REVIEW ARTICLE

An Expert Opinion on Diabetic Care for Lower-Income Patient Groups in India: In Relation to the Availability and Affordability of Diabetic Medication

Sanjay Kalra[1], Atul Dhingra[2], Mahesh DM[3], Manash Pratim Baruah[4], Mangesh Tiwaskar[5], Navneet Agrawal[6], Nilakshi Deka[7], Pramila Kalra[8], Shailaja Kale[9] and Santosh Revankar[10*]

[1]*Department of Endocrinology, Bharti Hospital, Karnal, India*
[2]*Department of Endocrinology, Superspeciality Clinics and Gangaram Bansal Hospital, Sri Ganganagar, India*
[3]*Department of Endocrinology, Aster Corporate Hospital, Banglore, India*
[4]*Department of Endocrinology, Apollo Excelcare Hospital, Guwhati, India*
[5]*Department of Diabetology, Shilpa Medical Research Centre, Mumbai, India*
[6]*Department of Diabetology, Diabetes, Obesity and Thyroid Centre, Gwalior, India*
[7]*Department of Endocrinology, Apollo Hospitals, Guwhati, India*
[8]*Department of Endocrinology, MSR Medical College, Banglore, India*
[9]*Department of Diabetology, KEM Hospital, Pune, India*
[10]*Scientific Services, USV Private Limited, Mumbai, India*

Abstract

The increasing burden of diabetes in India is imposing significant economic strain, particularly on lower socioeconomic groups. Therefore, the E-Tulip program aimed to improve healthcare outcomes for these patient groups with diabetes in India. Six nationwide continuing medical education sessions, each led by an expert healthcare professional (HCP) and attended by regional HCPs, focused on various aspects of 'Democracy in Diabetes Care'. Discussions from all the sessions were compiled to prepare this expert opinion. The recommendations provided tailored approaches for managing type 2 diabetes mellitus (T2DM) across different patient scenarios. Economic strategies emphasized affordability and adherence, advocating for metformin as a cost-effective first-line option and rationalizing dual (metformin + glipizide) and triple (glimepiride + metformin + pioglitazone) therapy choices based on glycemic control needs. Metformin was also endorsed for prediabetes to delay T2DM onset. The discussion on the availability and affordability of drugs will improve the knowledge of the HCPs, improving the care of lower-income diabetic patients through comprehensive management.

Keywords: *Metformin, prediabetes, type 2 diabetes mellitus, lower socioeconomic groups ,expert opinion.*

INTRODUCTION

An estimated 101 million individuals in India are affected by diabetes, accounting for 11.4% of the nation's population [1]. The diabetes crisis has peaked in certain highly developed states of the country, while many less developed states are still in the early phases of this epidemic [1]. Diabetes imposes a significant economic burden on affected individuals and healthcare systems, especially in low- to middle-income countries, given its chronic nature and the associated macrovascular and microvascular complications [2].

Traditionally associated with the affluent segments of Indian society, diabetes is now increasingly affecting individuals from lower socioeconomic groups, carrying significant health implications [3]. Diabetes places a substantial financial strain on individuals and households in India, with medication expenses accounting for a major portion of the overall cost of managing the disease [4]. An average Indian patient with diabetes faces considerable treatment expenses. These expenses are further escalated by the presence of one or more complications, such as diabetic foot disease or renal disease [5]. Additionally, the absence of insurance schemes and policies increases the expense of diabetes care. Poor medication adherence is highly prevalent in type 2 diabetes mellitus (T2DM), often associated with patient demographic factors such as low-income levels and the perceived burden patients face in acquiring their medications, including out-of-pocket costs [6].

While a multidisciplinary approach involving all stakeholders in the healthcare sector is crucial to diabetes care, patient-centered care emerges as a key method to ensure 'democracy in diabetes care'. It prioritizes patient decision-making in diabetes management, actively involving them in the planning and monitoring their treatment. Democracy in diabetes management advocates for health, diagnostic, and pharmaceutical equity.

In this regard, the E-Tulip program aimed to improve patient healthcare outcomes by increasing accessibility and affordability of diabetes care, emphasizing alternative therapies to improve treatment adherence

**Corresponding author: Santosh Revankar, Scientific Services, USV Private Limited, Mumbai, India; E-mail: usvpublications@gmail.com*
Received: June 24, 2024; Revised: October 30, 2024; Accepted: November 11, 2024
DOI: https://doi.org/10.37184/lnjpc.2707-3521.7.27

and ultimately empowering patients to manage their health within the realm of diabetes management. The present expert opinion document was developed with a particular focus on improving healthcare outcomes for lower-income patient groups with diabetes in India.

MATERIALS AND METHODS

Six continuing medical education (CME) sessions were held across India. Each session was led by an expert healthcare professional (HCP) and attended by regional HCPs. The HCPs belonged to tier 1 and tier 2 cities. The leading expert guided the session by discussing objectives and management strategies supported by scientific evidence and their experiences. The discussion was further extended during the Q&A session, where the expert HCP addressed questions from the session attendees. Discussions from all the sessions were compiled to prepare this expert opinion.

