Diabetes & Metabolic Syndrome: Clinical Research & Reviews 15 (2021) 891–899

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Pharmacological treatment of type 2 diabetes in Saudi Arabia: A consensus statement from the Saudi Society of Endocrinology and Metabolism (SSEM)

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ARTICLE INFO

Article history:
Received 13 December 2020
Received in revised form
14 March 2021
Accepted 4 April 2021

Keywords:
Diabetes
Pharmacological treatment
Saudi Arabia

ABSTRACT

Background and aims: The list of available treatment options for managing blood glucose in patients with type 2 diabetes (T2D) has grown over recent years making the task of choosing between traditional and newer glucose-lowering agents a difficult one for healthcare providers.
Methods: We summarize treatment algorithms developed by popular professional societies and propose a patient-centered and culture-driven recommendations for selecting diabetes medications for people with T2D in Saudi Arabia.
Results: Though most professional societies recognize patient's adherence to medications as an important factor in achieving glycemic targets, published algorithms schemes do not formally enlist adherence to medication as a deciding factor in the choice of glucose–lowering agents. Medication appeal to patients, an important determinant of medication adherence, is influenced by several factors including lifestyle, common beliefs, customs and traditions, health literacy, perception of health and disease, socioeconomic and cultural backgrounds, and religious commitments and obligations. In Saudi Arabia, poor adherence to therapy is a major obstacle to effective management of local people with T2D.
Conclusions: The Saudi population has a unique socioeconomic and cultural background that widely respect adherence to religion and culture; and the applicability of international guidelines for the management of T2D to the Saudi population has been called into question. In this consensus statement, we propose patient-centered and culture-driven recommendations that integrate medication-adherence and medication-cost into overall selection of diabetes medications for people with T2D in Saudi Arabia.

1. Introduction

The health, social, and economic burden of type 2 diabetes (T2D) is on the rise globally, with parts of the world, such as the Arab Gulf region, bearing a disproportionate burden of the disease. With a prevalence rate standing at 13.4%, Saudi Arabia has one of the highest rates of diabetes reported in the world with diabetes expected to affect 25% of the Saudi population by 2045 [1,2] The treatment of T2D consists of lifestyle and behavioral interventions along with glucose-lowering medications that aim to relieve symptoms and prevent long-term complications [3,4]. The list of glucose-lowering medications available in the market has been expanding over recent years leading to the emergence of a variety of practice patterns adopted in different parts of the world.

The recent introduction of new medications has enriched and extended therapeutic options available for the treatment of T2D but it has also presented healthcare providers with the difficult task of making choices between established old medications and novel new therapies. Many of the available guidelines for the management of T2D were developed for high-resource settings and advocate for expensive glucose lowering agents without defining the

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https://doi.org/10.1016/j.dsx.2021.04.003
1871-4021/

targeted setting or cost implications of those recommendations in real world setting. An additional challenge to address in the case of Saudi Arabia, is the relevance and applicability of these guidelines to the Saudi population who have a unique socioeconomic and cultural background that is different from anywhere else. Adherence to religion and culture is widely cherished and respected in Saudi Arabia.

Adherence to medications is generally poor among people with T2D and this has been linked to lower attainment of treatment targets for hemoglobin A1C (HbA1C), blood pressure, and low-density lipoprotein (LDL) cholesterol, and consequently higher healthcare costs and poorer clinical outcome [5–12]. Although, the importance of patient's adherence to medications is recognized in the general guidelines documents, it is however, not prioritized or listed as a deciding factor in the choice of glucose-lowering agents recommended in any of the current treatment algorithms of T2D. In Saudi Arabia, we find poor adherence to therapy a major clinical obstacle to effective management of local people with T2D [13,14]. Medication appeal and general acceptability to patients should be incorporated as part of patients' preferences and needs when selecting a glucose-lowering therapy for people with T2D [13–16].

