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# Preface

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by chronic hyperglycemia due to defects in insulin secretion or insulin action. It is the most common and clinically significant metabolic disorder with a significant health burden worldwide in recent decades.

This monograph provides information on the prevalence, phenotype clusters, challenges, and complications of T2DM in the Indian population. It also discusses the current approaches, unmet needs, and scope for the management of diabetes. It discusses the need for a fixed-dose combination and the rationale for combining dapagliflozin, sitagliptin and metformin in the management of T2DM. An overview of dapagliflozin, sitagliptin and metformin with respect to the mechanism of action, pharmacodynamics, and pharmacokinetics has been provided.

This monograph also includes clinical studies depicting the clinical safety and efficacy of the three drugs. It includes clinical studies on the efficacy in the elderly population and cardiorenal outcomes. Studies on the efficacy of sitagliptin in reducing body weight and improving glycemic control have also been discussed. Further, this monograph includes a clinical study indicating the anti-atherosclerotic effects of sitagliptin. Brief review on the efficacy and safety of metformin and lastly, it provides the guidelines and recommendations on the combination of sodium-glucose cotransporter-2 ($SGLT_2$) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors and metformin. This monograph provides a comprehensive overview of diabetes, the need for combination therapy, and the safety and efficacy of triple combination therapy of Sitagliptin, Dapagliflozin and Metformin.

# Overview of current trends related to type 2 diabetes

## Introduction

Diabetes is defined by the World Health Organisation (WHO) as "a metabolic disorder of multiple aetiologies characterised by chronic hyperglycemia with disturbance of carbohydrate, fat, and protein metabolism due to defects in insulin secretion or insulin action[1] ".

Type 2 diabetes (T2D) is the most common and clinically significant metabolic disorder which has become a global pandemic and a significant health burden worldwide in recent decades[1]. There is a relative insulin deficiency due to pancreatic β-cell dysfunction and insulin resistance in target organs[2]. Type 2 diabetic patients are more likely to suffer short and long-term complications, which often lead to their premature death[3].

## Diabetes mellitus: A growing burden

It was estimated that 90% of diabetes patients are diagnosed with type 2 diabetes and the majority of the remaining 10% of patients have type 1 diabetes (T1D)[1].

Diabetes affects more than 537 million individuals across the globe and is one of the leading causes of death worldwide[4]. (Figure 1)

**Globally, the number of people with diabetes was estimated to be 285, 366, 382, 415, and 425** million in the years 2009, 2011, 2013, 2015, and 2017, respectively[1].






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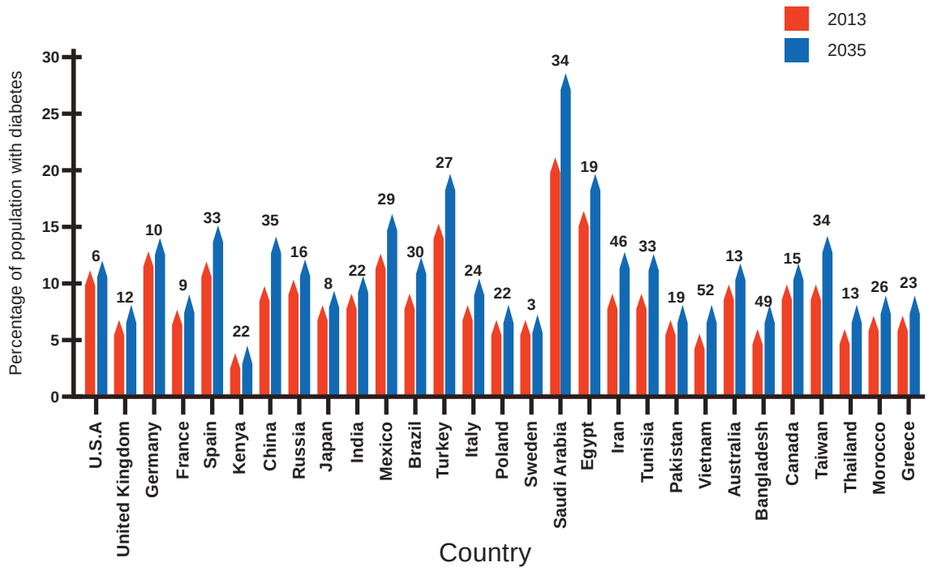
**Figure 1: The varying estimated prevalence of T2D in 2013 and projections for 2035, between ages 20-79 years[1].**




**Indian scenario from International Diabetes Federation (IDF)-2021 10th edition**


In India, the burden of diabetes has been increasing steadily since 1990 and has been increasing at a faster pace from the year 2000[6].
The largest national representative survey on diabetes and prediabetes was undertaken in India by the Indian Council of Medical Research (ICMR), and included data from 15 states/UTs of the country[6]. (Table 1)

**Table 1: Weighted prevalence of diabetes and prediabetes in 15 States/Union territory of India - the ICMR INDIAB study[6].**

| State/UT | Prevalence of diabetes (%) | | | Prevalence of prediabetes (%) | | |
|---|---|---|---|---|---|---|
| | Urban | Rural | Overall | Urban | Rural | Overall |
| Andhra Pradesh | 12.6 | 6.3 | 8.4 | 11.1 | 9.6 | 10.1 |
| Arunachal Pradesh | 5.8 | 4.9 | 5.10 | 14.2 | 12.3 | 12.8 |
| Assam | 12.4 | 4.4 | 5.5 | 13.6 | 11.6 | 11.9 |
| Bihar | 10.5 | 3.5 | 4.3 | 15.5 | 9.3 | 10.0 |
| Chandigarh | 14.2 | 8.3 | 13.6 | 14.5 | 14.7 | 14.6 |
| Gujarat | 9.5 | 5.1 | 7.1 | 8.4 | 11.5 | 10.2 |
| Jharkhand | 13.5 | 3.0 | 5.3 | 10.7 | 7.4 | 8.1 |
| Karnataka | 11.1 | 5.6 | 7.7 | 14.1 | 10.2 | 11.7 |
| Maharashtra | 10.9 | 6.5 | 8.4 | 15.2 | 11.1 | 12.8 |
| Manipur | 7.1 | 4.4 | 5.1 | 7.2 | 7.5 | 7.5 |
| Meghalaya | 8.9 | 3.5 | 4.5 | 7.4 | 10.6 | 10.0 |
| Mizoram | 7.9 | 3.6 | 5.8 | 6.2 | 5.8 | 6.0 |
| Punjab | 12.0 | 8.7 | 10.0 | 8.6 | 7.9 | 8.2 |
| Tamil Nadu | 13.7 | 7.8 | 10.4 | 9.8 | 7.1 | 8.3 |
| Tripura | 15.5 | 7.2 | 9.4 | 16.2 | 14.2 | 14.7 |

**India has the 2nd largest number of people (74.2 million) with diabetes in the world[4]**

**1/4th achieve glycemic targets, and even less achieve blood pressure control targets[4]**

## Pathophysiology of diabetes

T2DM is the most prevalent disease in overweight and obese individuals.The risk factors include lifestyle, genetic makeup, and aging.Insulin resistance and insulin deficiency connect the pathophysiology of obesity and diabetes. Insulin resistance occurs from genetic and environmental factors. T2DM in obese individuals is a result of insulin resistance and then hyperglycemia leading to β-cell death[7].
Obese type 2 diabetic individuals are also characterised by reduced β-cell mass likely due to increased cellular apoptosis[7]. (Figure 2)






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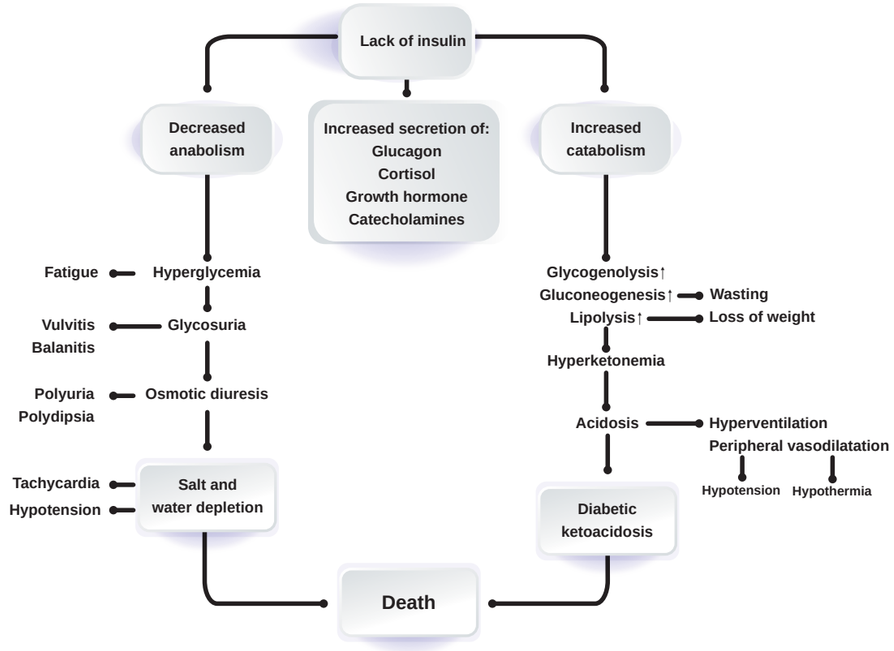
**Figure 2: Pathophysiology of diabetes mellitus[8]**




**The pathophysiological mechanisms include[9]:**

- Reduced insulin secretion from pancreatic β cells
- Increased glucagon secretion from pancreatic α cells
- Increased hepatic glucose production
- Neurotransmitter dysfunction and insulin resistance in the brain
- Increased lipolysis
- Increased renal glucose reabsorption
- Reduced incretin effect in the small intestine
- Reduced glucose uptake in peripheral tissues such as skeletal muscle, liver and adipose tissue

Hyperglycemia alone can impair pancreatic β-cell function and contributes to impaired insulin secretion[10].

A vicious cycle of hyperglycemia leading to an impaired metabolic state[10].

β-cell dysfunction occurs quite early and rapidly in Asian Indians[11].

**Due to the progressive decline in β-cell function, oral anti-diabetic drugs (OADs) can lose efficacy with prolonged use and a progression from monotherapy to combination (dual or triple) therapies may be necessary[11].**

Asian Indian phenotype has been associated with high levels of abdominal fat and insulin resistance even at low levels of body mass index (BMI), which is thought to be a factor for their increased tendency to develop type 2 diabetes[11].

Type 2 diabetes in Asian Indians appears to have a slightly different pathophysiology, with severe insulin deficiency[11].

Asian Indian population with type 2 diabetes are classified into **four phenotype** clusters with important implications for prognosis and management[11].

**CIRDD: Combined Insulin Resistant and Deficient Diabetes**

**IROD: Insulin Resistant Obese Diabetes**

**MARD: Mild Age-Related Diabetes**

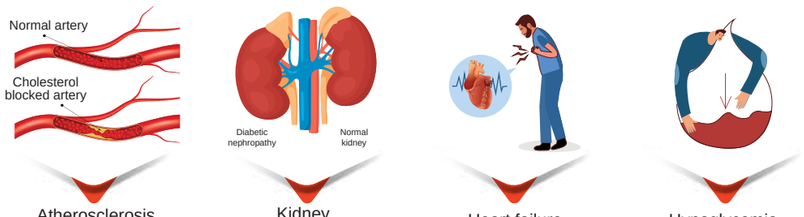
**SIDD: Severe Insulin Deficient Diabetes.**

**Novel subgroups with certain unique phenotypic and biochemical characteristics[11]**

**Persistent suboptimal glycemic control is invariably associated with the onset and progression of acute and chronic diabetic complications in diabetic patients[12].**

## Complications associated with diabetes in Indian population

The complications related to diabetes account for most of the morbidity and mortality associated with this disorder:[13-16]




Atherosclerosis | Kidney (Diabetic nephropathy) | Heart failure | Hypoglycemia





# SUMMARY

Type 2 diabetes mellitus (T2DM) is the most common and clinically significant metabolic disorder. It is progressive in nature and is characterized by the "Ominous octet" of eight factors that contribute to its pathophysiology. It is also associated with higher risk for myocardial infarction, stroke, microvascular events, and mortality.

Most Indian patients have uncontrolled diabetes (69%), as indicated by their inability to achieve the target level of $HbA_1c$. Moreover, the achievement of treatment targets with traditional oral antihyperglycemic agents and the adoption of healthy behaviour remains suboptimal in India. Further, the Asian Indian phenotype has unique characteristics that make it more susceptible to cardiometabolic risk.

Therapy with traditional oral antihyperglycemic agents is associated with a progressive decline in β-cell function. Thus, there is an increased need for compliance and the use of combination therapy to achieve the treatment targets. Further, it is imperative that the newer agents address the maximum number of pathophysiological factors of T2DM.

Dipeptidyl peptidase-4 (DPP-4) inhibitors and selective sodium-glucose cotransporter-2 ($SGLT_2$) inhibitors and Metformin are highly effective in the management of T2DM. The rational fixed dose combination of $SGLT_2$i and DPP4i and Metformin exhibit a synergistic effect resulting in improved glycemic control, reduced insulin resistance, and improved beta cell function. The combination of these drugs addresses 8 out of 8 pathophysiological factors of metabolic derangement. Further, the combination results in improved compliance.

These drugs do not cause hypoglycemia and do not increase weight. More importantly, cardiovascular trials have clearly demonstrated the cardiovascular safety of Metformin and sitagliptin, a reduction in cardiovascular events with dapagliflozin has been well documented as well. Therefore, the association of dapagliflozin, sitagliptin and metformin is an attractive option to achieve optimal blood glucose control in T2DM, considering all these factors.

- Genital Mycotic Infections in Females (e.g., Vulvovaginitis)
  Dapagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat appropriately.