Each CME session focused on a different aspect within the principal domain of 'Democracy in Diabetes Care'. This expert opinion document provides insights on managing T2DM in drug-naïve patients, addressing the economic burden of uncomplicated T2DM, multidisciplinary collaborative care for uncontrolled T2DM in lower-income groups, maximizing cost-effective pharmacotherapy in T2DM patients with atherosclerotic cardiovascular disease (ASCVD), achieving glycemic control and treatment of comorbidities in patients with T2DM, and evaluating the cost-effectiveness of intensive management approaches for T2DM patients with chronic kidney disease (CKD).

The HCPs referred to the American Diabetes Association (ADA) and the Research Society for the Study of Diabetes in India (RSSDI) guidelines, along with their clinical experience, to categorize the groups according to the criteria mentioned above, where dual and triple drug combinations are relevant. Parameters such as glycated hemoglobin (HbA1c), cardiovascular disease (CVD)/CKD history, body mass index (BMI; obesity), and variability in fasting plasma glucose (FPG) and postprandial glucose (PPG) are the most common indicators according to the guidelines for assessing the risk of complications and comorbidities in T2DM, where dual and triple drug combinations become pertinent.

Definition: The Reserve Bank of India (RBI) classifies cities based on population, with tier 1 cities having populations of 100,000 or more, and tier 2 towns ranging between 50,000 and 99,999.

DISCUSSION

This section talks about the various origins of the principal domains in the democracy of diabetic care. The E-Tulip program is a patient-centered initiative that fosters democracy in diabetes care, placing patients at the forefront of decision-making and actively involving them in managing their health. There has been a lack of expert opinion on improving healthcare outcomes for lower-income patient groups in the context of diabetes in India. This expert opinion report comprehensively discusses the insights and recommendations provided by the experts in all the CME sessions, aiming to empower Indian patients with diabetes to manage their health effectively (**Fig. 1**).

Changing Scenarios in Managing T2DM in Drug-Naïve Patients: Medical Therapy and Cost-Effectiveness

Patients with diabetes can be broadly classified as drug-experienced (those already on a particular antidiabetic drug or drug combination) and drug-naïve (those who never received any antidiabetic medication). Drug-naïve patients can be further categorized as prediabetes with HbA1c <6.2% or drug-naïve with HbA1c <7.5%, drug-naïve with HbA1c 7.5%- 8%, and drug-naïve with HbA1c >8%. According to the experts, patient treatment should adhere to the Law of Therapeutic Parsimony, which states that the least number of drugs, drug combinations, or drug preparations should be used, in the minimum required dose and frequency, to achieve the predetermined therapeutic outcomes [7]. However, monotherapy does not suffice for drug-naïve patients with HbA1c >7.5%, requiring dual oral therapy. This is supported by the American Association of Clinical Endocrinologists (AACE) consensus statement [8], which recommends early combination therapy with two agents if the initial HbA1c is >7.5%. Similarly, the ADA guidelines [9] recommend considering initial combination therapy for those presenting with HbA1c levels 1.5-2.0% above the glycemic goal.

Experts recommended the combination of metformin and glipizide as the most cost-effective treatment for dual therapy. Metformin + glipizide is a safe combination, reducing FPG levels, and HbA1c, with minimal risk of nocturnal hypoglycemia. The complementary modes of action of metformin and glipizide enable a safe and effective combination therapy that improves glycemic control without significant weight gain. Feinglos *et al.* demonstrated that adding 2.5 mg of glipizide to metformin significantly improved glucose control in patients with T2DM inadequately controlled by metformin alone, allowing a higher proportion of patients to achieve their HbA1c goals [10]. Additionally, glipizide/metformin tablets proved more effective than individual monotherapies in controlling HbA1c and FPG levels in patients previously uncontrolled on sulfonylurea (SU) treatment [10].

As per expert opinion, patients with an HbA1c level between 8.5% and 10% may require triple oral therapy, a recommendation in line with the guidelines [8, 9]. One of the most cost-effective combinations for this therapy includes glimepiride, metformin, and pioglitazone [10]. The triple dose combination of glimepiride + metformin + pioglitazone demonstrated improved glycemic control compared to placebo (-1.31% *vs* -0.33%; p<0.001), with an acceptable tolerability profile. Another study [10] confirmed the safety and efficacy of glimepiride +