Here, we briefly review select international guidelines focusing on the pharmacological management of T2D and discuss key similarities and differences among guidelines. We also propose a patient-centered therapeutic algorithm for the management of T2D in Saudi Arabia that is based on the contributions of three integral parts of diabetes management: existing scientific evidence, an instinctive knowledge of native T2D patients and the wider Saudi culture, and the cost burden and economic realities on the ground. This consensus statement is commissioned by the Saudi Society of Endocrinology and Metabolism (SSEM) to provide general guidance to health care providers and policy makers in Saudi Arabia. The proposed recommendations represent the professional views and clinical experiences of the authors of the statement and should by no means be considered to override or substitute for value clinical judgment.

2. Summary of professional societies' recommendations for the pharmacological management of type 2 diabetes

There appear to be key differences in the recommendations developed by various international professional societies for the treatment of T2D especially in the areas of first and second intensification of therapy. The primary position of metformin as a first line therapy in the treatment of T2D has also been recently questioned by some authorities. This evolving debate and divergent professional opinion has been stimulated by the recent findings of the Cardiovascular Outcome Trials (CVOTs). In this section, we briefly highlight common similarities and outstanding differences in the medications management algorithms of T2D adopted by popular professional societies and summarized in Table 1.

The National Institute for Health and Care Excellence (NICE) provides national guidance to improving health care in the United Kingdom (UK) and was published in 2015 and last updated in 2019 [17]. The NICE guidelines take into consideration medication cost and patient-related factors; and in contrast to other guidelines such as the American Diabetes Association (ADA) Standards of Medical Care, the NICE guidelines recommend limiting the use of glucagon-like peptide-1 (GLP-1) agonists to patients who failed to achieve adequate control on triple oral therapy. That said, the NICE guidelines are currently under review and this section of the guidelines is proposed to be updated. The NICE guidelines are also expected to revisit position with Neutral Protamine Hagedorn (NPH) and biosimilar long-acting as a cost-effective alternative insulin treatment option [18].

The ADA Standards of Medical Care in Diabetes are academically the most recognizable diabetes guidelines around the world [19]. The ADA has been among the first to embrace the results of CVOTs. In its most recent version of the Standard of Care it is recommended to add GLP-1 RA/sodium-glucose cotransporter 2 inhibitors (SGLT2i) to metformin in patients with established or at high risk of Atherosclerotic Cardiovascular Disease (ASCVD), and those with chronic kidney disease (CKD), or heart failure (HF) independent of hemoglobin HbA1C level. On the other hand, traditional oral medications such as sulfonylurea (SU) and to lesser extent Thiazolidinediones (TZDs) and Dipeptidyl Peptidase-4 (DPP4) inhibitors have been relegated lowest on the list of medications recommended on the algorithm scheme under most circumstances. An exemption has been made for use of SUs as second line therapy in poor and underprivileged patients who otherwise would find nothing else affordable on the list of medications advocated by the ADA. Overall, ADA recommendations seem to be driven more by academic findings than practical or cost related issues encountered by the common T2D patient in the real wide world.

The Scottish Intercollegiate Guidelines Network (SIGN) for the management of type 2 diabetes was published in 2017 and has recently been updated in 2020 [20]. The updated version of the SIGN guidelines is another example of how the recent CVOTs have shaped the guidelines on diabetes management. The 2020 SIGN has placed GLP-1RA/SGLT-2i to highest position in the algorithm scheme. In fact, these agents are now recommended as the initial therapy (in combination with metformin) in patients with ASCVD, high risk for ASCVD, or obesity/overweight. Similarly, SGLT2i inhibitors are advocated as initial therapy (in combination with metformin) in patients with HF or CKD.