- Hypersensitivity Reactions
  If a hypersensitivity reaction is suspected, discontinue **Istamet D-XR 1000**, assess for other potential causes for the event, and institute alternative treatment for diabetes.

- Pregnancy, Lactation
  Advise pregnant patients of the potential risk to a fetus with treatment with dapagliflozin, sitagliptin and extended release metformin hydrochloride tablets. Instruct patients to immediately inform their physician if pregnant or planning to become pregnant.

- Pancreatitis
  If pancreatitis is suspected, **Istamet D-XR 1000** should promptly be discontinued and appropriate management should be initiated.

## Special populations

- **Elderly:** Because sitagliptin is substantially excreted by the kidney, and because aging can be associated with reduced renal function, renal function should be assessed more frequently in elderly patients.
- **Pediatric use:** Safety and effectiveness of **Istamet D-XR 1000** in pediatric patients under 18 years of age **have not been established.**
- **Hepatic impairment:** Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. **Istamet D-XR 1000** is **not recommended in patients with hepatic impairment.**
- **Renal impairment:** No dose adjustment is needed in patients with an estimated glomerular filtration rate (eGFR) **greater than or equal to 45 ml/min/1.73 m². Istamet D-XR 1000 is not recommended in patients with an eGFR less than 45 ml/min/1.73 m².**

## Drug Interactions

The concomitant use of Istamet D-XR 1000 with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation (e.g., cationic drugs). Therefore, consider more frequent monitoring of patients.





## Diabetic nephropathy[13]

In India, diabetic nephropathy ranged from 0.9% to 62.3%. It is the main cause of end-stage renal disease (ESRD) and it is projected that 20% T2D patients reach ESRD during their lifetime. (Table 2)

Increasing prevalence of diabetes in India and increased burden of undiagnosed diabetes leads to irreversible l**ong-term vascular complications**[12]

**Table 2: Chronic complication of T2DM in India**[12]

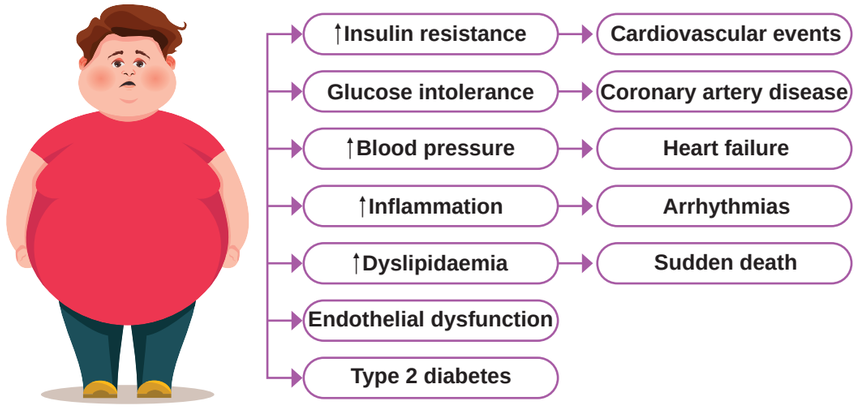
| Type of complication | Study population | Prevalence percentage | Author |
|---|---|---|---|
| Diabetic Retinopathy | 1414 | 4.8% | Raman et al 2012 [50] |
| | 1500 | 5.1% | Sosale et al 2016 [51] |
| | 4600 | 6.1% | Sosale et al 2014 [52] |
| | 306 | 15.36% | Manoj Kumar et al 2016 [53] |
| | 1715 | 17.6% | Pradeepa et al 2008 [54] |
| | 1414 | 18.0% | Raman et al 2009 [55] |
| | 5130 | 21.7% | Salil et al 2016 [56] |
| Diabetic Nephropathy | 1500 | 0.9% | Sosale et al 2016 [51] |
| | 4600 | 1.06% | Sosale et al 2014 [52] |
| | 306 | 5.56% | Manoj Kumar et al 2016 [53] |
| | 390 | 12.1% | Akila et al 2020 [57] |
| | 200 | 13% | Ravindran et al 2020 [58] |
| | 1629 | 26.1% | Pradeepa et al 2008 [59] |
| | 1716 | 26.9% | Unnikrish-n et al 2007 [60] |
| | 365 | 34.4% | Hussain et al 2019 [61] |
| | 6175 | 62.3% | Dash et al 2018 [62] |
| Diabetic Neuropathy | 1414 | 10.5% | Raman et al 2012 [50] |
| | 4600 | 13.15% | Sosale et al 2014 [52] |
| | 1500 | 13.2% | Sosale et al 2016 [51] |
| | 1401 | 18.84% | Rani et al 2010 [63] |
| | 306 | 20.26% | Manoj Kumar et al 2016 [53] |
| | 390 | 44.9% | Akila et al 2020 [57] |

## Hypoglycemia

- In diabetic patients, hypoglycemia is the biggest obstacle to tight glycemic control[14].
- ~96% reported any one symptom of hypoglycemia[14].
- Severe or recurrent hypoglycemic episodes can lead to significant psychosocial dysfunction and lower quality of life[14].
- Diabetes mellitus is 4 times more likely to cause HF in patients (25% of chronic heart failure patients and up to 40% of acute heart failure patients) than in non-diabetics[15].

**Cardiovascular disease is a common cause of death and morbidity in T2DM patients[16].**

**Figure 3: Relationships between high-risk obesity, intermediate cardiometabolic risk factors, and cardiovascular outcomes (obesity phenotypes, diabetes, and cardiovascular diseases)[16].**




**Patients with diabetes are at increased risk for cardiac events due to cardiovascular (CV) risk factors like obesity, hypertension, and dyslipidaemia[17].**





- Patients with a **history of serious hypersensitivity** (such as anaphylactic reactions or angioedema) to the active substances or any of the inactive ingredients in this formulation.
- Patients with **acute or chronic metabolic acidosis**, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

## Special warnings and precautions

- Lactic Acidosis

  If metformin-associated lactic acidosis is suspected, immediately discontinue **Istamet D-XR 1000** and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

  Lactic acidosis prone situations: Renal Impairment, Drug Interactions, Age 65 or Greater, Surgery and Other Procedures, Excessive Alcohol Intake, Hepatic Impairment.

- Ketoacidosis

  If ketoacidosis is suspected, **Istamet D-XR 1000** should be discontinued, the patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement.

- Volume Depletion

  Patients with impaired renal function (eGFR less than 60 mL/min/1.73 $m^2$), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension.

  Before initiating **Istamet D-XR 1000** in patients with one or more of these characteristics, assess volume status and renal function. Monitor for signs and symptoms of hypotension and renal function after initiating therapy.

- Serious Urinary Tract Infections

  Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving $SGLT_2$ inhibitors, including dapagliflozin. Treatment with $SGLT_2$ inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

- Hypoglycemia: FDC is added to an insulin secretagogue (e.g., sulfonylurea) or insulin.

  Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with **Istamet D-XR 1000**.

- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

  Patients treated with **Istamet D-XR 1000** presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue **Istamet D-XR 1000,** closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

# Istamet D XR

*(Dapagliflozin, Sitagliptin and Extended Release Metformin Hydrochloride Tablets)*[70]

**Each Film Coated Tablet of Istamet D XR Contains:**

- Dapagliflozin 10 mg
- Sitagliptin 100 mg
- Metformin 1000 mg ER
- Excipients q.s.

## Therapeutic Indication

Istamet D-XR 1000 is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

## Posology and method of administration

- Prior to initiation of Istamet D-XR 1000 assess renal function and periodically thereafter.
- Assess volume status and, if necessary, correct volume depletion prior to initiation.
- Dosage: Recommended dose of Istamet D-XR 1000 is once daily in the morning with food preferably at same time.
- Swallow Istamet D-XR 1000 tablets whole and never crush, cut, or chew.
- The maximum recommended daily dose is 10 mg dapagliflozin, 100 mg sitagliptin and 2000 mg metformin hydrochloride (extended release).
- If a daily dose is missed and it is greater than or equal to 12 hours until the next dose, the dose should be taken. If a daily dose is missed and it is less than 12 hours until the next dose, the missed dose should be skipped and the next dose taken at the usual time.

## Contraindication

**Istamet D-XR 1000** is contraindicated in:

- Patients with **moderate to severe renal impairment** (eGFR below 45 ml/min/1.73 $m^2$), end stage renal disease or patients on dialysis.

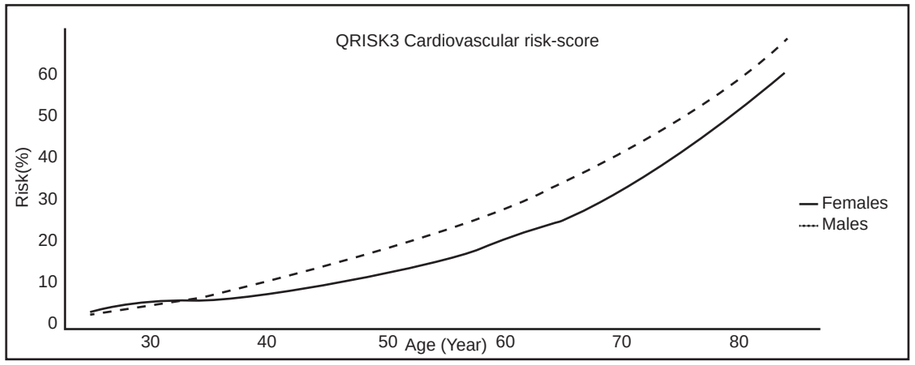




## Cardiovascular disease[18]

- The most common cardiovascular (CV) risk factor was a low HDL (high-density lipoprotein) value, according to the Lipid Association of India (LAI) criteria, with 68% of all subjects appearing to have at least one lipid abnormality.
- Smokers had a 7% higher CV risk than non-smokers and hypertensives almost 5% higher risk than normotensives.
- Most patients with T2DM were at very high risk of fatal CV events and males were at higher risk compared to females. (Figure 4)

**Figure 4: CV risk based on QRISK3 chart related to age and separated for sex[18]**




Atherosclerotic cardiovascular disease remains the principal cause of death and disability among patients with diabetes mellitus, especially in those with type 2 diabetes mellitus in whom it typically occurs 14.6 years earlier, with greater severity, and with more diffuse distribution than in individuals without diabetes mellitus[19].

**Appropriate and intensive management of CV risk factors is important in young people at risk of diabetes as well as in young people recently diagnosed with type 2 diabetes mellitus (T2DM)[18].**

**The Indian Council of Medical Research (ICMR)-India Diabetes (INDIAB) study demonstrates the control of cardiometabolic risk factors among adults with self-reported diabetes[4].**

- Poor achievement of glycemic targets despite widespread use of anti-diabetic drugs suggests a lack of timely escalation of treatment, which could be due to insufficient monitoring and follow-up.
- Number of individuals with diabetes across India have markedly elevated LDL cholesterol and are at high risk for adverse cardiovascular outcomes.
- State-wise assessment revealed that the highest mean $HbA_1c$ levels were found in Punjab, Bihar, Chandigarh, Haryana, and Karnataka.

**Achievement of treatment targets and adoption of healthy behaviours remains suboptimal in India[4]**

**There is an urgent need to improve awareness regarding healthy diet and importance of physical activity among the Indian population[4]**

## Current therapeutic approaches in management of T2DM

The physiology and treatment of diabetes are complex and need multiple interventions for successful disease management as follows[20,21]:
First-line therapy depends on comorbidities, patient-centred therapy factors, as well as management needs and usually includes metformin and comprehensive lifestyle changes[21].

**Non-pharmacological measures: Diet, physical activity, and behavioral therapy**

**Pharmacological measures: Glucose-lowering medications**

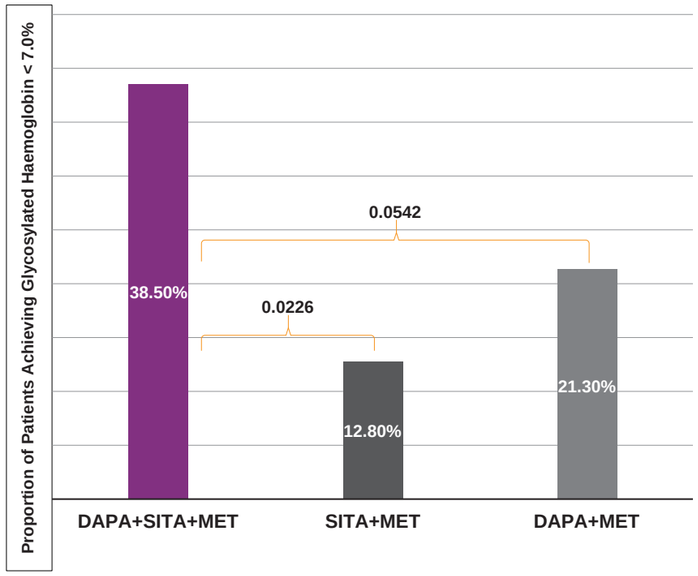




## Guidelines recommendations on combination of $SGLT_2$i and DPP4i FDC

**Various international guidelines recommend the use of combination drug therapy of SGLT-2 inhibitors + DPP-4 enzyme inhibitors in patients with type 2 diabetes mellitus inadequately controlled on metformin:**

- Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes – 2021 by American Diabetes Association.
- Consensus statement by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) on the comprehensive type 2 diabetes management algorithm – 2020.
- Research Society for the Study of Diabetes in India (RSSDI)-ESI clinical practice recommendations for the management of type 2 diabetes mellitus 2020.
- International Diabetes Federation (IDF), Global Guideline for Type 2 Diabetes, 2017.
- Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update; Diabetes Canada Clinical Practice Guidelines Expert Committee.




