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Review Article

Maximizing treatment benefits in type 2 diabetes by affordable oral anti diabetes agents in India

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ABSTRACT

Diabetes mellitus (DM) is a global epidemic with number of cases rising exponentially with each decade. What makes it more concerning is its association with numerous complications like cardiovascular diseases, end-stage renal disease, neuropathy, and retinopathy. In India, the management of this disease mainly involves out-of-pocket expense and contributes to catastrophic health expenditure and distress financing. Thus, the need of the hour is to make oral anti diabetes agents (OADs) affordable and accessible so that maximum number of patients can avail treatment benefits in diabetes care. This review article focuses on the currently available low cost OADs such as sulfonylureas, metformin, thiazolidinediones, alpha glucosidase inhibitors, dipeptidyl-peptidase 4 (DPP4) inhibitors and sodium-glucose co-transporter-2 (SGLT2) inhibitors explaining their efficacy and safety from recent clinical evidence and those going off patent and becoming much affordable in their generic form. This information will help family physicians make rational choices for their type 2 DM (T2DM) patients.

Keywords: Diabetes mellitus, Oral anti diabetes agents, Efficacy, Safety, Affordable therapy

INTRODUCTION

Diabetes mellitus (DM) is a global epidemic which affected an estimated 463 million persons worldwide in 2019; and is projected to reach 578 million by 2030 and 700 million by 2040.[1] The increasing prevalence of DM is attributed to a variety of factors, including the rise in the aging population, ethnicity, change in lifestyle, obesity, socioeconomic status, and urbanization.[2] The increasing prevalence in DM is associated with a significant increase in complications like cardiovascular diseases, end-stage renal disease, neuropathy, and retinopathy.[3] Notable points regarding health economics of diabetes in India are private healthcare are the predominant provider of diabetes care with government setups providing only around 20% of care, expenditure done on diabetes care is largely out-of-pocket expense and contributes to catastrophic health expenditure in 45% of patients, 23% meet this expenditure by borrowing from banks and money lenders, also known as distress financing.[4] The need of the hour is affordable, accessible, available and appropriate oral anti diabetes agents (OADs) which helps to maximize the treatment benefits in diabetes care. This review article discusses on the currently available, cost effective affordable oral anti diabetes agents in the current era.

Overview of mechanism of actions of the affordable OADs

Figure 1 explains the pathophysiologic abnormalities in type 2 diabetes mellitus (T2DM) and various sites of action of different affordable OADs.

Role of metformin in management of hyperglycemia and beyond

Metformin is the most common prescribed OAD in the world and shall continue to maintain its position despite of recent introduction of several new classes of oral agents for T2DM management. Metformin is effective as monotherapy and, in combination with both insulin secretagogues (sulfonylureas) and thiazolidinediones (TZDs) and may obviate the need for insulin treatment. Several fixed-dose combination pills containing metformin and other agents are available. Metformin remains a safe and effective agent for the therapy of patients with type 2 DM. It is still in most circumstances the agent of choice for first line initial therapy of the typical obese patient with T2DM and mild to moderate hyperglycemia. Reduction in mortality in people with diabetes and COVID-19 among metformin users compared to non-users are well documented.[5]

Metformin use significantly reduced mortality in women with obesity or T2DM in observational study from individuals hospitalized with COVID-19. This sex-specific finding is probably due to metformin reducing tumour necrosis factor alpha (TNF-alpha) in females over males. Metformin benefits in COVID-19 might be through TNF-alpha effects.[6] Metformin use was associated with nearly 70% reduction in mortality in people with diabetes and COVID-19. It may provide a protective approach in this high-risk population.[7] The various benefits of metformin therapy have been summarized in Table 1.

Sulfonylureas

Sulfonylureas (SUs) has been used consistently for the past six decades for T2DM treatment, having stood the test of time, considered as contemporary classic in diabetes management. There are three generations of SU. Glimepiride and gliclazide MR are usually called as modern SUs. Modern SUs differs from other conventional SUs in several aspects. It is associated with a greater efficacy, lower risk of hypoglycemia, less weight gain, good cardiovascular safety profile, pleiotropic benefits and offers optimal glycemic control in a cost-effective manner.[8] Table 2 shows classification of SUs based on the generation, as conventional and modern based on hierarchy of development, and lastly, based on duration of action (short, intermediate and long-acting).