The Research Society for the Study of Diabetes in India-Endocrine Society of India (RSSDI-ESI) Clinical Practice Guidelines for the management of T2D was last updated in 2020 to provide clinical guidance on the management of T2D in India and neighboring countries [21]. The RSSDI-ESI guidelines highlight the "Asian Indian phenotype" of T2D and include Indian-tailored recommendations regarding when and how to screen for T2D. Therapeutically, traditional oral agents seem to dominate first- and second-line therapies and as such RSSDI-ESI guidance closely mirrors those developed by current NICE guidelines.

The International Diabetes Federation (IDF) Clinical Practice Recommendations for Managing Type 2 Diabetes in Primary Care was developed in 2005 and last updated in 2017 [22]. The IDF recommends lifestyle intervention with or without metformin as the initial treatment of T2D; SUs, DPP-4is, and SGLT2is are all considered preferred add-on options after metformin when intensification of therapy is indicated. Addition of GLP-1 agonist to metformin, in the 1st intensification of therapy, is not recommended in routine practice unless weight loss is deemed a clinical priority and the drug perceived to provide an economically viable treatment option. Similarly, GLP-1 agonist can be added, as an alternative to insulin, in the 2nd intensification step if weight loss "has been insufficient".

2.1. The adoption of international guidelines for the management of T2D in Saudi Arabia

When it comes to choosing a glucose lowering agent, "*One size does not fit all*" is true not only for individual T2D patients but this can also be extended to the type of culture at hand. People with T2D differ in their lifestyles, common beliefs, customs and traditions, health literacy, perception of health and disease, socioeconomic status, racial/ethnic backgrounds, and religious commitments and obligations [23–27]. Therefore, there will never be a universal set of guidelines that can be considered applicable and overly convenient

Table 1
Select International Guidelines for Managing Type 2 Diabetes (Ordered by date of publication).