**Proportion of Patients Achieving Glycosylated Haemoglobin < 7.0% at Week 16**

## Conclusion

FDC of Dapagliflozin 10 mg, Sitagliptin 100 mg and Metformin HCl ER 1000 mg was superior in comparison to both two drug combinations (Sitagliptin phosphate 100 mg and Metformin HCl SR 1000 mg [combi pack] tablets; and FDC of Dapagliflozin 10 mg and Metformin HCl ER 1000 mg tablets) in terms of $HbA_1c$ reduction at Week 16. The study drugs were safe and well tolerated.

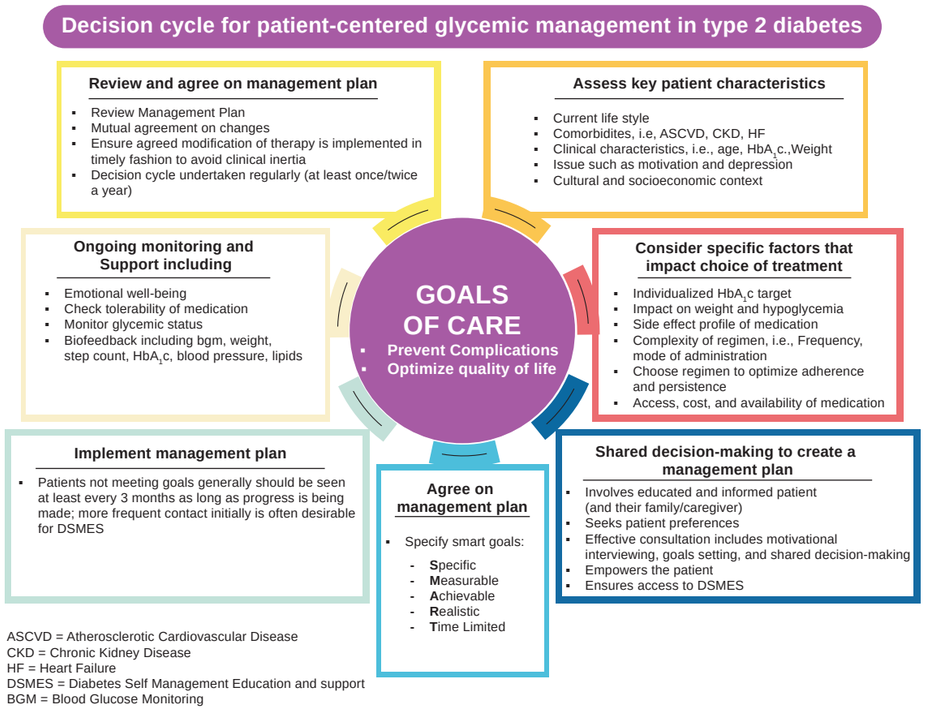




## ADA 2022 guideline recommendation on patient-centered care goals[21]

- In adults with overweight/obesity at high risk of type 2 diabetes, care goals should include
  - Weight loss or prevention of weight gain
  - Minimizing progression of hyperglycemia
  - Attention to CV risk and associated comorbidities
- A successful medical evaluation depends on beneficial interactions between the patient and the care team.
- The use of person-centred, strength-based, empowering language that is respectful and free of stigma in diabetes care and education can help to inform and motivate people.
- The person with diabetes, family or support people, and health care team should together formulate the management plan, which includes lifestyle management, to improve disease outcomes and well-being. (Figure 5)

**Figure 5: Decision cycle for patient-centred glycemic management in type 2 diabetes[21].**



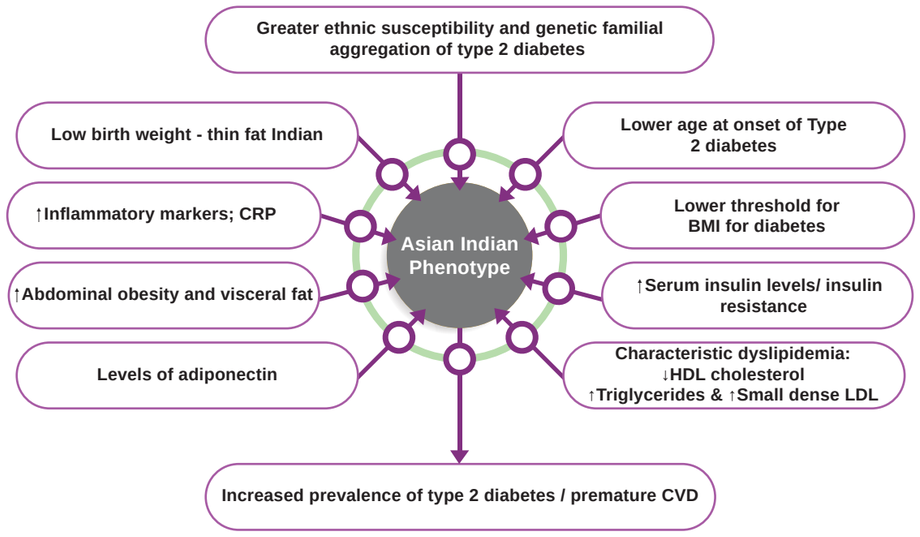

ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self Management Education and support
BGM = Blood Glucose Monitoring

**The goals of treatment for diabetes are to prevent or delay complications and optimize quality of life[21]**

## Challenges in treatment management of T2DM in Indian patients

Challenges in India include variable diet pattern, habits, poor compliance, poor treatment adherence, clinical inertia, and late diagnosis with comorbidities[22].
Asian Indians exhibit a peculiar collection of abnormalities that makes them more prone to diabetes and insulin resistance than Caucasians of similar BMI, due to their excess body fat, visceral fat, and insulin resistance[23]. (Figure 6)

**Figure 6: The Asian Indian phenotype[23]**



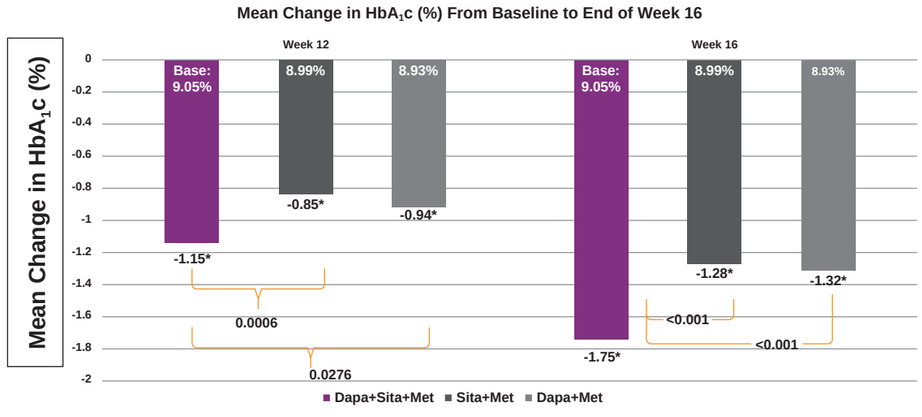

CRP: C-reactive protein; IR: Insulin resistance; CVD: Cardiovascular disease;
BMI: Body mass index





## Findings

- At week-16 mean reduction of $HbA_1c$ was significantly superior in test arm (FDC of Dapagliflozin, Sitagliptin and Metformin HCl ER) when compared to both Sitagliptin Phosphate 100 mg and Metformin HCl SR tablets 1000 mg and Dapagliflozin 10 mg and Metformin HCl ER tablets 1000 mg (-1.75 vs -1.28 vs -1.32, p<0.001, p<0.001 respectively).
- At week-12 mean reduction of $HbA_1c$ was significantly more in test arm (FDC of Dapagliflozin, Sitagliptin and Metformin HCl ER) when compared to both Sitagliptin Phosphate 100 mg and Metformin HCl SR tablets 1000 mg and Dapagliflozin 10 mg and Metformin HCl ER tablets 1000 mg (-1.15 vs -0.85 vs -0.94, p<0.0006, p<0.0276 respectively).
- Proportion of patients achieving $HbA_1c$ <7% at Week 16 was superior in test arm (FDC of Dapagliflozin, Sitagliptin and Metformin HCl ER) when compared to both Sitagliptin Phosphate 100 mg and Metformin HCl SR tablets 1000 mg and Dapagliflozin 10 mg and Metformin HCl ER tablets 1000 mg (38.5% vs 12.8% vs 21.3%, p<0.001, p<0.0023 respectively).
- None of the patient required rescue medications during the study.



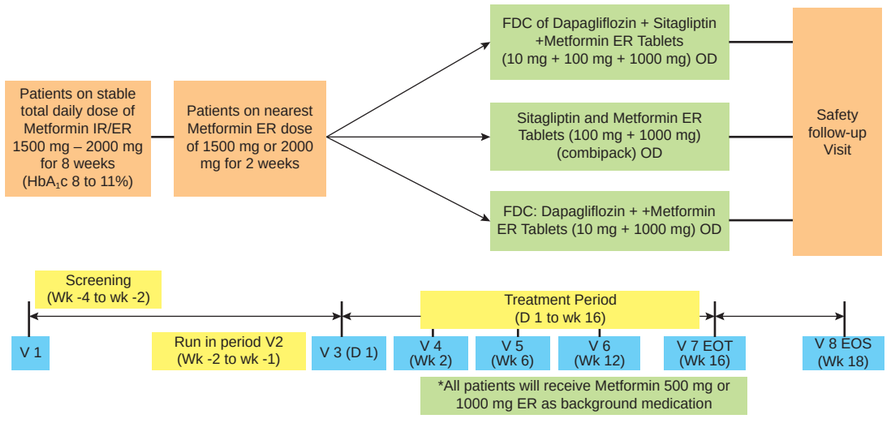
## Clinical evidence on the efficacy and safety of combination (DPP4i + SGLT2i + Metformin) in patients with T2DM – 269

### Study objective

Efficacy, safety and tolerability of FDC of Dapagliflozin, Sitagliptin and Metformin HCl ER tablets (10 mg + 100 mg + 1000 mg) OD in comparison to Co-administration of Sitagliptin Phosphate 100 mg and Metformin HCl SR tablets 1000 mg OD, and FDC of Dapagliflozin 10 mg and Metformin HCl ER tablets 1000 mg OD.

### Study design and methodology

- This was a Phase III, randomized, three arm, multicenter, open label, parallel-group, active controlled comparative study. The study was conducted at total 15 geographically distributed centres in India. The study was initiated only after the receipt of Regulatory and Ethics Committee (EC) approval. Total 471 patients were screened to randomize 415 patients from 15 geographically distributed centres in India.
- After obtaining the informed consent, patients were screened by various assessments as mentioned in Schedule of Assessment. The patients on stable total daily dose of Metformin immediate release IR/ER (1500-2000 mg) for at least 8 weeks and $HbA_1c$ 8 to 11% (both inclusive) at the time of screening had to undergo run-in period for 2 weeks wherein patients received the nearest Metformin ER dose (1500 or 2000 mg/day).
- Patients were provided Metformin ER dose for run-in period as per below figure.

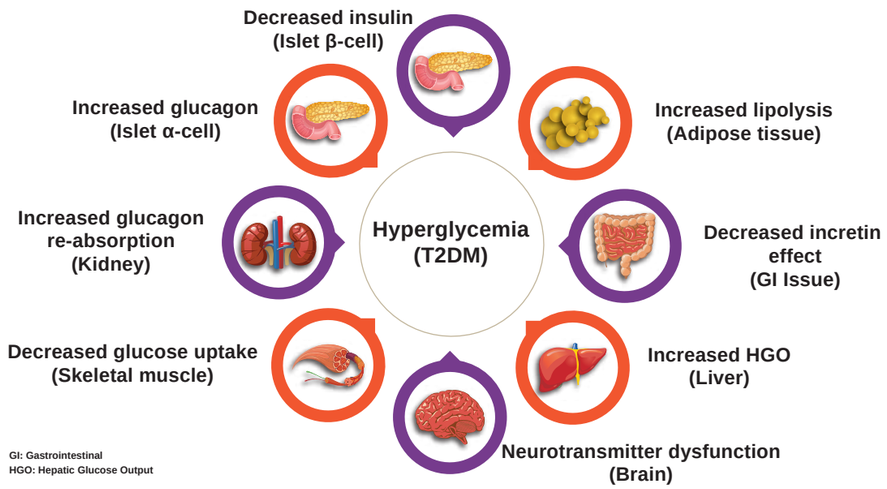







### Metabolic derangements in type 2 diabetes

**Figure 7: Eight metabolic derangements in type 2 diabetes[24]**




GI: Gastrointestinal
HGO: Hepatic Glucose Output

### Unmet needs and scope in management of T2DM

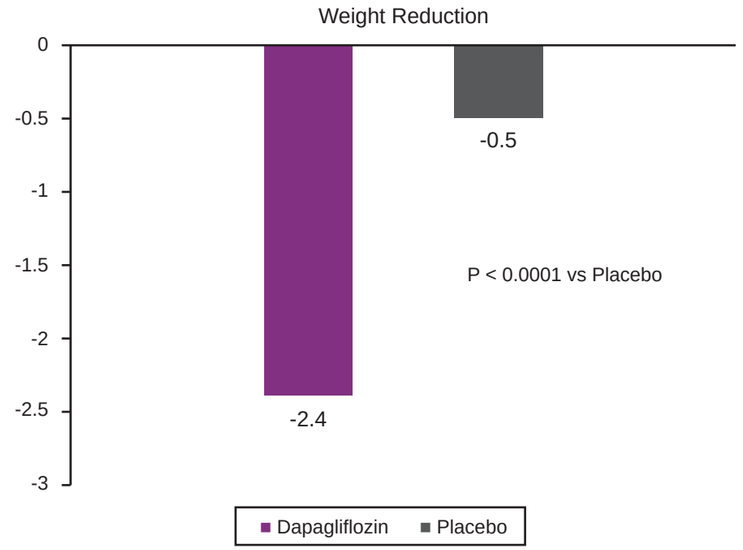
- T2DM remains uncontrolled in 69% of Indian patients[24].
- Patient remains uncontrolled with an average $HbA_1c$ of 9%[23].
- Treatment with traditional oral antihyperglycemic agents necessitates use of insulin for increased blood glucose control[25].
- Further, glucotoxicity and lipotoxicity of these drugs cause malfunction of the pancreatic β-cells due to apoptosis[25].
- Indian patients already have a decline in β-cells and management of DM in such cases with traditional agents (sulfonylureas) eventually leads to uncontrolled DM[26].
- Thus, oral antihyperglycemic agents that can control blood glucose levels by glucose stimulated insulin secretion (GSIS) and preserve the function of pancreatic β-cells are needed[25].
- Multiple pathophysiological mechanisms of hyperglycemia must be addressed in a combination approach to ensure glycemic control[24].
- Need for additional treatments that provide both glycemic and non-glycemic benefits, especially since the control of diabetic comorbidities is less than optimal in most patients[24].