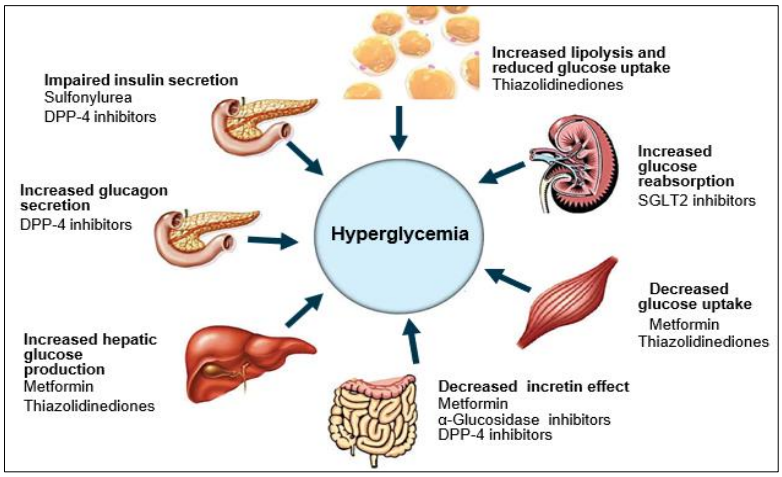

Figure 1: Causes of hyperglycemia in type 2 diabetes mellitus and drugs used for its management.

DPP4 - Dipeptidyl peptidase-4; SGLT2 -Sodium-glucose co-transporter-2.

Table 1: Benefits of metformin.[5-7]

Parameters	Benefit
Glucose	Improved glycemic control (FPG 50-70 mg%, HbA1c 1.5-2%)
Lipids	Reduced triglycerides, reduced total cholesterol, reduced LDL cholesterol, increased HDL cholesterol
Weight loss, no hypoglycemia	Weight reduction, low incidence of hypoglycemia or reduced serum insulin
Blood pressure	Blood pressure reduction
Atherostatic	Increased fibrinolytic activity (reduced PAI-1 levels), reduced platelet aggregation, reduced fibrinogen levels
Endothelial modulator	Improved vascular relaxation, reduced C-reactive protein
Ovulation GDM, pregnancy	Increased ovulation in PCOS, reduced gestational DM in PCOS, reduced first trimester pregnancy loss in PCOS
COVID-19	Reduction in mortality in people with diabetes and COVID-19

FPG-Fasting plasma glucose; HbA1c-glycated hemoglobin, LDL-low density lipoproteins, HDL-high density lipoproteins, PAI-1-plasminogen activator inhibitor-1, PCOS-polycystic ovary syndrome.

Table 2: Classification of SUs.[8-10]

Classification	Molecules
Classification based on generation	
First-generation	Tolbutamide, chlorpropamide
Second-generation	Glipizide, glibenclamide, gliclazide
Third generation	Glimepiride
Classification based on hierarchy of development	
Conventional	Tolbutamide, glibenclamide
Modern	Glimepiride, gliclazide MR, glipizide MR
Classification based on mechanism of action	
Short-acting	Tolbutamide
Intermediate-acting	Glipizide, gliclazide
Long acting	Glibenclamide,glimepiride, glipizide MR, gliclazide MR

Monotherapy with modern SUs

A study evaluated the efficacy and safety of once daily administration of glimepiride in doses of 1 mg, 4mg and 8 mg in people with type 2 diabetes mellitus. At the end of the study there was 1.2%, 1.8% and 1.9% more reduction in HbA1c levels in the glimepiride 1 mg, 4 mg and 8 mg groups respectively, compared to placebo.[11] In a systematic review and meta‑analysis, SU monotherapy was found to lower glycated hemoglobin (HbA1c) by 1.51% more than placebo.[12] Another meta‑analysis of randomized clinical trials validated the comparing the efficacy of metformin and glimepiride monotherapy, reported that glimepiride was as effective as metformin in achieving glycemic control.[13]

Early combination therapy with modern SUs and metformin

Modern SUs and metformin have a complimentary mechanism of action. Metformin with its insulin‑sensitizing property facilitates insulin uptake by the peripheral tissues and enhances the glucose utilization in adipose and intestinal tissues. Modern SUs increase insulin secreting capacity of β-cells. Both together may reduce hepatic glucose overproduction.[14]