	IDF Guideline (2018)	RSSDI-ESI (2020)	NICE guidelines (2019)	ADA guidelines (2021)	SIGN Guidelines (2020)
Initial Drug Treatment	-Start with lifestyle modification ± metformin -Metformin is the preferred first-line therapy -Start with SU (not glibenclamide/glyburide), AGI, or DPP4 inhibitor if metformin is contraindicated/not tolerated -Initial combination therapy (preferably metformin + SU, DPP4 inhibitor, or SGLT2 inhibitor) to be considered if baseline HbA1C is 1–2% above target -Start with insulin (preferable basal insulin) if symptomatic with signs of acute decompensation	-Start with both metformin + lifestyle -Dual therapy may be indicated initially if a single therapy is unlikely to achieve glucose targets	-Start with lifestyle modification -If HbA1C rises to 6.5% (47.5 mmol/mol) on lifestyle interventions→ offer metformin -Dual therapy is not recommended as the initial treatment. -Repaglinide is recommended as a clinically- and cost-effective initial drug therapy when metformin is contraindicated/not tolerated	-Start with both metformin + lifestyle -SU is not a recommended option -Consider early introduction of insulin if there is evidence of catabolism, symptoms of hyperglycemia, or HbA1C>10% (85.8 mmol/mol). -Initial dual therapy should be considered in patients with HbA1C levels 1.5–2% above target.	-***For all patients with T2D***: Lifestyle counseling -***For patients with ASCVD***: *Consider initiating both metformin+ (GLP-1 or SGLT2i) *Recommend Metformin as 1st line therapy *Recommend SGLT2i or GLP1 as a second-line therapy -***For patients with HF***: *Consider initiating metformin + SGLT2i *Recommend Metformin as 1st line therapy *Recommend SGLT2i or GLP1 as a second-line therapy -***For patients with CKD***: *Consider initiating metformin + SGLT2i *Recommend Metformin as 1st line therapy if eGFR>30 *Recommend SGLT2i as a second-line therapy if eGFR>45 *GLP-1 as third-line therapy *DPP-4i as fourth-line treatment *Consider renal doses in all medications -***For patients at high CV risk:*** *Consider initiating metformin+ (GLP-1 or SGLT2i) *Metformin as 1st line therapy *SGLT2i or GLP1 as a second-line therapy *Newer-generation SUs or glinides when drug cost must be minimized * Pioglitazone in patients with NAFLD and where insulin resistance predominates -***For patients with obesity/ overweight:*** *Consider initiating metformin+ (GLP-1 or SGLT2i) * Metformin as 1st line therapy *SGLT2i or GLP1 as a second-line therapy * Where possible, avoid SUs, glinides, pioglitazone, and insulin
First Intensification of Therapy	Use dual therapy if target HbA1C is not achieved in 3–6 months -Dual therapy options: Preferred: metformin + (SU, DPP-4i, or SGLT-2i) Other options: metformin + (AGI or GLP-1 agonist if weight loss is a priority and the drug is affordable)	-Escalate therapy if HbA1C is >7% after 3 months of therapy as follows: *A) If HbA1C is > 7 to ≤ 7.5% (53 to 58.5 mmol/mol) → Add another oral agent (SU, TZD, SGLT-2i, DPP-4i, or AGI)* *B) If HbA1C is > 7.5% (58.5 mmol/mol) → Add premixed insulin*)	-Use dual therapy as the 2nd step -Dual therapy options: 1) metformin + (DPP-4i *or* SU *or* pioglitazone) 2) metformin + SGLT-2 inhibitor is offered only if: *SU is contraindicated or * risk or consequences of hypoglycemia are significant -If metformin is not tolerated→ combine any of the following oral agents as alternative (DPP-4i, SU, & pioglitazone). SGLT-2 inhibitor is an option only if SU is contraindicated or risk or consequences of hypoglycemia are significant Note: SGLT-2i and DPP-4 combination is not offered as an option	-If the patient has high-risk indicators or established ASCVD, CKD, or HF→ Add GLP-1 agonist or SGLT-2i -If the patient is not at high-risk for ASCVD, CKD, or HF → Add DPP-4i, or GLP-1, or SGLT-2i, or TZDs	
Second Intensification of Therapy	-Use triple therapy if target HbA1C is not achieved after 3–6 months on dual therapy -Most common add-on therapy is basal insulin -GLP-1 agonist can be added (as an alternative to insulin) if weigh loss has been insufficient -Triple oral therapy may be effective before adding an injectable	-Use triple therapy by adding a 3rd oral agent or start insulin or GLP-1 agonists	-Use triple therapy by adding a 3rd oral agent or start insulin-based therapy -The general recommendation for insulin is to use NPH twice daily; followed by short acting insulin -Pre-mixed biphasic insulin is offered as an option -Detemir/glargine to be considered if: * Patient needs assistance to inject insulin *Or* *Patient has recurrent hypoglycemia	-If the patient has high ASCVD risk→ Use GLP-1 & SGLT2i in combination ***Or*** add one of the following: *DPP4i (if not on GLP-1) *Basal insulin *TZD *SU (note: SU is in the bottom of the list) -If the patient has low ASCVD risk → Use any triple therapy	
When isGLP-1 agonist or SGLT-2 inhibitor Recommended?	-**Adding** GLP-1 agonist to metformin, in the 1st intensification of therapy, is offered as an option if weight loss is a priority and the drug is affordable -GLP-1 agonist can be added, as an alternative to insulin, in the 2nd intensification of therapy if weigh loss has been insufficient -Use of SGLT-2 inhibitors is suggested as a drug of choice to be combined with	-Consider GLP-1 agonist if glucose targets are not achieved with 3 oral agents -SGLT-2 inhibitors are offered as add-on options to metformin in the 1st intensification of therapy, particularly in patients with ASCVD, heart failure, CKD, or overweight	-The recommendation to use GLP-1 agonist is limited to those who failed the triple therapy (or could not tolerate it) and have the following: * BMI of ≥35 and psychological or other medical problems associated with obesity ***OR*** * BMI ≥35 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other	-The recommendation to add GLP-1/SGLT2i to metformin is ***independent*** of baseline HbA1C or HbA1C target in patients of high-risk or established ASCVD, CKD, or HF	-Compared to the 2018 version, the recommendation to use GLP-1/SGLT-2i has been moved up in the algorithm. - Now these agents are to be considered as the initial therapy (in combination with metformin) in patients with: ASCVD, high risk for ASCVD, obesity/overweight. -Compared to the 2018 version, the recommendation to use