Domain	Patient population	Monotherapy	Dual oral therapy (Metformin + SU)	Triple oral therapy (Metformin + SU + TZD)
Changing scenarios in managing T2DM in drug-naïve patient: Medical therapy and cost-effectiveness	Drug-naïve patients	Prediabetes with HbA1c <6.2% or drug-naïve with HbA1c <7.5%	Drug-naïve with HbA1c 7.5%- 8%	Drug-naïve with HbA1c >8%
Addressing the economic burden of uncomplicated T2DM: Strategies for cost-effective therapies and improved adherence	Patients with uncomplicated T2DM	FPG 130-150 mg/dL, PPG 140-180 mg/dL, and HbA1c >6.5%	FPG 150-170 mg/dL, PPG 180-240 mg/dL, and HbA1c >7.5%	FPG >170 mg/dL, PPG >240 mg/dL, and HbA1c >8.5%
Multidisciplinary collaborative care in managing uncontrolled T2DM in lower-income groups	Uncontrolled T2DM in lower-income patient groups	Patients who are not receiving any anti-diabetic medication and have an HbA1c >7%	Patients receiving metformin monotherapy with an HbA1c >7.6%	Patients receiving dual anti-diabetic therapy with an HbA1c >8.4%
Maximizing cost-effective pharmacotherapy in T2DM patients with ASCVD	Patients with T2DM and comorbid ASCVD	HbA1c >6.5%	HbA1c >7.5%	HbA1c >8.5%
	Patients with T2DM (aged 40 to 75 years)*	Statin therapy for ASCVD risk	Aspirin for low bleeding risk	Aspirin + Atorvastatin Cost-effective therapy
Achieving glycemic control and treatment of comorbidities in patients with T2DM	Patients with T2DM and accompanying comorbidities	Patients (aged 45 years; HbA1c >7.5%) accompa- nied by dyslipidemia (TG >200 mg/dL; LDL-C >160 mg/dL; HDL-C <40 mg/dL)	Patients (aged 45 years; HbA1c 7.5-8.5%) accompanied by mild DKD (eGFR=55 ml/min/1.73 m^2)	Patients (aged 45 years; HbA1c >8.5%) who have a family history of CVD and hypertension, in addition to dyslipidemia (TG >200 mg/dL; LDL-C >160 mg/dL; HDL-C <40 mg/dL)
	Patients with T2DM (aged 40 to 75 years)*	Statin therapy for ASCVD risk	Aspirin for family history of CVD, hypertension, dyslipidemia, and a low bleeding risk	Aspirin + Atorvastatin Cost-effective therapy
Evaluating the cost-effectiveness of intensive management approaches for T2DM patients with CKD	Patients with T2DM and comorbid CKD	Patients with HbA1c >6.5% and mild CKD (eGFR=73 mL/min/1.73m^2)	Patients with HbA1c >7.5%, and mild CKD (eGFR=68 mL/ min/1.73m^2)	Patients with HbA1c >8.5%, and moderate CKD (eGFR=55 mL/min/1.73 m^2)

*Recommended by the ADA and ACC/AHA guidelines
ACC, American College of Cardiology; ADA, American Diabetes Association; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PPG, postprandial glucose; SU, sulfonylurea; T2DM, type 2 diabetes mellitus; TG, triglycerides; TZD, thiazolidinedione.

- Metformin
- Metformin + glipizide
- Metformin + glimepiride/gliclazide
- Metformin + glimepiride/glipizide
- Metformin + glipizide/glimepiride/gliclazide
- Metformin + pioglitazone + glimepiride

Fig. (1): Democracy in Diabetes Care: Cost-effective therapeutic options for patients with T2DM.

pioglitazone + metformin in achieving glycemic goals, significantly reducing triglycerides (TG), low-density lipoproteins (LDL), and total cholesterol, with no serious adverse events or drug interactions reported.

The progression of diabetes can be prevented or delayed in prediabetes or in drug-naïve patients with HbA1c <7.5% using metformin. This perspective aligns with the approval granted by the Drugs Controller General of India (DCGI) [11] for metformin sustained-release tablets, which are indicated for reducing the risk or delaying the onset of T2DM in adult, overweight patients with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG), and/or increased HbA1c levels. These patients are at high risk of developing T2DM and continue to progress towards it despite implementing intensive lifestyle changes for 3 to 6 months. Moreover, the ADA [12] recommends considering metformin therapy for preventing T2DM in high-risk adults, particularly those aged 25-59 years with a BMI ≥35 kg/m2, higher FPG (≥110 mg/dL), and HbA1c (≥6.0%), and those with a history of gestational diabetes mellitus (GDM).

According to the RSSDI guidelines [13], initiating metformin therapy is advisable if patients with prediabetes do not experience any improvement with lifestyle modifications after six months. Additionally, it is recommended to add metformin (500 mg, twice daily) for younger individuals who have one or more additional risk factors for diabetes, if they are overweight or obese with IFG + IGT, or IFG with HbA1c >5.7%. The International Diabetes Federation (IDF) [14] has acknowledged metformin as a cost-effective pharmacological option for individuals at high risk of developing diabetes.

Addressing the Economic Burden of Uncomplicated T2DM: Strategies for Cost-Effective Therapies and Improved Adherence

Recognizing the gravity of the disease, adherence to the prescribed treatment is crucial for patients [15]. The maximum advantages of several effective medications can only be attained when patients comply with the prescribed treatment regimens. However, the high out-of-pocket expenses for medications present a significant challenge for many adults managing diabetes, leading to reduced adherence to treatment. Initiatives aimed at reducing these costs could potentially improve adherence rates for all patients [16]. Considering these challenges, clinicians should actively identify patients with diabetes who are struggling with medication costs and assist them by adjusting their medication regimens, emphasizing the importance of each prescribed medication, and providing information on affordable drug options.