In a randomized, open-label, parallel group, multicenter trial, a fixed dose combination (FDC) of glimepiride plus metformin therapy provided significantly greater reduction in A1C (−1.2 versus −0.8%, p<0.0001) and fasting plasma glucose (FPG) (−35.7 versus −18.6 mg/dl, p<0.0001) compared with metformin up-titration. Furthermore, a significantly greater proportion of patients with FDC glimepiride and metformin achieved A1C <7% (74.7 versus 46.6%, p<0.0001) at the end of the study.[15]

Safety profile of modern sulfonylureas

Although modern SUs are well tolerated there is always a query among the scientific community on its safety profile in terms of beta cell dysfunction, hypoglycemia, weight gain and cardiovascular safety.[16]

Evidence suggests that β-cell de-differentiation, rather than cell death, is responsible for β-cell failure in T2DM. Cellular differentiation, is not a unidirectional process. In some instances, differentiation is disrupted, and beta cells revert to a less-differentiated or precursor-like state. The mechanisms which are implicated in β-cell dedifferentiation include oxidative stress, hypoxia inflammation and endoplasmic reticulum stress. In dedifferentiation, β-cells do not die; rather, they undergo metabolic and structural reconfiguration, which ultimately leads to defective insulin secretion.[17] SUs has been wrongly assumed to cause beta cell death in people with T2DM and this has been clearly explained by the findings from various long-term studies like action in diabetes and vascular disease: preterax and diamicron modified release controlled evaluation (ADVANCE) trial and its ability to protect against autophagy-associated β-cell death. A recent study that evaluated the effects of exenatide, sitagliptin, and glimepiride on β-cell secretory capacity in early T2DM, indicated that it was glimepiride but not exenatide or sitagliptin, that enhanced β-cell secretory capacity.[18] With the available scientific evidence it is clear that SUs are not harmful to β-cell mass or function. when used early during T2DM the modern SUs appears to improve β-cell secretory capacity.[17,18]

Hypoglycemia is one of the important clinical concerns associated with the use of SUs. It is more common with old generation SUs such as glibenclamide than the modern SUs. The GUIDE study conducted to evaluate the efficacy and safety of two modern SUs (gliclazide and glimepiride), reported hypoglycemia in 66% and 69% of patients treated with gliclazide and glimepiride respectively. Further, there were no episodes of hypoglycemia that required external assistance or nocturnal symptomatic episodes, indicating the safety of modern SUs.[19] The strategic timing of antiretroviral treatment (START) study also reported a comparable incidence of hypoglycemia in patients treated with glimepiride and sitagliptin.[20] Another meta-analysis reported lower rates of severe hypoglycemia with gliclazide compared to other antidiabetic drugs.[21]

In the management of T2DM, treatment with SUs has been always linked to weight gain. It is important to note that treatment of T2DM with several other medications including thiazolidinediones and insulin are also associated with weight gain. Weight gain associated with SUs may not be bad, in fact it could be considered as an indicator for reduction in glucotoxicity. Weight gain with sulfonylureas could be attributed to enhanced utilization of ingested glucose and subsequent lowering in glycosuria.[22] There are multiple clinical evidence available now to explain that the modern SUs have a weight neutral profile. Once daily administration of glimepiride was associated with weight neutralizing/reducing effect over a period of 1.5 years.[23] In recent CAROLINA trial, after an initial weight gain, there was a decrease in weight in people receiving glimepiride.[24]

Modern SUs (glimepiride and gliclazide MR) are associated with a lower risk of all- cause and CV-related mortality compared to conventional SUs in T2DM patients.[25] The results of the recent CAROLINA demonstrated no difference in the composite of time to cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke between the linagliptin and glimepiride groups.[24,26] In a study of gliclazide MR, of 4.3 years follow‑up with people with diabetes co‑treated with perindopril-indapamide combination, was associated with 15% reduction in major macro- and micro-vascular events , 28% reduction in risk of all renal events and 18% reduction in all-cause death.[27] In a meta-analysis of 47 randomized controlled trials (RCTs) involving 37,650 type 2 diabetes mellitus patients of 52-week duration, the association between modern SUs and all-cause and cardiovascular mortality (CV) was assessed. The analysis revealed that Modern SUs are not associated with an increased risk of myocardial infarction, all-cause and cardiovascular mortality.[28] Figure 2 explains the various pleiotropic benefits of modern SUs.