- It is essential to reduce the occurrence of hypoglycemia or weight gain, as recurrent distressing side effects of traditional antidiabetic agents reduces the morale of not only the patient but also the treating physician[24].
- An oral treatment option that not only meets all of the pressing needs but additionally improves the compliance of patients is required[24].

**There is a need for evaluating health outcomes of diabetes medication and delivery systems that can improve adherence and $HbA_1c$ control[27].**







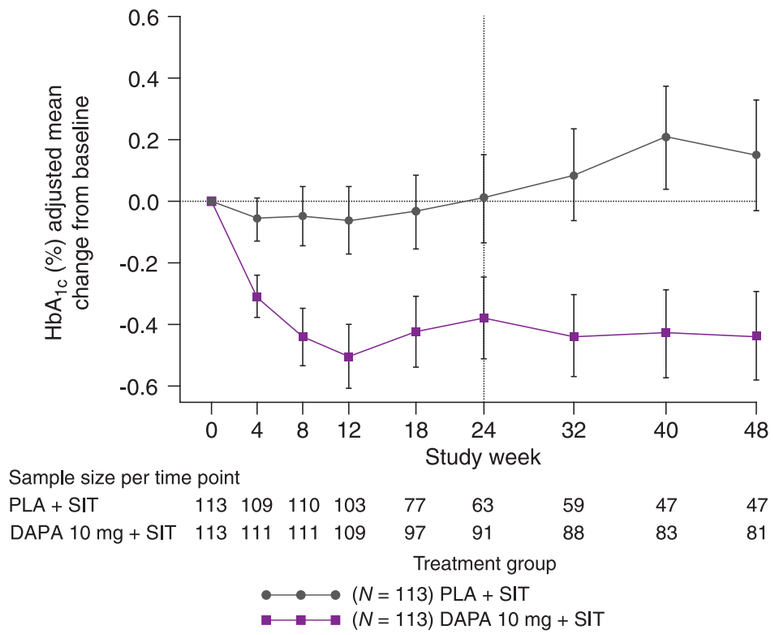

**Weight reduction in Dapagliflozin + Sitagliptin + Metformin subgroup (n=226)**

## Conclusion

Dapagliflozin 10 mg + Sitagliptin 100mg or in triple combination with Sitagliptin plus Metformin – well tolerated and led to clinically meaningful reductions in glycemic parameters & body weight, sustained through 48 weeks of treatment.

## Findings

- A statistically significant reduction from baseline in $HbA_1c$ was observed in the dapagliflozin group compared with placebo at week 24 excluding data after rescue (placebo subtracted, – 0.5% P,0.0001).
- Dapagliflozin also decreased $HbA_1c$ significantly versus placebo when added to sitagliptin plus metformin (stratum 2: placebo subtracted, – 0.4%P, 0.0001).
- Dapagliflozin also reduced $HbA_1c$ level significantly in patients with baseline $HbA_1c$>8% versus placebo when added to sitagliptin plus metformin (stratum 2: placebo subtracted, – 0.8%P, 0.0001).
- Glycemic benefits observed at week 24 were maintained through week 48; across the groups.
- A statistically significant reduction from baseline in body weight was observed in the dapagliflozin group versus placebo when added to sitagliptin plus metformin -2.4kgs P,0.0001).
- Weight benefits observed at week 24 were maintained through week 48; across the groups.




**$HbA_1c$ reduction in Dapagliflozin + Sitagliptin + Metformin subgroup (n=226)**





# $SGLT_2$ Inhibitors

**The role of $SGLT_2$i in treatment of T2DM**

## Introduction

Sodium-glucose cotransporter 2 ($SGLT_2$) inhibitors are a novel class of medications that manage T2DM through urinary excretion of glucose[28].

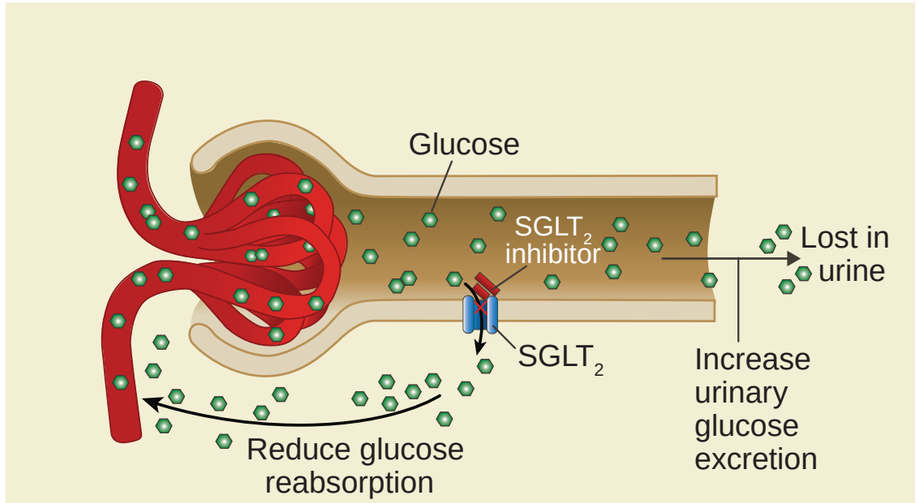
The $SGLT_2$i such as dapagliflozin, canagliflozin, and empagliflozin, represent a class of oral hypoglycemic agents that increase urinary excretion of glucose which results in lower blood glucose levels in an insulin-independent manner, with a lower risk of hypoglycemia, as well as mild diuresis[29].

The potential to reduce risk of cardiovascular death in patients with type 2 diabetes, along with the benefit of weight reduction, makes these agents useful for the primary care provider[28].

## Mechanism of action

Sodium-glucose cotransporter 2 inhibitors are designed to increase urinary excretion of glucose to help manage type 2 diabetes. These drugs provide haemoglobin A1C ($HbA_1c$) reduction, promote weight loss, and remain hypoglycemic-neutral when not used in combination with insulin or insulin secretagogue. Canagliflozin, empagliflozin, and dapagliflozin have shown cardiovascular benefit[28,30]. (Figure 8)

**Figure 8: Mechanism of action of the newest antihyperglycemic class, $SGLT_2$ inhibitors.**




$SGLT_2$: Sodium-glucose cotransporter 2

## A comparative analysis of $SGLT_2$i (Pharmacokinetic and pharmacodynamic differences)

The available $SGLT_2$ inhibitors share similar pharmacokinetic characteristics, with a rapid oral absorption, a long elimination half-life allowing once-daily administration, an extensive hepatic metabolism mainly via glucuronidation to inactive metabolites, the absence of clinically relevant drug-drug interactions, and a low renal elimination as parent drug. $SGLT_2$ co-transporters are responsible for reabsorption of most (90%) of the glucose filtered by the kidneys[30]. (Table 3)





# Clinical evidence on the efficacy and safety

## Clinical evidence on the efficacy and safety of combination (DPP4i + SGLT2i + Metformin) in patients with T2DM – 111

### Study objective

To assess the efficacy and safety of Dapagliflozin as add-on therapy in patients with type 2 diabetes who were inadequately controlled with a dipeptidyl peptidase-4 inhibitor with or without Metformin.

### Study design and methodology

A 24-week, multicentre, randomized, double-blind, placebo-controlled study.

During a 10-week dose-stabilization period, all patients received sitagliptin 100 mg/day (patients initially taking vildagliptin switched to sitagliptin.

↓

A 2-week placebo lead-in period followed, after which patients with a lead-in $HbA_1c$ value >7.0% (53 mmol/mol) and <10.0% (86 mmol/mol) were randomized equally to dapagliflozin 10 mg or placebo for a 24-week double-blind period.

↓

Randomized patients were stratified by concomitant metformin use at baseline.

↓

In stratum 1, study treatment was added to sitagliptin monotherapy;
In stratum 2, study treatment was added to sitagliptin plus metformin IR (>1,500 mg/day, administered BID with meals).

↓

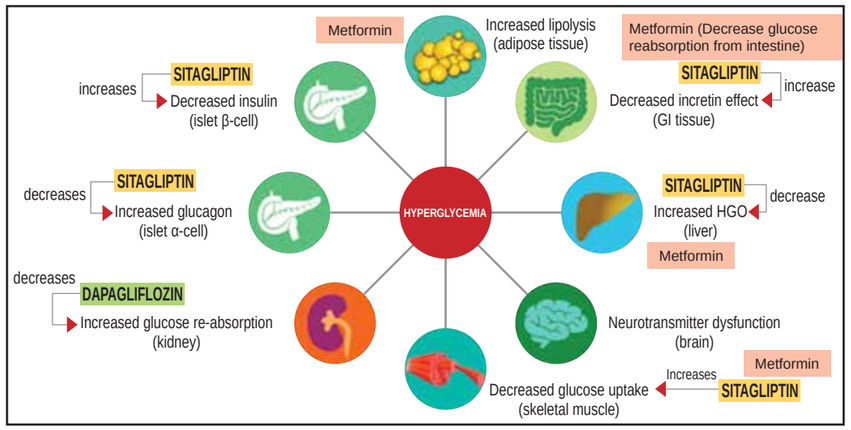
No other OADs were permitted. After completion of the double-blind period, patients could participate in a 24-week, site- and patient-blind extension period.

## A Metformin and incretin-based therapy has following benefits[58]:

- DDP4 inhibitor prolongs the duration of active glucagon-like peptide 1 (GLP-1) by inhibiting DPP4 peptidase, an enzyme which cleaves the active form of the peptide.
- This action results in an improvement of insulin secretion as a physiological response to feeding.
- The mechanism of DPP4 inhibitors is complementary to that of metformin which improves insulin sensitivity and reduces hepatic glucose production, making this combination very useful for achieving adequate glycemic control.
- Metformin has also been found to increase plasma GLP-1 levels, probably by either direct inhibition of DPP4 or by increased secretion, leading to reduced food intake and weight loss.

## Fixed dose combination of $SGLT_2$i, DPP4i and Metformin targeting metabolic derangements

**Figure 25: Illustration of complementary effect of DPP4i and $SGLT_2$i on metabolic derangements in type 2 diabetes mellitus[24].**




**The combination addresses 8 out of 8 metabolic derangements in T2DM patients**





**Table 3: Main pharmacokinetic parameters of the three sodium-glucose co-transporter type 2 inhibitors already commercialised in various countries[30].**

| | Dapagliflozin | Canagliflozin | Empagliflozin |
|---|---|---|---|
| Trade Name | Forxiga® (Europe);Farxiga™ (USA) | Invokana® (Europe and USA) | Jardiance® (Europe and USA) |
| Tablets (mg) | 5, 10 | 100, 300 | 10, 25 |
| Pharmacokinetic parameters | | | |
| Oral bioavailability (%) | 78 | ≈ 65 | >60 |
| Food effect | Not clinically relevant | Not clinically relevant | Not clinically relevant |
| tmax (h) | 1-2 | 1-2 | 1 |
| Volume of distribution (L) | 118 | 119 | 74 |
| Plasma protein binding (%) | 91 | 98 | 86 |
| $t_{1/2}$(h) | 12.2 | 11-13 | 12.4 |
| Metabolism | Extensive glucuronidation to inactive conjugates (primarily dapagliflozin 3-O glucuronide) | Extensively metabolised by O-glucuronidation to two major inactive metabolites (M5 and M7) | Extensively metabolised by glucuronidation and to a lesser extent oxidation to 6 inactive metabolites |
| Elimination | Primarily in urine as inactive metabolites: <2% eliminated as unchanged drug in urine | Elimination in urine and faeces: <1% eliminated as unchanged drug in urine | Eliminated in urine and faeces 28.6 % excreted unchanged in urine |
| Drug interaction | Not clinically relevant | Not clinically relevant | Not clinically relevant |

NA not applicable, $t_{1/2}$ elimination half-life, $t_{max}$, time to maximum (peak) drug concentration

## Dapagliflozin is a highly selective $SGLT_2$ inhibitor due to its high safety and efficacy[30]

### Dapagliflozin: An overview

Dapagliflozin is a highly potent, reversible, and selective sodium-glucose cotransporter-2 inhibitor indicated worldwide for the treatment of type 2 diabetes mellitus (T2DM). Oral dapagliflozin once-daily is approved for use as monotherapy (in patients who are intolerant of metformin) and as add-on combination therapy (with other glucose-lowering agents, including insulin) for T2DM when diet and exercise alone do not provide adequate glycemic control[31].