In addressing the economic burden of uncomplicated T2DM, patients can be categorized into three groups: those with FPG 130-150 mg/dL, PPG 140-180 mg/dL, and HbA1c >6.5%; those with FPG 150-170 mg/dL, PPG 180-240 mg/dL, and HbA1c >7.5%; and those with FPG >170 mg/dL, PPG >240 mg/dL and HbA1c >8.5%.

The ADA and the RSSDI guidelines recommend metformin as first-line therapy for patients with T2DM (HbA1c >6.5%) when lifestyle modifications have failed to produce a significant reduction in glycemic load. Metformin, a proven therapy for T2DM, is safe and effective in delaying or preventing the disease in high-risk individuals [17]. Metformin is also one of the most cost-effective oral therapeutic options for managing T2DM.

For patients on metformin monotherapy with increased glycemic levels (HbA1c >7.5%), intensifying the current treatment is an option. The commonly prescribed initial doses for metformin are 500 mg twice daily or 850 mg once daily. As the effectiveness of metformin correlates with dosage, intensification of treatment would include increasing the metformin dose gradually, either by 500 mg weekly or 850 mg biweekly, until the maximum tolerable dose is reached [18,19]. If glycemic targets cannot be achieved through the intensification of metformin monotherapy within three months, combination therapy should be considered. Clinical studies have reported a greater reduction in HbA1c and FPG with metformin/SU fixed-dose combination (FDC) compared to metformin up-titration [10]. The combination of metformin + glipizide represents the most affordable dual therapy option for patients with uncomplicated T2DM.

In cases where dual therapy proves insufficient in achieving glycemic targets, or in the case of patients with an HbA1c >8.5%, the implementation of triple oral therapy becomes necessary. While several options exist for triple combination oral antidiabetic medications, the combination of glimepiride + metformin + pioglitazone represents the most cost-effective oral triple therapy option for patients with uncomplicated T2DM.

Multidisciplinary Collaborative Care in Managing Uncontrolled T2DM in Lower-Income Groups

People with diabetes and their families encounter complex and multifaceted challenges while incorporating diabetes management into their daily routines [20]. Thus, a multidisciplinary approach to diabetes care is important, involving various HCPs such as diabetes educators, pharmacists, representatives from pharmaceutical companies, and doctors from different specialties. For instance, managing gestational diabetes may necessitate collaboration with gynecologists and neonatologists, while preventing diabetic foot complications may require the expertise of surgeons or podiatric surgeons. The emphasis should not solely be on physicians but rather on adopting a comprehensive approach that includes accessible and affordable diabetes care, education, awareness, and diligent monitoring through diabetes self-management education to ensure effective management. Recent studies have demonstrated that implementing a multidisciplinary team approach significantly improves the outcomes of diabetes treatment and helps prevent or minimize diabetes-related complications [21].

To manage uncontrolled T2DM in lower-income groups, patients can be categorized as those with T2DM who are not receiving any anti-diabetic medication and have an HbA1c >7%, those receiving metformin monotherapy with an HbA1c >7.6%, and those receiving dual anti-diabetic therapy with an HbA1c >8.4%. For newly diagnosed patients with uncontrolled T2DM with an HbA1c >7%, metformin is considered the cost-effective choice among single oral hypoglycemic agents compared to alternatives such as gliclazide, glimepiride, teneligliptin, and voglibose [22]. Most experts agreed that metformin combined with lifestyle modifications is sufficient for the effective treatment of this patient category.

Patients with uncontrolled T2DM, characterized by an HbA1c level >7.6% despite three months of metformin therapy, are typically considered suitable candidates for initiating dual oral anti-diabetic therapy. This generally involves treatment with metformin combined with a second oral anti-diabetic medication, such as an SU. Fixed-dose combinations containing SUs have demonstrated benefits in reducing medication costs, improving convenience, and improving patient adherence [10]. Among sulfonylureas, glipizide is the most cost-effective option [23]. Moreover, glipizide is suitable for use in patients with compromised renal function. Studies indicate that the FDC of metformin + glipizide incurs the lowest annual cost compared to other combinations.

Triple oral anti-diabetic therapy is necessary for patients with uncontrolled T2DM who remain unresponsive to dual therapy and have an HbA1c >8.4%. Pioglitazone represents a suitable add-on medication for use in patients with T2DM who do not show any contraindications to the drug. Pioglitazone has also been shown to provide the added benefit of reducing both visceral fat volume and its metabolic activity in patients with T2DM [24]. A fixed-dose combination of metformin + glimepiride + pioglitazone proves to be more cost-effective compared to other combinations [25]. For this reason, this FDC is recognized as the most prevalent triple FDC used in India [26].

Maximizing Cost-Effective Pharmacotherapy in T2DM Patients with ASCVD

Cardiovascular disease is one of the most frequently observed comorbidities in patients with T2DM. Patients with T2DM may have overt CVD or may display advanced risk factors for CVD. Cardiovascular disease results in various negative health effects, including increased morbidity and mortality, loss of productivity, and a considerable amount of disability. Additionally, the cost of treatment for patients with T2DM increases drastically in the presence of comorbid ASCVD, such as ischemic heart disease (IHD) and stroke [27].