Thiazolidinediones

Thiazolidinediones (TZDs) are the only OAD agents that function predominantly as insulin sensitizers in peripheral and hepatic tissues by binding to and activating nuclear peroxisome proliferator-activated receptor γ (PPARγ) expressed in those tissues. In India, pioglitazone is used at 15-30 mg/day mostly with metformin and sulfonylureas. Pioglitazone comes with a great efficacy parameter. TZDs have been constantly under the authority scrutiny for their cardiovascular safety. PROactive study, pioglitazone lowered the composite of all-cause mortality, non-fatal myocardial infarction, and stroke in T2DM patients with at risk of macrovascular events along with improvements in HbA1c, triglycerides, LDL, and HDL levels.[29] Pioglitazone had been linked with a possible increased risk of bladder cancer, possibly in a dose-and time-dependent manner.[30] However data from a retrospective study in India involving T2DM patients found no evidence of bladder cancer in any of the group, including patients with age >60 years, duration of diabetes >10 years, and uncontrolled diabetes.[31] Beneficial effects and possible risks have been enlisted in Table 3.

Alpha glucosidase inhibitors

These agents delay the absorption of consumed carbohydrates by competitively inhibiting the α-glucosidase enzymes at the enterocyte brush border. This inhibition delays the digestion of starch and sucrose and maintains levels of postprandial blood glucose excursions. In India, acarbose and voglibose are the most used drugs in this class. The action of these agents is independent of insulin action and hence are devoid of hypoglycemic adverse effects. They are used ideally used to target the post prandial hyperglycemia. In India, this class of drug is usually used either as combination with Metformin or combination with metformin and sulfonylureas.[33] Table 4 enlists efficacy and safety studies of metformin, glimepiride and voglibose combination either as FDC or as triple therapy.

DPP4 inhibitors

DPP4 inhibitors enhance circulating concentrations of active GLP-1 and gastric intestinal polypeptide (GIP). These incretins stimulate insulin secretion, suppresses glucagon synthesis, lower hepatic gluconeogenesis, and slow gastric emptying. Their major effect is the regulation of insulin and glucagon secretion; they are weight neutral.[35] Teneligliptin is the first of its kind low-cost gliptin approved in India, which made gliptin therapy available for everyone. Teneligliptin is effective as single dose of 20 mg and shown renal safety, recent studies TREAT-INDIA 1 and TREAT-INDIA 2 both have established cardiovascular safety.[36-38] Recently the patent expiry of vildagliptin had seen multiple generic versions with affordable cost of therapy and is available as single or as FDC with metformin.[39] Sitagliptin is in line for patent expiry and likely to have generic versions available in upcoming years. DPP-4 inhibitors are efficient in improving glycaemia both as monotherapy and as add-on to metformin, sulfonylurea and TZDs in patients with inadequate glycemic control.[40] Table 5 provides a list of recent trials with teneligliptin.

SGLT2 inhibitors

They provide insulin-independent glucose-lowering by blocking glucose reabsorption in the proximal renal tubule. The capacity of tubular cells to reabsorb glucose is reduced by SGLT2 inhibitors leading to increased urinary glucose excretion and consequently, correction of the hyperglycemia.[42] Remogliflozin is the recently approved SGLT2 inhibitor in India which comes with an affordable cost of therapy. The antidiabetic agent was shown to be effective, safe, and well-tolerated in a pivotal study.[43] Remogliflozin demonstrated non-inferiority to existing SGLT2 inhibitor, namely dapagliflozin. The drug demonstrated comparable results in glycemic, non-glycemic, and safety parameters as compared to

dapagliflozin.[43,44] Another well-known drug in this class is dapagliflozin, recent developments of expiry of the patency of dapagliflozin there are multiple generic brands are to be available in affordable cost in upcoming days. The most common AEs involving this class of OADs are genital mycotic infections and euglycemic ketosis in wrongly selected patient (type 1 diabetes, LADA).[45] To summarize, Table 6 provides an overview of the efficacy, CV safety and side effects of various classes of OADs.