## Pharmacological properties[31]

- Dapagliflozin is a highly potent (inhibitory constant 0.55 nmol/L) and reversible $SGLT_2$ inhibitor, that is >1400 times more selective for $SGLT_2$ than $SGLT_1$.
- SGLT is the main transporter responsible for glucose absorption in the gut.
- Dapagliflozin increases the amount of glucose excreted in the urine and improves both fasting (FPG) and post-prandial plasma glucose levels in patients with T2D.
- Dapagliflozin-induced glycuresis in patients with T2D was associated with caloric loss and a modest reduction in bodyweight, as well as mild osmotic diuresis and transient natriuresis.
- A modest decrease in blood pressure (BP) was also seen.
- Dapagliflozin is rapidly absorbed after oral administration, with peak plasma concentration usually reaching within 2 hours.
- The mean steady-state volume of distribution of dapagliflozin is 118 L and it is ~91% protein bound.
- Dapagliflozin pharmacokinetics are not affected by food to a clinically meaningful extent.
- Dapagliflozin is largely metabolized by UDP Glucuronosyltransferase Family 1 Member A9 (UGT1A9) to its major inactive metabolite 3-O-glucuronide.
- The metabolites of dapagliflozin do not contribute to its glucose-lowering effects.
- Dapagliflozin and its metabolites are largely excreted in the urine, with 75% in urine and 21% in faeces.
- After single-dose dapagliflozin 10 mg in healthy subjects, the mean plasma terminal elimination half-life of dapagliflozin was 12.9 h.

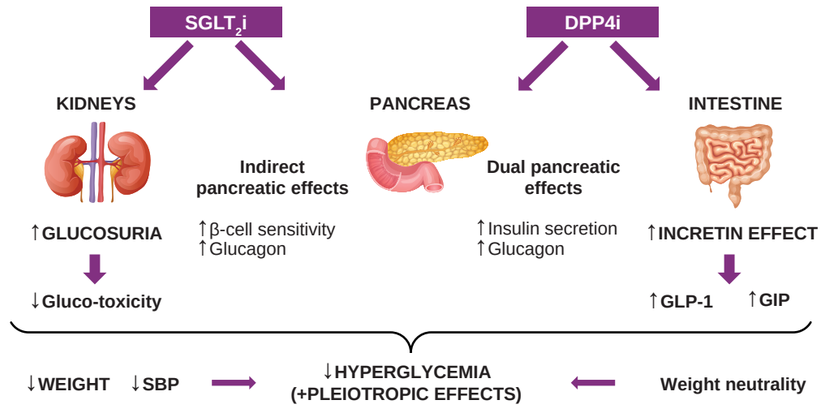
## Clinical benefits of dapagliflozin[31]

- Dapagliflozin lowers glucose levels independently of insulin action.
- It provides effective glycemic control and reduces body-weight and blood pressure.
- A statistically significant reduction from baseline $HbA_1c$ between 0.82% and 0.97% for a 10 mg dapagliflozin dose was seen.
- Dapagliflozin monotherapy was effective to control the level of FPG –1.30mmol/L ( P<.00001).
- Reduces rate of cardiovascular (CV) death or hospitalization in heart failure (HHF), does not adversely affect major adverse CV events (MACE), and reduces progression of renal disease.
- Low risk of hypoglycemia, while genital infections and diabetic ketoacidosis (DKA) are more common compared with placebo.





**Figure 24: Illustration of complementary glucose-lowering activities of DPP4i and $SGLT_2$i in type 2 diabetes mellitus[24].**




GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide-1; SBP: Systolic blood pressure.

### A $SGLT_2$i + DPP4i is a suitable option for T2DM patients for the following reasons[24]:

$SGLT_2$ Inhibitors increase renal excretion of glucose

↓

Decreases Glucotoxicity

↓

Helps reduce body weight and blood pressure (extra glycemic benefits)

↓

**↑The rate of endogenous glucose production (EGP)**

↓

Addition of DPP4i- significantly lowers glucagon

↓

Combination would prevent such increase in EGP, which is triggered by the increase in glucagon

## Advantages of fixed-dose combination[62]

Simpler dosage improves therapy adherence and treatment outcomes

↓

Reduces pill burden

↓

Reduces medication error

↓

Allow drugs with synergistic combination

↓

Reduces frequency of administration

↓

Adherence brings better clinical outcomes, thereby preventing complications and hospitalization

## Rationale on combination of Dapagliflozin + Sitagliptin + Metformin[63,64,65,66]

| Metformin | Dapagliflozin | Sitagliptin |
|---|---|---|
| • First line therapy[1]<br>• Most common drug in FDC with DPP-4i and $SGLT_2i$[1]<br>• Demonstrated efficacy, weight neutrality, safety and cardiovascular benefits[1] | • Insulin independent mechanism[2]<br>• Decreases blood glucose, weight loss with minimal risk of hypoglycemia[2]<br>• Shown benefit in diabetes related heart failure with or without prior ASCVD (DECLARE-TIMI)[2] | • Most extensively studied gliptin<br>• Reduces $HbA_1c$ effectively[3]<br>• Has minimal risk of hypoglycemia[3],<br>• Is weight neutral[3]<br>• Proven cardiovascular safety (TECOS)[4] |

## Complementary mechanism of actions of DPP4i/ $SGLT_2i$/ Metformin

## DPP4i and $SGLT_2i$ in the management of T2DM

The additional glucose-lowering effect appears to be more marked when a gliflozin is added to a gliptin. Combining two pharmacological options is safe and does not induce hypoglycemia[67]. (Figure 24)





## Clinical evidence on safety and efficacy of Dapagliflozin

### Effect of dapagliflozin on CV outcomes DECLARE-TIMI 58

## Study objective[32]

Study by Wiviott MD et al. evaluated the effects of dapagliflozin on CV and renal outcomes in patients who had or were at risk for atherosclerotic CV disease.

## Study design and methodology

- A randomised, double-blind, multinational, placebo-controlled study enrolled 17,160 patients with type 2 diabetes who had or were at risk for atherosclerotic CV disease.
- Patients were assigned to receive either dapagliflozin or placebo.
- The primary efficacy outcomes were MACE and a composite of cardiovascular death or hospitalization for heart failure.
- Secondary efficacy outcomes were a renal composite and death from any cause.

## Findings

In patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease, treatment with dapagliflozin did not result in a higher or lower rate of MACE than placebo but did result in a lower rate of cardiovascular death or hospitalization for heart failure.

## Primary and secondary outcomes

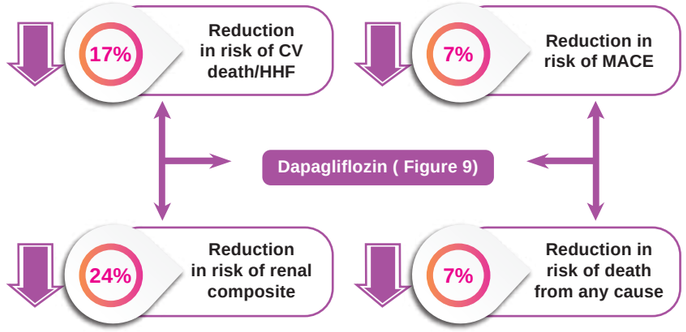
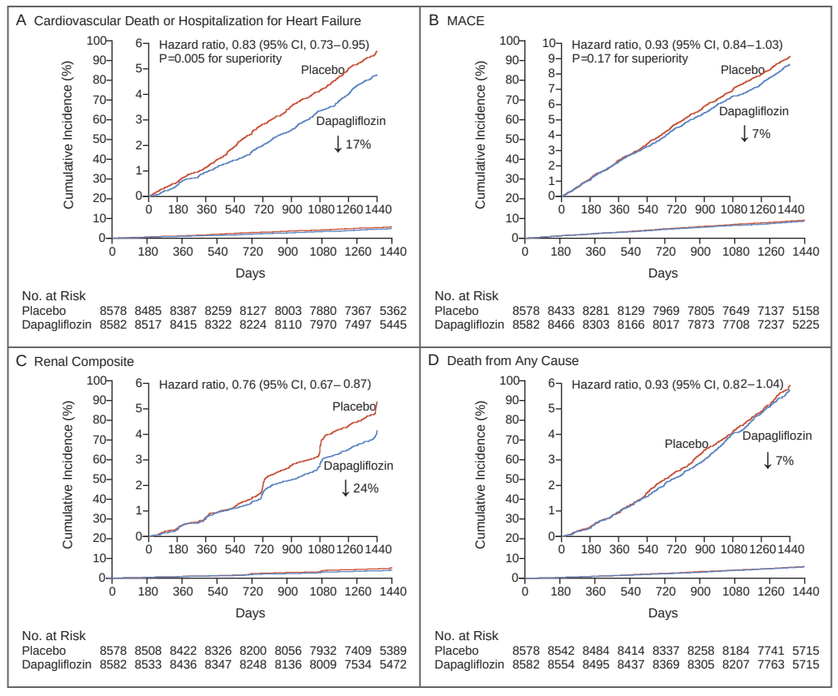



**Figure 9: Major cardiovascular and renal outcomes and death from any cause[32].**




**Dapagliflozin showed significant reduction in CV death/HHF, MACE, renal composite, and death from any cause[32].**





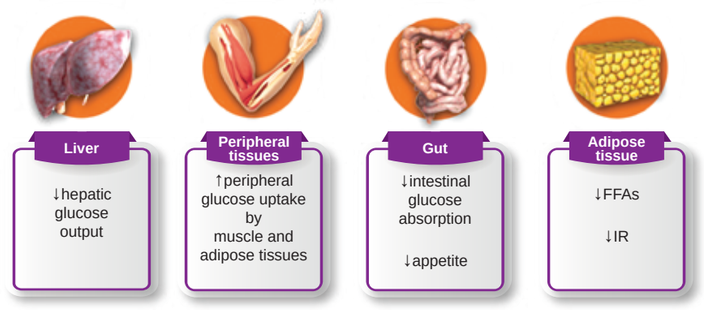
# Need for fixed-dose combination in T2DM management

- An aggressive glycemic control is beneficial not only for short-term, but also for long-term T2DM patients[55] .
- Only 18-22% of patients on dual therapy (DPP4i + Met/$SGLT_2$i + Met) with mean baseline $HbA_1c$ of 8.9% were able to achieve target $HbA_1c$ < 7%[1,2].
- Weight gain and hypoglycemia – adversely affect patient adherence & quality of life – impacting glycemic goals[3].
- High pill burden and complex treatment regimens → ↓ adherence[4] – each 10% increase in OAD medication adherence was associated with a 0.1% $HbA_1c$ reduction (p = 0.0004).
- Progressive loss of β-cell function, necessitate patients requiring multiple OADs with differing MOA to achieve target $HbA_1c$ levels[7].
- FDCs →improve patient compliance, glycemic control[5] and have potential to decrease risk of complications[6].
- To achieve glycemic target without side effects or tolerability issues, it is important to consider certain aspects of drug interactions when two drugs are administered as FDCs[62].

## Important aspects while choosing FDCs in the management of T2DM[62]

- Drug in combination should have different mechanism of actions.
- The pharmacokinetics of drugs must not be too different from each other.
- The combination should not have additive effect that can induce supra-additive toxicity.
- The combination can be chosen based on the recommendation of treatment guidelines IDF 2017, ADA 2020, and RSSDI 2020.

## Metformin: Proposed mechanisms of action




## Clinical benefits of Metformin[58]

## Metformin in the management of adult diabetic patients

- Current guidelines recommend early initiation of metformin as a first-line drug for mono-therapy and combination therapy for patients with T2DM.
- This recommendation is based primarily on metformin's glucose-lowering effects, relative-ly low cost, and generally low level of side effects, including the absence of weight gain[58,59].
- Metformin's first-line position was strengthened by the United Kingdom Prospective Diabetes Study (UKPDS) observation that the metformin-treated group had risk reduc-tions of 32% (p = 0.002) for any diabetes-related endpoint, 42% for diabetes-related death (p = 0.017), and 36% for all-cause mortality (p = 0.011) compared with the control group.
- The UKPDS demonstrated that metformin is as effective as sulfonylurea in controlling blood glucose levels of obese patients with type 2 diabetes mellitus[60].
- Metformin has also shown to be effective in normal weight patients[61].

## Metformin effects on vasculo-protection

| Study | Design | Duration | Key findings |
|---|---|---|---|
| UKPDS 33 [18] | Prospective | 10 yr | Significant reduction in all-cause mortality, diabetes related mortality, and any end-point related to diabetes. |
| Sgambato *et al.* [72] | Retrospective | 3 yr | Trend towards reduction in angina symptoms (p = 0.051). Significant lower re-infarction rates. |
| Johnson *et al.* [24] | Retrospective | 9 yr | Reduction of all-cause mortality and of cardiovascular mortality |
| Kao *et al.* [74] | Prospective | 2 yr | Significant risk reduction for any clinical event, myocardial infarction and all-cause mortality |
| Jadhav *et al.* [76] | Prospective | 8 weeks | Improved maximal ST depression, Duke score, and chest pain incidence |
| Kooy *et al.* [75] | Prospective | 4, 3 yr | Reduction of the risk of developing macrovascular disease |





## DECLARE-TIMI 58 subset based on HF status

### Study objective[33]

DECLARE-TIMI 58 trial by Kato et al., demonstrated the efficacy and safety of dapagliflozin according to baseline HF status and systolic left ventricular ejection fraction (EF).

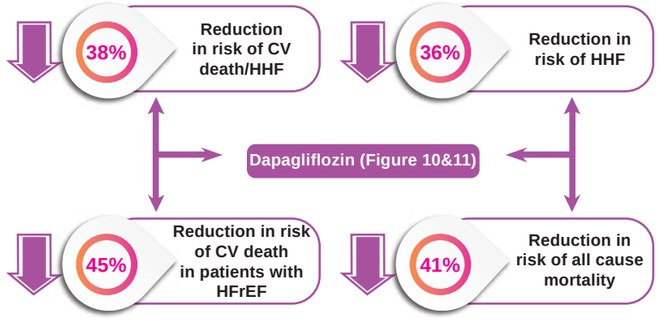
### Study design and methodology

- DECLARE-TIMI 58 was a randomised, double-blind, multinational cardiovascular outcome trial comparing 10 mg dapagliflozin with placebo.
- Study enrolled 17,160 patients with T2DM with either established atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for ASCVD, and with a creatinine clearance ≥60 mL/min.
- Patients were followed up for 4.2 years with regular visits and laboratory testing.