Patients with T2DM and comorbid ASCVD can be categorized based on their HbA1c levels as those with HbA1c >6.5%, HbA1c >7.5%, and HbA1c >8.5%, respectively. In patients with T2DM (HbA1c >6.5%) at risk of ASCVD, metformin serves as an ideal and cost-effective drug, offering various benefits beyond its antihyperglycemic properties. These include improving insulin resistance, lipid homeostasis, glucose turnover, and the gut microbiome. Metformin has also demonstrated cardioprotective benefits by positively impacting mitochondrial bioenergetics, and substrate utilization, reducing cardiocyte apoptosis, lowering oxidative stress, and enhancing endothelial function. Additionally, it has a positive impact on plasma triglyceride levels, low-density lipoprotein levels, and total cholesterol levels in patients with diabetes. Metformin provides a comprehensive and cost-effective approach to managing diabetes, considering not only glycemic control but also cardiovascular health.

For patients with T2DM (HbA1c >7.5%) at risk of ASCVD, SUs can be considered a viable addition to metformin therapy, particularly for those experiencing postprandial hyperglycemia and facing challenges in affording newer medications like sodium-glucose cotransporter-2 (SGLT2) inhibitors. Sulfonylureas, such as glimepiride and gliclazide, offer durable glycemic control and are relatively cost-effective. Moreover, managing postprandial hyperglycemia with SUs has been shown to reduce cardiovascular morbidity and mortality, making them a valuable option for certain patients, especially in the early stages of diabetes management. Considering the safety and long-term cost-effectiveness of SUs is crucial when treating patients with T2DM at risk of ASCVD.

In patients with T2DM (HbA1c >8.5%) at risk of ASCVD, a triple-drug combination becomes necessary. An ideal approach for patients at high cardiovascular risk may include metformin, dipeptidyl peptidase 4 (DPP-4) inhibitors, and SGLT2 inhibitors. However, cost considerations are essential because discontinuation of treatment due to high costs can compromise the intended benefits. Furthermore, the appropriateness of using glitazones, such as pioglitazone, has been emphasized. It has been shown that glitazones, when used in patients with high HbA1c and moderate BMI, can yield favorable cardiovascular outcomes, especially in younger patients. The combination of glimepiride + metformin + pioglitazone has been suggested as a cost-effective approach for patients at risk of CVD who are not very obese, as it may provide glycemic control with minimal side effects. Close monitoring for heart failure symptoms is advised for such patients.

According to recommendations from the ADA, the American College of Cardiology (ACC), and the American Heart Association (AHA), patients with T2DM aged 40 to 75 years who are at risk of ASCVD should be considered for statin therapy, while those with low risk of bleeding should be prescribed aspirin. In this context, the dual pharmacological combination of aspirin and atorvastatin represents a cost-effective approach for managing the

risk of ASCVD and bleeding in patients with long-term T2DM [28-30].

Achieving Glycemic Control and Treatment of Comorbidities in Patients with T2DM

Patients with T2DM and accompanying comorbidities can be categorized as those with T2DM (aged 45 years; HbA1c >7.5%) accompanied by dyslipidemia (TG >200 mg/dL; low-density lipoprotein cholesterol [LDL-C] >160 mg/dL; high-density lipoprotein cholesterol [HDL-C] <40 mg/dL); those with T2DM (aged 45 years; HbA1c 7.5-8.5%) and mild diabetic kidney disease (DKD) (estimated glomerular filtration rate [eGFR]=55 ml/min/1.73m^2); and those with T2DM (aged 45 years; HbA1c >8.5%) who have a family history of CVD and hypertension, in addition to dyslipidemia (TG >200 mg/dL; LDL-C >160 mg/dL; HDL-C <40 mg/dL).

For patients in the first category (HbA1c >7.5%), combining metformin with SUs is a viable treatment option, especially for those with postprandial hyperglycemia and financial constraints regarding newer medications like SGLT2 inhibitors. Fixed-dose combinations using modern SUs like glimepiride and glipizide offer safety and efficacy as second-line agents when metformin alone is insufficient. They are cost-effective, convenient, and promote patient adherence [10]. Metformin/SU therapy effectively lowers blood glucose, similar to metformin/DPP-4 combinations, and reduces LDL and TG levels [31]. Additionally, according to the ADA, statin therapy is recommended for patients with diabetes aged 40 to 75 years who exhibit one or more risk factors for ASCVD, including dyslipidemia, to reduce LDL-C concentration to desired target levels <70 mg/dL [32].

For patients in the second category (HbA1c 7.5-8.5%), the combination of metformin and SUs represents the most frequently prescribed antidiabetic medications for those with T2DM with DKD [33]. Modern SUs, such as glipizide, glimepiride, and gliclazide are safe to use in CKD stages 1-4 and generally require minimal to no dose adjustments in affected patients [34].

Sulfonylurea glipizide has been shown to exhibit the additional beneficial effect of blocking renal interstitial fibrosis, a crucial metabolic change in late-stage DKD [35]. Moreover, among all metformin/SU combinations, the combination of metformin and glipizide has been demonstrated to be the most cost-effective, incurring the lowest average total direct cost and average cost-effectiveness ratio (ACER) [25].