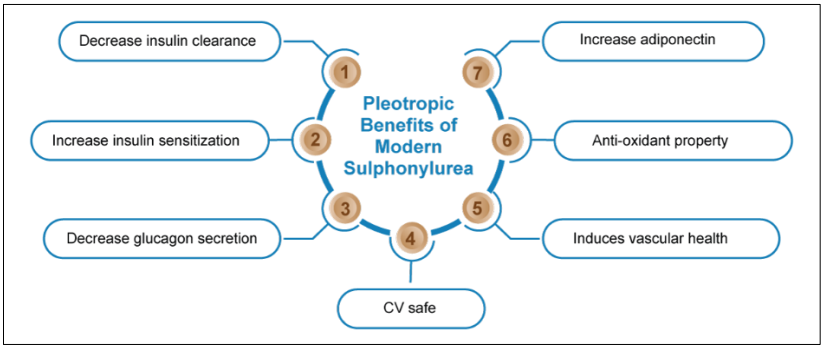

Figure 2: Pleiotropic benefits of modern sulfonylureas.[8]

Table 3: Benefits and risks associated with pioglitazone therapy.[32]

Benefit	Risk
Potent, durable HbA1c reduction	Fat weight gain – but decreases visceral, hepatic and muscle fat content
Low risk of hypoglycaemia	Fluid retention/heart failure
Improves insulin resistance	Bone fractures (distal long bones, trauma related)
Improves beta-cell function	Bladder cancer (not established)
Prevents IGT progression to T2DM	
Improves cardiovascular risk factors (↑HDL, ↓triglyceride, ↓blood pressure, ↓inflammation)	
Reduces microalbuminuria	
Decreases cardiovascular events in high-risk diabetic patients (PROactive, IRIS, meta- analysis)	
Reduces cardiovascular events in diabetic patients with chronic kidney disease	
Improves endothelial dysfunction	
Improves NASH/NAFLD	

IGT: impaired glucose tolerance; T2DM: type 2 diabetes mellitus; HDL: high-density lipoprotein; NASH/NAFLD: nonalcoholic steatohepatitis/nonalcoholic fatty liver disease

Table 4: Efficacy and safety studies of metformin, glimepiride and voglibose combination either as FDC or as triple therapy.[34]

Author	Drug dosage	Efficacy and safety results
Hari et al	Metformin 500 mg (SR#) + glimepiride 1/2 mg + voglibose 0.2 mg OD. (FDC)	Significant reduction in FPG (181±10.2 mg/dl to 116±2.97 mg/dl; p<0.0001), PPG (239±11.2 mg/dl to 140±4.42 mg/dl; p<0.0004), and HbA1c (9.07±0.346 to 6.51±0.129; p<0.0001). All of the patients tolerated the drug and no adverse events were reported.
Faruqui et al	Metformin 500 mg (SR#) + glimepiride 0.5 mg + voglibose 0.2 mg BD. (FDC)	Significant decrease in HbA1c value 10.6±1.3 versus 6.6±0.4 (p<0.0001), FPG levels 208.33 mg/dl versus 118.06 (p<0.0001), and PPHG levels 360.14 mg/dl versus 168.36, (p<0.0001). None of the patients complained about adverse events including nausea, vomiting and headache at the given doses of medication.

Continued.

Author	Drug dosage	Efficacy and safety results
Rao et al	Metformin 500 mg (SR#) + glimepiride 1/2 mg + voglibose 0.2 mg BD. (FDC)	Significant decrease in HbA1c (8.86±0.7111 gm/dl versus 8.0±0.66 gm/dl, fasting (137±17.64 mg/dl versus 116.8±6.129 mg/dl, p<0.0001) and postprandial blood glucose level (237.8±59.22 mg/dl versus173.4±27.6 p<0.0004) was observed from baseline. This triple combination was well tolerated.
Jindal et al	Metformin 500 mg BD + glimepiride 2 mg BD + voglibose 0.2 mg TDS	Significant reduction (p<0.001) in FPG, PPG and HbA1c over a period of 6 months. Side effects such abdominal pain, headache, diarrhea, flatulence, sweating and hot flushes are observed.
Murti et al	Dual therapy group; metformin 500 mg + glimepiride 1 mg; triple therapy group: metformin 500 mg + glimepiride 1 mg + voglibose 0.3 mg	Even though significant reduction in FPG, PPG, and HbA1c was observed from baseline to end of study in both dual and triple therapy groups, it was larger in triple therapy group.
Pankivn et al	Group I: metformin + glimepiride + voglibose 0.2 mg TDS. Group II: metformin + glimepiride	Decrease in HbA1c was high in group group I (1.5 [1.1; 1.9] % (p<0.05) than group II (0.1 [0.09; 0.6] % (p>0.05) after 12 weeks of treatment. Body weight reduced significantly by 2.1 kg in group I while no response was observed in group II. Safety was proven in terms of functional states of liver and kidney.