### Primary endpoint

- Composite of cardiovascular death/HHF and its components.
- All-cause mortality.

### Findings




**25%** significant risk reduction in major adverse cardiac events with dapagliflozin compared to placebo.
**35%** significant risk reduction in renal-specific end-point with dapagliflozin compared to placebo.

**Figure 10: Kaplan-Meier curves stratified by different heart failure (HF) categories[33].**

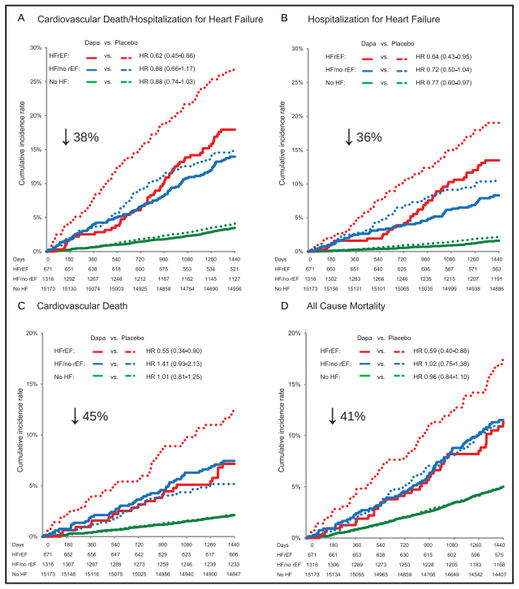
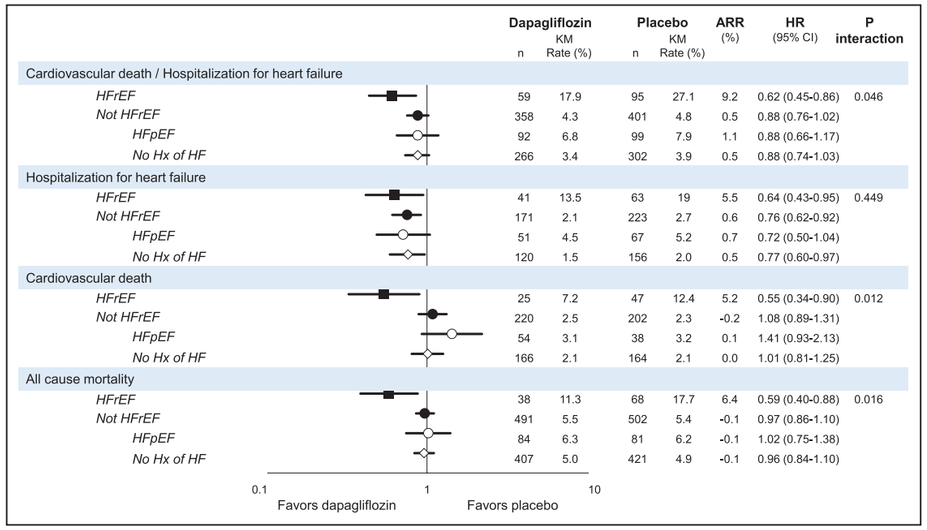



**Figure 11: Cardiovascular outcomes by heart failure (HF) category[33].**




**Dapagliflozin showed significant reduction in CV death/HHF and all-cause mortality in patients with HFrEF[33].**





# An overview on Metformin

## Introduction

- The discovery of metformin began with the synthesis of galegine-like compounds derived from Gallega officinalis, a plant traditionally employed in Europe as a drug for diabetes treatment for centuries[55].
- In 1950, Stern et al. discovered the clinical usefulness of metformin while working in Paris. They observed its glucose lowering capacity and that metformin toxicity also displayed a wide safety margin[55].
- Metformin acts primarily at the liver by reducing glucose output and secondarily, by augmenting glucose uptake in the peripheral tissues, chiefly muscle.
- These effects are mediated by the activation of an upstream kinase, liver kinase B1 (LKB-1), which in turn regulates the downstream kinase adenosine monophosphatase co-activator, transducer of regulated CREB protein 2 (TORC2), resulting in its inactivation which consequently downregulates transcriptional events that promote synthesis of gluconeogenic enzymes[56].
- Inhibition of mitochondrial respiration has also been proposed to contribute to the reduction of gluconeogenesis since it reduces the energy supply required for this process[57].
- Metformin's efficacy, safety profile, cardiovascular and metabolic effects, and its ability to be associated with other antidiabetic agents makes this drug the first glucose lowering agent of choice when treating patients with type 2 diabetes mellitus (T2DM).

## Metformin: Pharmacokinetic properties[55]

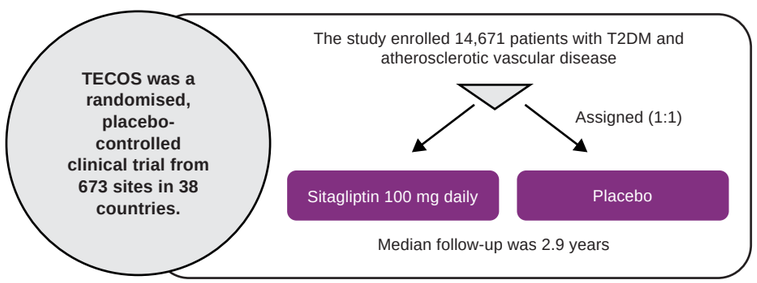
- Oral bioavailability 50-60%.
- Lacks dose proportionality with increasing doses: decreased absorption at higher doses.
- Food decreases extent and slightly delays absorption.
- Poorly protein bound.
- Does not undergo hepatic metabolism.
- Excreted unchanged in urine: 90% of absorbed drug excreted within first 24 hrs.
- Plasma half-life 6.2 hr.

## CV safety with sitagliptin TECOS trial

### Study objective[54]

McGuire DK et al. assessed the association of sitagliptin use with hospitalization for HF (hHF) and related outcomes.

### Study design and methodology




### Findings

Among patients with type 2 diabetes and established cardiovascular disease, adding sitagliptin to usual care did not appear to increase the risk of major adverse cardiovascular events, hospitalization for heart failure, or other adverse events.

**Sitagliptin use in high-risk T2DM patients does not alter hHF risk.**

Sitagliptin treatment for type 2 diabetes is effective and well tolerated.
Sitagliptin offers a novel therapeutic approach for the treatment of type 2 diabetes.

TECOS: Trial evaluating cardiovascular outcomes with sitagliptin; HF: Heart failure; CV: Cardiovascular

**Due to a progressive decline in β-cell function, oral antidiabetic agents lose efficacy with prolonged use and a progression from monotherapy to combination (dual or triple) therapy may be necessary[11].**





## DAPA-HF

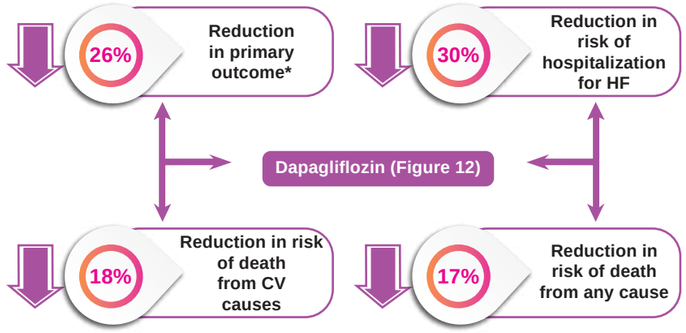
### Study objective[34]

DAPA-HF trial evaluated efficacy and safety of the $SGLT_2$ inhibitor dapagliflozin in patients with heart failure and a reduced ejection fraction regardless of the presence or absence of diabetes.

### Study design and methodology

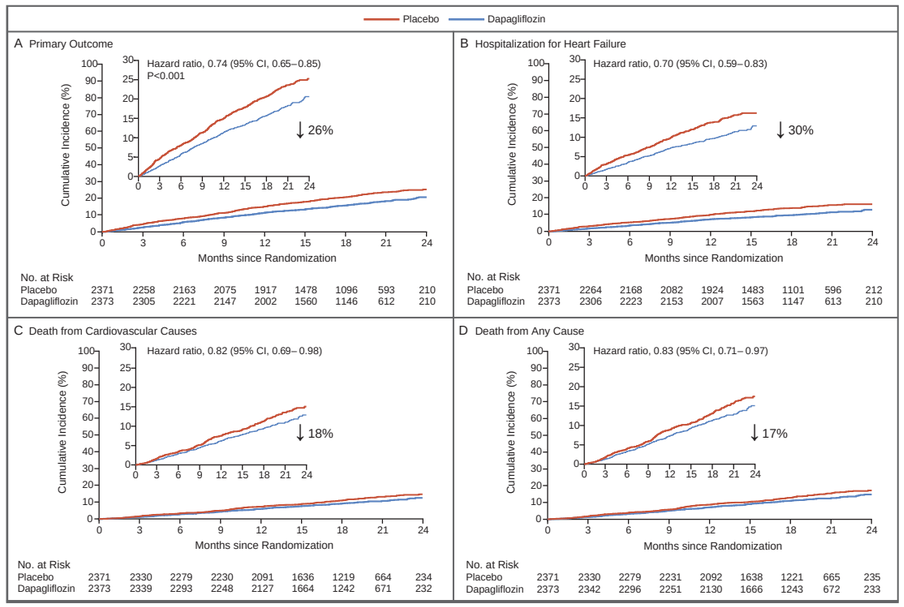
- DAPA-HF trial enrolled 4,744 patients with New York Heart Association (NYHA) class II, III, or IV heart failure and an ejection fraction of 40% or less.
- Patients were assigned to receive either dapagliflozin (at a dose of 10 mg once daily) or placebo, in addition to recommended therapy.
- Primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death.

### Findings




***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.**

**Figure 12: Cardiovascular outcomes[34]**




**Dapagliflozin reduced the risk of worsening heart failure or death from cardiovascular causes compared with placebo, regardless of diabetes status[34].**





## Effect of sitagliptin on body weight

### Study objective[53]

Hussain M et al. evaluated effect of sitagliptin on blood sugar, body weight, blood pressure, and serum lipid profile in type 2 diabetic patients.

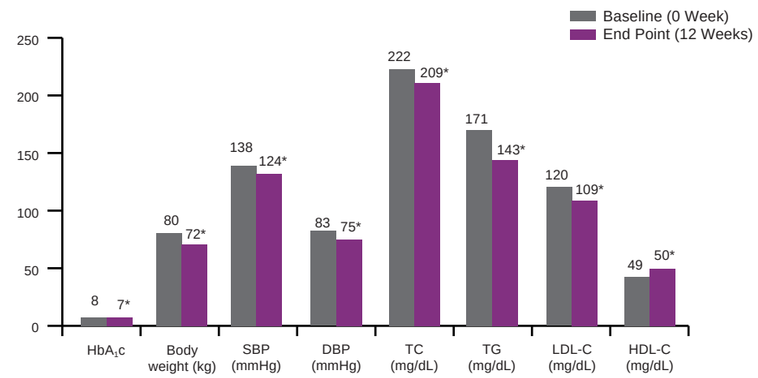
### Study design and methodology

- The 12 weeks, open label, observational study enrolled 78 patients with diabetes and poor glycemic control.
- Patients were assigned to receive sitagliptin 50 mg twice daily for 12 weeks.

### Findings

- Sitagliptin showed significant reduction in body weight from 80.21 kg +/- 7.156 at base-line to 71.74 kg +/- 6.567 at 12 weeks ($p<0.05$). (Figure 24)
- Sitagliptin showed significant reduction in $HbA_1c$ from 8.184% +/- 0.467 at baseline to 7.0200% +/- 0.459 at 12 weeks ($p<0.05$).
- Significant reduction was reported in
  -Blood pressure at 12 weeks (Figure 24)
  -Serum level of cholesterol

**Figure 24: Clinical and biochemical parameters of patients[53]**




*p<0.05. $HbA_1c$: Haemoglobin $A_1c$; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TC: Total cholesterol; TG: Triglycerides; LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol

**Use of sitagliptin improves not only blood glucose control, but also weight, blood pressure, and lipid profile in type 2 diabetic hyperlipidaemia patients[53]**

**Table 5: Summary of clinical adverse events (AEs)[52].**

| | Placebo (n = 178) | Sitagliptin (n = 352) |
|---|---|---|
| **Number (%) of patients with one or more** | | |
| Clinical AE | 27 (15.2%) | 82 (23.3%) |
| Drug-related clinical AE | 3 (1.7%) | 10 (2.8%) |
| Serious clinical AE | 2 (1.1%) | 6 (1.7%) |
| Serious, drug-related clinical AE | 1 (0.6%) | 1 (0.3%) |
| **Number (%) of patients who** | | |
| Discontinued due to an AE | 2 (1.1%) | 5 (1.4%) |
| Discontinued due to a drug-related AE | 1 (0.6%) | 2 (0.6%) |
| Discontinued due to a serious AE | 2 (1.1%) | 3 (0.9%) |
| Discontinued due to a serious, drug-related AE | 1 (0.6%) | 1 (0.3%) |
| Died | 0 | 1 (0.3%) |
| **Number (%) of patients who had** | | |
| Hypoglycemia | 0 | 0 |
| Any gastrointestinal AE | 1 (0.6%) | 18 (5.1%) |
| **Prespecified selected gastrointestinal AEs** | | |
| Abdominal pain | 0 | 3 (0.9%) |
| Nausea | 0 | 0 |
| Vomiting | 0 | 0 |
| Diarrhoea | 0 | 0 |

**Sitagliptin 100 mg once daily was associated with low gastrointestinal adverse events and no reported hypoglycemic events[52]**





## Effect of dapagliflozin in renal outcome DAPA - CKD

### Study objective[35]

Study by Heerspink HJ et al. assessed the long-term efficacy and safety of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes.