For patients belonging to the third category (HbA1c >8.5%), a triple-drug combination becomes necessary. An ideal approach for patients displaying multiple risk factors for CVD may include metformin, DPP-4 inhibitors, and SGLT2 inhibitors. The results of the PROspective pioglitAzone Clinical Trial In macrovascular Events (PROactive) study showed that pioglitazone can reduce the risk of secondary macrovascular events in a high-risk patient population with T2DM and established macrovascular disease [36]. The combination of glimepiride + metformin + pioglitazone has been suggested as a cost-effective approach for patients at risk of cardiovascular disease who are not very obese, as it may provide better glycemic control with minimal side effects. Close monitoring for heart failure symptoms is advised for such patients [32].

Additionally, those with a family history of CVD, hypertension, dyslipidemia, and a diminished risk of bleeding may be prescribed aspirin. In this context, the combination of aspirin and atorvastatin emerges as a cost-effective strategy for managing both ASCVD and bleeding risks in patients with long-term T2DM [31, 37, 38].

Evaluating the Cost-Effectiveness of Intensive Management Approaches for T2DM Patients with CKD

Patients with T2DM and comorbid CKD can be categorized as those with T2DM, HbA1c >6.5%, and mild CKD (eGFR=73 mL/min/1.73m^2); those with T2DM, HbA1c >7.5%, and mild CKD (eGFR=68 mL/min/1.73m^2); and those with T2DM, HbA1c >8.5%, and moderate CKD (eGFR=55 mL/min/1.73m^2).

For patients falling under the first category, metformin represents an ideal and cost-effective drug that offers various benefits beyond its antihyperglycemic properties, including improving insulin resistance, lipid homeostasis, glucose turnover, and gut microbiome. According to the KDIGO 2022 clinical practice guideline for diabetes management, metformin is recommended for treating patients with T2DM, CKD, and an eGFR ≥30 ml/min/1.73m^2. Dose adjustment for metformin is generally necessary when eGFR is <45 ml/min/1.73m^2 and for some patients when eGFR is between 45 and 59 ml/min/1.73m^2.

For patients in the second category, SUs can be considered a viable and cost-effective treatment as an add-on to metformin therapy, especially for patients who exhibit postprandial hyperglycemia and have difficulty affording newer medications like SGLT2 inhibitors. Metformin/SU combination represents the most frequently prescribed antidiabetic medications for T2DM patients with CKD [39]. The use of modern SUs, such as glipizide, glimepiride, and gliclazide, in patients with T2DM and CKD (stages 1-4) is considered safe and requires minimal to no dose adjustments.

For patients belonging to the third category (HbA1c >8.5%), the use of a triple oral anti-hyperglycemic combination therapy becomes necessary. Both SUs and pioglitazone represent viable and low-cost treatment add-ons to metformin therapy. In patients with T2DM and CKD (stages 1-4), the use of pioglitazone is considered safe and does not require any dose adjustments. The use of pioglitazone has also been linked to reduced

progression of renal disease in patients with or at risk of T2DM [39]. Fixed-dose combination (metformin + glimepiride + pioglitazone) is far more cost-effective than other combinations [25].

To conclude the discussion, it is important to consider that most HCPs who attended the CME sessions were from tier 1 and tier 2 cities. While they did not engage directly with patients during the sessions, they are expected to prescribe the affordable therapy options covered in the discussions to different patient groups, including those in rural areas and lower-income patients, thereby ensuring accessibility.

CONCLUSION

This comprehensive expert opinion document sheds light on strategies to empower individuals with diabetes in effectively managing their condition. Through insights and recommendations shared in CME sessions, the report underscores the importance of tailored treatment approaches, such as utilizing cost-effective therapies like metformin-based combinations, to address diverse patient needs and economic realities. Continuing medical education sessions primarily enhance the expertise and skills of HCPs. However, for lower-income patient groups, these sessions are particularly valuable as they bridge the gap between HCPs and patients. By updating medical knowledge and clinical practices, CME sessions enable HCPs to deliver better patient care, which, in turn, helps improve patient outcomes. Additionally, patient education about their disease and prevention strategies is crucial, as it empowers patients to manage their conditions effectively. While drug availability and affordability are important, comprehensive patient education plays a key role in advancing patient knowledge and improving health outcomes across different income populations. Thus, by emphasizing adherence, optimizing treatment options, and advocating for affordable diabetes care, this document paves the way for more equitable and accessible diabetes management, ultimately leading to improved patient health outcomes.

FUNDING

USV Private Limited, Mumbai, funded this initiative.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

The authors thank Rupika Pawar from Sqarona Medical Communications LLP (Pune) for providing medical writing assistance.