Table 5: Summary of teneligliptin trials.[41]

Author	Study design	Dose	Baseline values	Results
Eto et al	Randomized, double blinded, placebo controlled, parallel study (n=99)	Teneligliptin- 10 mg (n=34), 20 mg (n=33)	HbA1c-8.3% FPG-1621 mg/dl	DPP4 inhibition rate at 24 hours was 66.9±4.17%
Kadowaki et al	Interim analysis (n=11,627)	Teneligliptin- 20 mg/day	HbA1c-7.57% FPG-147.6 mg/dl	Overall ADRs; 3.46% and most common ADRs were hypoglycemia (0.32%) and constipation: 0.27%
Kim et al	Phase 3, randomized, double blind, non-inferiority study (n=201)	Teneligliptin- 20 mg/day (n=103), sitagliptin- 100 mg/day (n=98)	HbA1c-8.11%	At 24 weeks, reduction from baseline in HbA1c : teneligliptin: -1.03±0.10%, sitagliptin: -1.02-0.10%
Kadowaki et al	Double blinded, placebo controlled, parallel group study (n=204)	Teneligliptin-20 mg (n=103)	HbA1c-8.1% FPG-l.50-7 mg/dl	Significant reduction in HbA1c and FPG were observed with teneligliptin treatment
Hashikata et al	Single-center, pilot-study (n=27)	Teneligliptin-20 mg, 40 mg	HbA1c -7.5% LVEF -63.7% E-13.4	Teneligliptin improves left ventricular diastolic function and endothelial function in patients with diabetes

Table 6: Overview of affordable OADs.[5,8,20,24,31]

Class of OADs	Efficacy	Effect on weight	CV effects	Key side effects	Summary
Biguanides: metformin[5]	High	Weight loss/weight neutral	Beneficial CV effects, reduces LDL-C and increases HDL-C	Lactic acidosis	First-line drug therapy of choice for T2DM
Modern sulfonylureas: glimepiride, gliclazide XR	High	Lesser weight gain/versus older Sus[8,20]	Glimepiride had shown similar CV safety to DPP4i[24]	Hypoglycemia and weight gain[20]	Second line drug[8]
TZDs: pioglitazone[31]	High	Weight gain[31]	Increased risk of MI, CHF, increased	Weight gain, CV outcomes[31]	Second line drug, to be avoided in patients with or at risk for heart failure[31,46]

Continued.

Class of OADs	Efficacy	Effect on weight	CV effects	Key side effects	Summary
			levels of LDL-C, triglycerides		
AGIs: acarbose, voglibose	Intermediate	Weight neutral[47]	Neutral effect on CV outcomes[48]	Flatulence, diarrhea	Main for PPG, low risk of hypoglycemia, CV safety to be evaluated[48,50]
DPP-4Is: enaligliptin, vildagliptin	Intermediate	Weight neutral[35]	Neutral effect on CV outcomes[51]	GI effects, pancreatitis[52,53]	Caution to be exercised while prescribed in patients with heart failure and pancreatitis[52,54]
SGLT2Is: remogliflozin, dapagliflozin	Intermediate	Weight loss[44]	Beneficial CV effects[44]	Mycotic infections of the genital tract and osmotic diuresis[45,55]	Favored as the second-line agent of choice in T2DM patients with a history of CVD[56]

AGIs: Alpha-glucosidase inhibitors, CHF: congestive heart failure, CV: cardiovascular, HDL-C: high-density lipoprotein-cholesterol, DPP-4: dipeptidyl peptidase, GI: gastrointestinal, MI: myocardial infarction, LDL-C: low-density lipoprotein-cholesterol, SGLT2i: sodium-glucose co-transporter 2 inhibitors, DM: diabetes mellitus T2DM: type 2 DM, TZDs: thiazolidinediones, SU: sulfonylureas, CVD: CV disease

CONCLUSION

With number of cases of T2DM rising rapidly in India, treatment benefits and incurring expenditure need to be balanced out carefully. The selection of the OADs to be responsible patient centered approach. Metformin and modern SUs combination is the most used combination in India and are time tested affordable, available, accessible drug combination in offering optimal glycemic control, pleiotropic benefits, with CV safety profile in a cost-effective manner. Other low-cost drugs belonging to the class of AGIs and TZDs are available to be used appropriately as 2nd or 3rd line agents. Recently available low cost DPP4 inhibitors and SGLT2 inhibitors are welcome in the affordable T2DM treatment armamentarium and to be used wherever appropriate.

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