### Study design and methodology

- A randomised, double-blind, placebo-controlled, multicentre clinical trial enrolled 4,304 patients with estimated glomerular filtration rate (eGFR) of 25 to 75 ml/min/1.73 $m^2$ and urinary albumin-to-creatinine ratio of 200-5000 mg.
- Patients were assigned to receive dapagliflozin 10 mg once-daily and follow-up visit at 2 weeks, 2, 4, and 8 months.

### Primary endpoint

- Composite of a sustained decline in the estimated GFR of at least 50%.
- End-stage kidney disease.
- Death from renal or cardiovascular causes.

### Findings

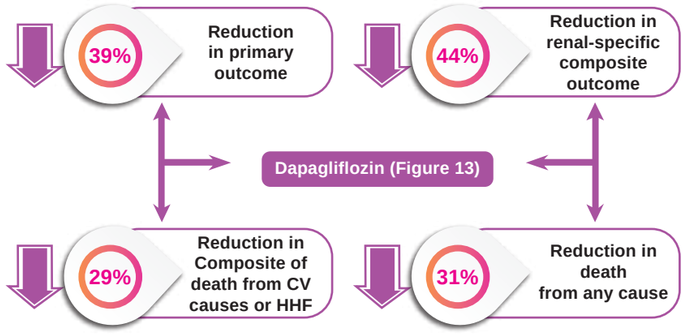
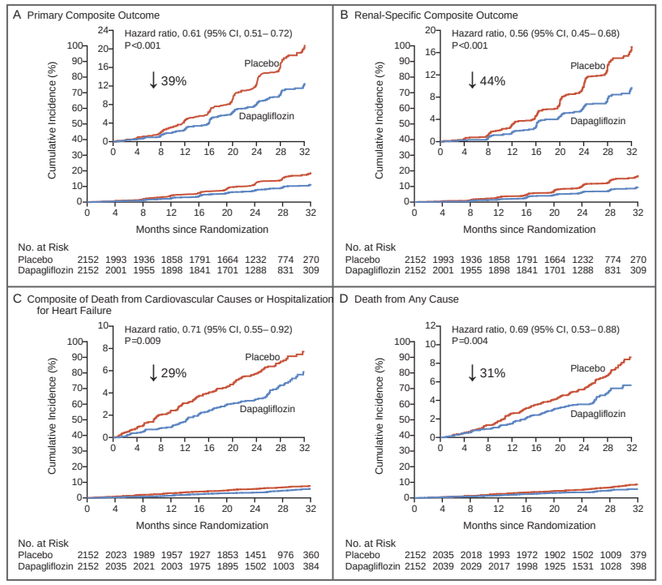


**Figure 13: Primary and secondary outcomes[35].**




**Composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin in patients with diabetes and CKD[35].**





## Hypoglycemia in Type 2 diabetes treated with Sitagliptin monotherapy

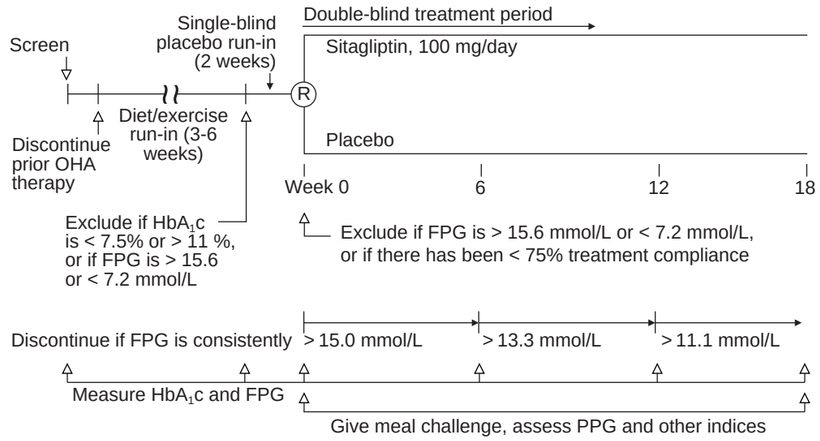
### Study objective[52]

The study by Mohan V et al. evaluated the efficacy and safety of sitagliptin monotherapy in patients with type 2 diabetes inadequately controlled on diet and exercise.

### Study design and methodology

- A randomised, placebo-controlled, double-blind, 18-week trial, enrolled 530 patients with $HbA_1c$ ≥7.5% and ≤11.0% (mean baseline 8.7%).
- Patients were assigned to receive sitagliptin 100 mg once daily or placebo. (Figure 23)

**Figure 23: Study design[52]**




FPG: Fasting plasma glucose; PPG: Post prandial glucose; $HbA_1c$: Glycated haemoglobin; OHA: oral hypoglycemic agents

### Findings

- No hypoglycemic events were reported in patients receiving sitagliptin 100 mg. (Table 5)
- Sitagliptin significantly ($p < 0.001$) reduced mean $HbA_1c$ (-1.0%), fasting plasma glucose (-1.7 mmol/L), and 2-h postprandial glucose (-3.1 mmol/L).

## Effect of sitagliptin in renal outcome

### Study objective[51]

The study by Mori H et al. aimed to determine effect of sitagliptin on microalbuminuria in patients with type 2 diabetes mellitus.

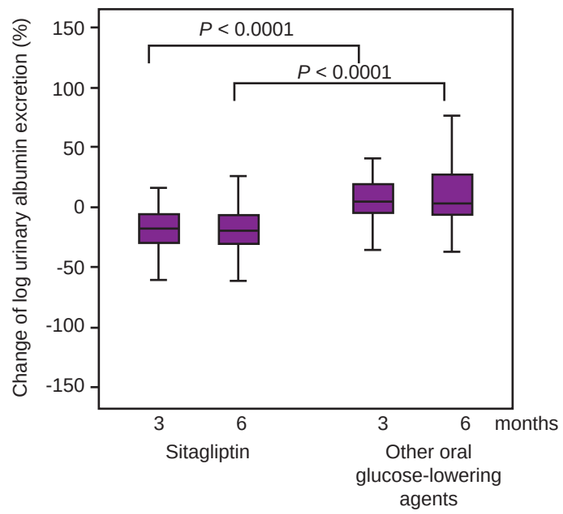
### Study design and methodology

- The study enrolled 85 patients with type 2 diabetes and were randomised to sitagliptin 50 mg or other oral glucose-lowering agents.
- The primary outcome was changes in urinary albumin excretion at 6 months.

### Findings

- Significant and comparable reduction in $HbA_1c$ and fasting plasma glucose were found in both groups.
- Sitagliptin significantly reduced urinary albumin excretion within 6 months, especially in patients with high urinary albumin at baseline. (Figure 22)

**Figure 22: Mean percentage change in log urinary albumin excretion[51].**




**The study concluded that sitagliptin improved albuminuria, in addition to improving glucose level in patients with T2DM[51]**





## Effect of dapagliflozin in elderly patients

### Study objective[36]

The study by Cahn A et al. evaluated the efficacy and safety of dapagliflozin in the elderly (age ≥65 years) and very elderly (age ≥75 years).

### Study design and methodology

- The study enrolled 17,160 patients, including (n=6,811) ≥65 years age and (n=1,096) ≥75 years age, with T2DM and established atherosclerotic cardiovascular disease or risk factors.
- Patients were randomly assigned to receive dapagliflozin or placebo in addition to standard of care and followed for a median period of 4.2 years.
- Age-related treatment effects and age-based treatment interactions were studied within age subgroups.

### Findings

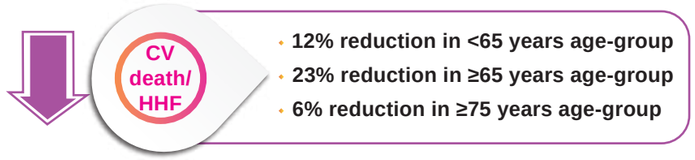



**Figure14: Efficacy outcomes by age-groups[36].**

| | Dapagliflozin | | Placebo | | | | |
|---|---|---|---|---|---|---|---|
| CVD / HHF | n/N (%) | Rates per 1000 person-years | n/N (%) | Rates per 1000 person-years | Hazard ratio (95% CI) | p value | p interaction |
| <65 years | 189/4631 (4.1%) | 10.2 | 211/4622 (4.6%) | 11.6 | 0.88 (0.72, 1.07) | | |
| 65-<75 years | 176/3413 (5.2%) | 12.8 | 225/3398 (6.6%) | 16.7 | 0.77 (0.63, 0.94) | | |
| ≥ 75 years | 52/538 (9.7%) | 25.2 | 60/558 (10.8%) | 28.2 | 0.94 (0.65, 1.36) | | |

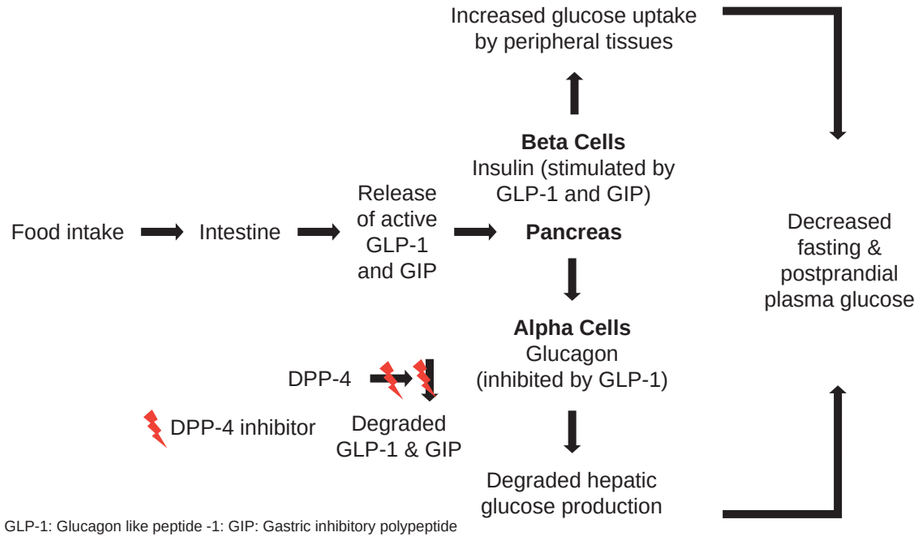
**The study concluded that dapagliflozin was equally effective and safe in patients of all ages[36]**

# An overview on DPP-4 inhibitors

## Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors are oral agents which can be used safely in elderly patients. The drugs are highly effective for the treatment of T2DM in the elderly, as they control basal and postprandial hyperglycemia, and are easy to tolerate, with low risk of hypoglycemia, and without significant drug interactions, or weight gain[29]. (Figure 15)

**Figure 15: Physiology of the post-prandial regulation of glucose homoeostasis by the incretin system and the action of DPP-4 inhibitors[39].**




GLP-1: Glucagon like peptide -1: GIP: Gastric inhibitory polypeptide

Sitagliptin was the first agent introduced in 2006. The most widely used substances are sitagliptin, linagliptin, vildagliptin, saxagliptin, and alogliptin[39]. Anagliptin, gemigliptin, teneligliptin, and evogliptin are used in Asian countries[39,40]. DPP-4 inhibitors are implemented into the treatment algorithms of type 2 diabetes mellitus in many national and international guidelines[39]. (Figure 16)





## Effect of sitagliptin in elderly population

### Study objective[50]

The study by Hsieh C et al. demonstrated the durability of sitagliptin and evaluated changes in clinical chronic complications following 48 months of monotherapy with sitagliptin in elderly diabetic patients with type 2 diabetes (T2DM).

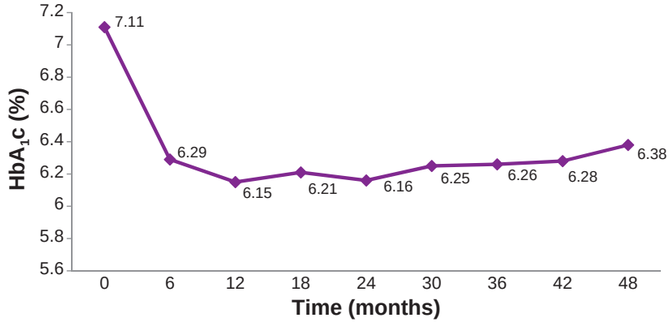
### Study design and methodology

- The study enrolled 76 drug-naive patients (40 women and 36 men) with T2DM who received 25-100 mg of sitagliptin therapy.
- The fasting plasma glucose and glycated haemoglobin (HbA1c) was measured every 3-6 months.

### Findings

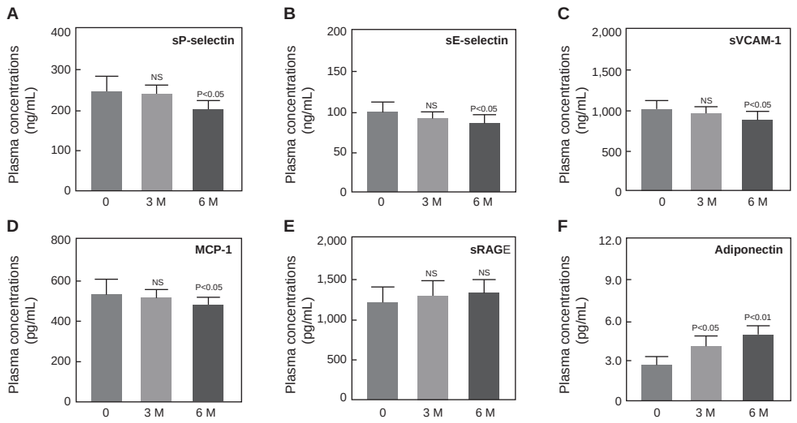
- The $HbA_1c$ level was significantly reduced after 6 months of therapy (7.1% +/- 0.8% to 6.3% +/- 0.2%). (Figure 21)
- No significant changes were reported in FPG, creatinine, serum total cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, body mass index, and microvascular complications.