REFERENCES

1. Anjana RM, Unnikrishnan R, Deepa M, Pradeepa R, Tandon N, Das AK, *et al.* Metabolic non-communicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). Lancet Diabetes Endocrinol 2023; 11(7): 474-89. DOI: https://doi.org/10.1016/s2213-8587(23)00119-5
2. Karachaliou F, Simatos G, Simatou A. The challenges in the development of diabetes prevention and care models in low-income settings. Front Endocrinol (Lausanne) 2020; 11:518. DOI: https://doi.org/10.3389/fendo.2020.00518
3. Unnikrishnan R, Anjana RM, Mohan V. Diabetes mellitus and its complications in India. Nat Rev Endocrinol 2016; 12(6): 357-70. DOI: https://doi.org/10.1038/nrendo.2016.53
4. Oberoi S, Kansra P. Economic menace of diabetes in India: a systematic review. Int J Diabetes Dev Ctries 2020;40(4):464-75. DOI: https://doi.org/10.1007/s13410-020-00838-z
5. Kumpatla S, Kothandan H, Tharkar S, Viswanathan V. The costs of treating long-term diabetic complications in a developing country: a study from India. J Assoc Physicians India 2013; 61(2): 102-9.
6. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. Patient Prefer Adherence 2016; 10: 1299-307. DOI: https://doi.org/10.2147/PPA.S106821
7. Kalra S, Gupta Y, Sahay R. The law of therapeutic parsimony. Indian J Endocrinol Metab 2016; 20(3): 283-4. DOI: https://doi.org/10.4103/2230-8210.180008
8. Samson SL, Vellanki P, Blonde L, Christofides EA, Galindo RJ, Hirsch IB, *et al.* American Association of Clinical Endocrinology consensus statement: comprehensive type 2 diabetes management algorithm - 2023 update. Endocr Pract 2023; 29(5): 305-40. DOI: https://doi.org/10.1016/j.eprac.2023.02.001
9. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes-2024. Diabetes Care 2024; 47(Suppl 1): S158-78. DOI: https://doi.org/10.2337/dc24-S009
10. Kalra S, Bahendeka S, Sahay R, Ghosh S, Fariduddin Md, Orabi A, *et al.* Consensus recommendations on sulfonylurea and sulfonylurea combinations in the management of type 2 diabetes mellitus - International Task Force. Indian J Endocrinol Metab 2018; 22(1): 132-57. DOI: https://doi.org/10.4103/ijem.ijem_556_17
11. Recommendations of the SEC (Endocrinology & Metabolism) made in its 91st meeting held on 25.08.2022 & 26.08.2022 at CDSCO (HQ), New Delhi. Available from: Recommendations Endocrinology & Metabolism 25.08.2022 & 26.08.2022.pdf (cdsco.gov.in)
12. American Diabetes Association. Standards of Care in Diabetes-2023 Abridged for Primary Care Providers. Clin Diabetes 2022; 41(1): 4-31. DOI: https://doi.org/10.2337/cd23-as01
13. RSSDI clinical practice recommendations for the management of type 2 diabetes mellitus 2022. Int J Diabetes Dev Ctries 2022; 42(Suppl 1): 1-143. DOI: https://doi.org/10.1007/s13410-022-01129-5
14. International Diabetes Federation. Cost-effective solutions for the prevention of type 2 diabetes. Brussels, Belgium: International Diabetes Federation, 2016. Available from: www.idf.org/preventiontype2diabetes
15. Swain SP, Samal S, Sahu KS, Rout SK. Out-of-pocket expenditure and drug adherence of patients with diabetes in Odisha. J Family Med Prim Care 2018; 7(6): 1229-35. DOI: https://doi.org/10.4103/jfmpc.jfmpc_24_18
16. Kirkman MS, Rowan-Martin MT, Levin R, Fonseca VA, Schmittdiel JA, Herman WH, *et al.* Determinants of adherence to diabetes medications: findings from a large pharmacy claims database. Diabetes Care 2015; 38(4): 604-9. DOI: https://doi.org/10.2337/dc14-2098
17. Aroda VR, Ratner RE. Metformin and type 2 diabetes prevention. Diabetes Spectr 2018; 31(4): 336-42. DOI: https://doi.org/10.2337/ds18-0020
18. Mahabaleshwarkar R, DeSantis A. Metformin dosage patterns in type 2 diabetes patients in a real-world setting in the United States. Diabetes Res Clin Pract 2021; 172: 108531. DOI: https://doi.org/10.1016/j.diabres.2020.108531

19. Vieira IH, Barros LM, Baptista CF, Rodrigues DM, Paiva IM. Recommendations for practical use of metformin, a central pharmacological therapy in type 2 diabetes. Clin Diabetes 2022; 40(1): 97-107.
DOI: https://doi.org/10.2337/cd21-0043

20. Young-Hyman D, de Groot M, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M. Psychosocial care for people with diabetes: a position statement of the American Diabetes Association. Diabetes Care 2016; 39(12): 2126-40.
DOI: https://doi.org/10.2337/dc16-2053

21. Tan HQM, Chin YH, Ng CH, Liow Y, Devi MK, Khoo CM, *et al.* Multidisciplinary team approach to diabetes. An outlook on providers' and patients' perspectives. Prim Care Diabetes 2020; 14(5): 545-51.
DOI: https://doi.org/10.1016/j.pcd.2020.05.012

22. Joyson BS, Jacob MS, Mathew F, Thomas J, Sushilkumar PL. Identification, assessment, and analysis of the cost-effectiveness of oral hypoglycemic agents for pharmacoeconomic evaluation in a tertiary care teaching hospital. World J Pharm Res 2019; 8(12): 1229-42.