**Figure 21: Change in the $HbA_1c$ levels from baseline at 6-month intervals[50]**




**Sitagliptin has a durable effect and stabilizes microvascular complication progression in elderly patients[50]**

**Figure 20: Plasma concentrations of sP-selectin (A), sE-selectin (B), sVCAM-1(C), MCP-1(D), sRAGE (E), and adiponectin (F) before and after sitagliptin treatment in diabetic patients.**

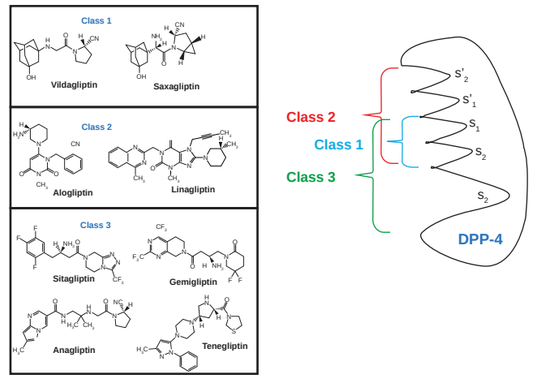



**In type 2 diabetics, sitagliptin has an adiponectin-dependent anti-atherothrombotic effect that may be beneficial for primary prevention of atherothrombosis[49].**





**Figure 16: Classes of DPP-4 inhibitors with the various commonly used DPP-4 inhibitors (left side) and the binding domains of the various classes to specific areas of the DPP-4 molecule (right side) according to Tomovic et al. and Nabeno et al[39].**




The various DPP-4 inhibitors do not form a homogenous class of molecules, and they show different interactions with the active site of the enzyme molecule[39].

## DPP-4 inhibitors and their clinical characteristics[39]

The DPP-4 inhibitors available demonstrate a high efficacy in inhibiting DPP-4, and under clinical conditions DPP-4 is inhibited by >80-90%. GLP-1 plasma concentrations are induced postprandial by this inhibition and glucose-dependent insulin secretion is stimulated and glucagon secretion is inhibited. The DPP-4 inhibitors have good bioavailability and their pharmacodynamics and pharmacokinetics are suitable for clinically sufficient DPP-4 inhibition by once-daily administration. DPP-4 inhibitors are capable of lowering $HbA_1c$ by ~0.5% - 1%. The reduction in $HbA_1c$ relative to placebo was greater in the Indian subpopulations because the mean $HbA_1c$ increased from baseline in placebo-treated patients in India. Compared with placebo, the LS-mean (95% CI) reductions in $HbA_1c$ with sitagliptin treatment were -1.4% (-1.7% to -1.0%) in India. The most important and common indication for DPP-4 inhibitors is their add-on use in patients who are not sufficiently controlled on metformin monotherapy. Fixed dose combinations of DPP-4 inhibitors with metformin are available and may safely be used in patients on this treatment combination. DPP-4 inhibitors can be administered in patients with impaired kidney function due to the good safety and tolerability.

## Pharmacokinetic and pharmacodynamic properties of DPP-4 inhibitors

Dipeptidyl peptidase-4 inhibitor (DPP-4i) represent a heterogeneous class of small molecules with differences in chemistry, in pharmacokinetic characteristics as absorption, distribution, metabolism, and excretion routes and in pharmacodynamic characteristics as potency and selectivity of DPP-4 inhibition[41]. (Table 4)

**Table 4: Main pharmacokinetic and pharmacodynamic properties of DPP-4 inhibitors[41]**

| | Sitagliptin | Vildagliptin | Saxagliptin | Alogliptin | Linagliptin |
|---|---|---|---|---|---|
| Daily recommended dose | 100 mg | 100 mg | 5 mg | 25 mg | 5 mg |
| **Pharmacokinetic properties** | | | | | |
| Oral bioavailability | 87% | 85% | 75% | 70% | 30% |
| Volume distribution | 198 l | 71 l | 151 l | 300 l | 368-918 l |
| Fraction bound to proteins | 38% | 9.3% | < 10% | 20% | 70% |
| Half-life ($T_{1/2}$) | 8-14 h | 2-3 h | 2.2-3.8 h | 12.4-21.4 h | 120-184 h |
| Kidney excretion | 87% | 85% | 75% | 76% | 5% |
| Liver excretion | 13% | 4.5% | 22% | 13% | 85% |
| Proportion excreted unchanged | 79% | 23% | 24% | 95% | ~90% |
| Substrate for CYP3A4/5 | Low | No | Yes | No | No |
| Active metabolites | ND | No | Yes | ND | ND |
| Inactive metabolites | ND | Yes | No | ND | ND |
| **Pharmacodynamic properties** | | | | | |
| In vitro DPP -4 inhibition ($IC_{50}$) | 19 nM | 62 nM | 50 nM | 24 nM | 1 nM |
| Selectivity for DPP-4 versus DPP-8/DPP-9 | > 2,600 | < 100 | < 100 | > 14,000 | > 10,000 |

- Sitagliptin has a higher selectivity for DPP-4 than for the other enzymes of the same family (e.g., FAP, DPP-8, and DPP-9).
- The oral bioavailability of sitagliptin is the highest among all the gliptins.
- Sitagliptin is a "competitive enzyme inhibitor" which inhibits the enzyme in a dose dependent manner and has immediate dissociation.





## Effect of sitagliptin in atherosclerosis

Atherosclerosis associated with diabetes may be caused by hypercoagulability, hyperaggregability of platelets, as well as an increase in platelet-activation markers[49].

### Study objective[49]

Study by Omoto S et al. assessed the effects of sitagliptin on the circulating levels of soluble receptor for advanced glycation end products (sRAGEs), monocyte chemoattractant protein-1 (MCP-1), selectins, and adiponectin in patients with type 2 diabetes.

### Study design and methodology

- The study enrolled 72 non-diabetic and 113 diabetic patients and were assigned for sitagliptin monotherapy if their diet/exercise therapy had continued unchanged for 3 months.
- Levels of soluble P-selectin (sP-selectin), soluble E-selectin (sE-selectin), soluble vascular cell adhesion molecule-1 (sVCAM-1), MCP-1, sRAGEs, and adiponectin were assessed after 3 and 6 months of treatment.

### Findings

- Sitagliptin therapy at 3 and 6 months significantly reduced plasma levels of sP-selectin, sE-selectin, sVCAM-1, and MCP-1 relative to baseline, while significantly increasing adiponectin levels. (Figure 20)
- Reductions in sP-selectin, sE-selectin, sVCAM-1, and MCP-1 during sitagliptin therapy were significantly greater in responders, defined as patients with a significant increase in adiponectin levels, than in non-responders.
- Responders showed a significant increase in the plasma concentration of sRAGEs.

- Significant reduction in fasting plasma glucose (FPG) with sitagliptin compared to placebo (MD = 1.20, 95% CI 1.03 to 1.38). (Figure 18)
- Sitagliptin significantly improved the homeostasis model assessment of β-cell (HOMA-β index) (MD = -10.84, 95% CI -14.07 to -7.80) compared to placebo. (Figure 19)
- No significant difference was observed between the sitagliptin and active treatments in incidence of hypoglycemia adverse experiences (Relative risk [RR]= 0.38, 95% CI 0.14 to 1.08) or serious adverse experiences (RR = 1.15, 95% CI 0.83 to 1.65).

**Figure 18: Mean difference in change in fasting plasma glucose (mmol/L) for sitagliptin vs. placebo in adults with type 2 diabetes[48].**

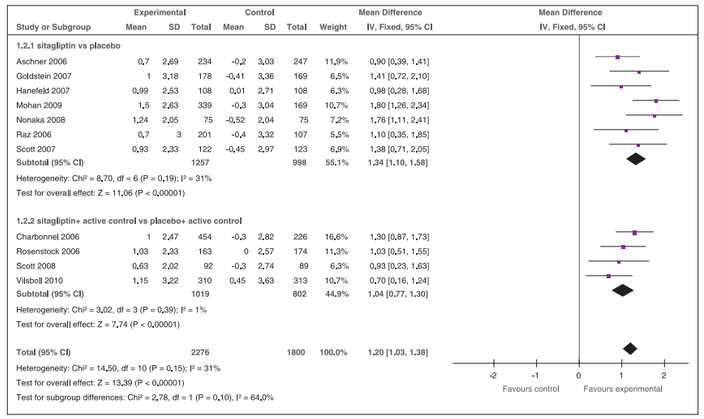
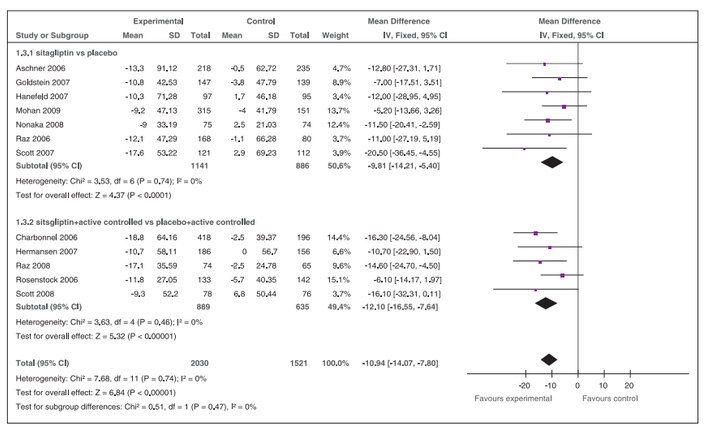



**Figure 19: Mean difference in change in HOMA-β for sitagliptin vs. placebo in adults with type 2 diabetes[48].**








# Sitagliptin: A comprehensive overview

## Introduction[42]

The DPP4-inhibitor sitagliptin has been approved in more than 130 countries globally as monotherapy and in combination with other anti-hyperglycemic drugs for the treatment of adult patients with T2DM.
Extensive clinical experience over the last 10 years in clinical trials as well as real-world settings has firmly established the glycemic efficacy of oral sitagliptin.

## Pharmacodynamic properties[41]

Sitagliptin exhibits potent, highly selective inhibition of DPP-4 with inhibitory concentration ($IC_{50}$) values for DPP-8 and DPP-9 >2600-fold greater.
A single dose or multiple doses of sitagliptin 50-600 mg/day significantly decreased the activity of DPP-4 and increased GLP-1 and gastric inhibitory polypeptide (GIP) levels post-prandial, for both patients with T2DM and non-diabetic obese individuals.

## Pharmacokinetic properties[41]

- Oral sitagliptin is rapidly absorbed after a single 100 mg dose, with peak plasma concentrations attained 1-4 h post-dose. The area under the plasma concentration-time curve (AUC) from time zero to infinity increased in a dose-proportional manner with single doses of sitagliptin 25-400 mg. The absolute bioavailability of sitagliptin is 87% and its oral absorption is not affected by food. ~80% of an administered dose is eliminated as unchanged drug in the urine.
- In vitro studies indicate that CYP3A4 and, to a lesser extent, CYP2C8 are involved in the limited hepatic metabolism of sitagliptin. The apparent terminal elimination half-life of sitagliptin is 12.4 h and renal clearance is ~350 mL/min.
- Dosage adjustments are required in patients with moderate and severe renal impairment since plasma AUC levels increased approximately 2 to 4-folds. However, no dosage adjustments are required in patients with mild renal impairment.
- Sitagliptin is a p-glycoprotein substrate, but does not inhibit p-glycoprotein mediated transport of digoxin and is considered unlikely to cause interactions with other drugs that utilize these pathways. Sitagliptin is not associated with clinically meaningful changes in the pharmacokinetic properties of metformin, sulfonylureas, simvastatin, warfarin, or oral contraceptives. Similarly, coadministration of metformin or ciclosporin with sitagliptin did not markedly alter the pharmacokinetics of sitagliptin.

**The therapeutic benefit of sitagliptin as monotherapy or as a combination shows significant improvement in achieving glycemic control[43]**

## Clinical benefits of sitagliptin

The clinical benefits of sitagliptin are as follows:

Convenient once-daily regimen and low potential for drug-drug interactions[28]

Improves glycemic control as monotherapy or combination with antihyperglycemic drugs[28]

Does not increase or reduce the rate of 4-point MACE and 3-point MACE outcomes after a median of 3 years follow-up[28]

Generally well tolerated, with low risk of hypoglycemia[28]

Neutral effects on bodyweight[28]

No dose adjustment is required on the basis of age, gender, race or body mass index[28]

No dosage adjustments are necessary in patients with mild renal impairment[28]

Reduces proteinuria, ameliorates renal function, and produces anti-inflammatory effect in early-stage diabetic nephropathy[30]

Improves serum gamma-glutamyl transpeptidase in non-alcoholic fatty liver disease (NAFLD)[31]

Shows pleotropic impacts towards cardiovasculars system either with or without diabetes[32]





## Clinical evidence on safety and efficacy of sitagliptin

### Effect of sitagliptin in glycemic control

#### Study objective[48]

The study aimed to evaluate the benefits of sitagliptin in patients with T2DM.

#### Study design

Meta-analysis of randomised clinical trials (18 trials) evaluating efficacy of sitagliptin therapy in management of type 2 diabetes mellitus.

#### Findings of the study

**Significant reduction in $HbA_1c$ with sitagliptin as compared to placebo (MD = 0.74, 95% CI 0.63to 0.85) (Figure 17)**

**Figure 17: Mean difference in change in haemoglobin A1C($HbA_1c$) percentage value for sitagliptin vs. placebo in adults with type 2 diabetes[48].**