23. Singh A, Dutta S, Varma A, Beg M, Kumar H, Kaur A. A drug utilization and pharmacoeconomic study of anti-diabetic drugs prescribed to type 2 diabetes mellitus patients visiting the medicine outpatient department of a tertiary care hospital of North India. Int J Basic Clin Pharmacol 2016; 5(4): 1220-7.
DOI: https://doi.org/10.18203/2319-2003.ijbcp20162219

24. Kodama N, Tahara N, Tahara A, Honda A, Nitta Y, Mizoguchi M, *et al.* Effects of pioglitazone on visceral fat metabolic activity in impaired glucose tolerance or type 2 diabetes mellitus. J Clin Endocrinol Metab 2013; 98(11): 4438-45.
DOI: https://doi.org/10.1210/jc.2013-2920

25. Saju S, Varghese FV, Deena RS, Nivetha NR. Pharmacoeconomic evaluation: cost-effectiveness analysis of oral antidiabetic therapy in a tertiary care hospital. Int J Pharm Sci Rev Res 2021; 66(1): 31-7.
DOI: http://dx.doi.org/10.47583/ijpsrr.2021.v66i01.008

26. John M, Gopinath D, Kalra S. Triple fixed drug combinations in type 2 diabetes. Indian J Endocrinol Metab 2015; 19(3): 311-3.
DOI: https://doi.org/10.4103%2F2230-8210.152739

27. Banu S, Baburaj A, Johncy N, Chandur VK, Siva S. A study on cost analysis in diabetic patients with cardiovascular complications in a tertiary care teaching hospital. Int J Health Sci Res 2020; 10: 2. https://www.ijhsr.org/IJHSR_Vol.10_Issue.4_April2020/3.pdf

28. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, *et al.* 10. Cardiovascular disease and risk management: standards of medical care in diabetes-2023. Diabetes Care 2023; 46(Suppl 1): S158-90.
DOI: https://doi.org/10.2337/dc23-S010

29. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, *et al.* 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Circulation 2019; 140(11): e596-646.
DOI: https://doi.org/10.1161/CIR.0000000000000678

30. Papazafiropoulou AK, Melidonis A, Antonopoulos S. Aspirin in primary prevention of cardiovascular disease in diabetes. Arch Med Sci Atheroscler Dis 2021; 6: e109-14.
DOI: https://doi.org/10.5114/amsad.2021.105596

31. Gillani SW, Syed Sulaiman SA, Menon V, Rahamathullah N, Elshafie RM, Rathore HA. Effect of different antidiabetic medications on atherosclerotic cardiovascular disease (ASCVD) risk score among patients with type-2 diabetes mellitus: A multicenter non-interventional observational study. PLoS One 2022; 17(6): e0270143.
DOI: https://doi.org/10.1371/journal.pone.0270143

32. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, *et al.* 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes—2023. Diabetes Care 2023; 46(Supplement_1): S140-57.
DOI: https://doi.org/10.2337/dc23-S009

33. Zhao JZ, Weinhandl ED, Carlson AM, St Peter WL. Glucose-lowering medication use in CKD: analysis of US medicare beneficiaries between 2007 and 2016. Kidney Med 2020; 3(2): 173-82.
DOI: https://doi.org/10.1016%2Fj.xkme.2020.09.016

34. Bailey CJ, Day C. Diabetes therapies in renal impairment. Br J Diabetes Vasc Dis 2012; 12(4): 167-71.
DOI: https://doi.org/10.1177/1474651412458811

35. Yang G, Zeng G, Wu JP, *et al.* Glipizide blocks renal interstitial fibrosis by inhibiting AKT signaling pathway. Eur Rev Med Pharmacol Sci 2017; 21(4): 867-72.

36. Erdmann E, Dormandy J, Wilcox R, Massi-Benedetti M, Charbonnel B. PROactive 07: pioglitazone in the treatment of type 2 diabetes: results of the PROactive study. Vasc Health Risk Manag 2007; 3(4): 355-70.

37. Garber AJ, Handelsman Y, Grunberger G, Einhorn D, Abrahamson MJ, Barzilay JI, *et al.* Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2020 Executive Summary. Endocr Pract 2020; 26(1):107-39.
DOI: https://doi.org/10.4158/cs-2019-0472

38. Alkhail BA, Iftikhar R, Shaikh AA. Use of Aspirin and Statin as primary prevention for cardiovascular diseases. Pak J Med Sci 2016; 32(6): 1336-9.
DOI: https://doi.org/10.12669%2Fpjms.326.10615

39. Ho CC, Yang YS, Huang CN, Lo SC, Wang YH, Kornelius E. The efficacy of pioglitazone for renal protection in diabetic kidney disease. PLoS One 2022; 17(2): e0264129.
DOI: https://doi.org/10.1371/journal.pone.0264129