(*continued on next page*)

Table 1 (*continued*)

	IDF Guideline (2018)	RSSDI-ESI (2020)	NICE guidelines (2019)	ADA guidelines (2021)	SIGN Guidelines (2020)
	metformin, when initial combination therapy is considered; or to be added to metformin, when first intensification of therapy is indicated.		significant obesity-related comorbidities. -Continuation of GLP-1 agonist is recommended only if beneficial metabolic response is seen (i.e. reduction in HbA1C by 1% and a weight loss of at least 3% of initial weight) -Use of SGLT-2 inhibitors is offered as an option in first intensification (i.e. add-on therapy to metformin) only if SU is contraindicated or if the risk or consequences of hypoglycemia are significant		SGLT-2i has been moved up in the algorithm. - Now SGLT2i is to be considered as the initial therapy (in combination with metformin) in patients with: HF or CKD.
Additional comments	-A small section about the cardiovascular effects of glucose-lowering agents is included in the guidelines with a statement advising health care providers to consider the findings of the CVOT's when selecting a glucose-lowering agent in patients with CVD.	-The use of premixed insulin is preferred over basal bolus regimen.	-There is a focus on supporting the patient to aim for an HbA1C target throughout the algorithm. * If the person is on DPP-4i, SGLT-2i, or Pioglitazone → aim for HbA1C of 6.5% (47.5 mmol/mol) * If the person is on SU → aim for HbA1C of 7% (53 mmol/mol) -The focus is on medication classes as opposed to individual drugs within classes.		-Insulin to be considered when other therapies have been explored

Abbreviations: NICE, National Institute for Health and Care Excellence; ADA, American Diabetes Association; SIGN, Scottish Intercollegiate Guidelines Network; RSSDI-ESI, Research Society for the Study of Diabetes in India-Endocrine Society of India; IDF, International Diabetes Federation; AGI, Alpha-glucosidase inhibitor; SU, Sulphonylurea; TZD, thiazolidinediones; SGLT-2, Sodium-glucose Cotransporter-2; DPP-4i, dipeptidyl peptidase-4 inhibitors, GLP-1, Glucagon-like peptide-1; ASCVD, Atherosclerotic cardiovascular disease; CKD, Chronic Kidney Disease.

to all people with T2D and at all times and settings; thus it is prudent to "localize" clinical recommendations to ensure optimal suitability to native T2D population. Such an approach will likely enhance adoption of the guidelines by national health care providers in Saudi Arabia and, more importantly, improve adherence of local T2D patients to recommended medications. Moreover, the genetic susceptibility, phenotype, and progression of T2D differ across populations. For example, the "Asian Indian Phenotype" is characterized by a higher visceral adiposity and risk of metabolic abnormalities compared to White Caucasians at any given body mass index (BMI) [28]. While data regarding the epidemiology, genotype, and phenotype of T2D in Saudi Arabia is scarce, the available data indicates a remarkable rise in the incidence of T2D in Saudi Arabia over the past decades and points to several predisposing factors to this pandemic including the socioeconomic transformation that took place in the country along with the high rate of consanguinity [29]. More research is needed to better characterize the genotype, phenotype, and natural history of T2D in Saudis.

As outlined above, most of the updated guidelines from international professional societies have prioritized novel glucose-lowering agents in their treatment algorithms. While most of these novel agents have evidently shown cardiovascular, and in some cases renal benefits, compared to placebo; there are several barriers preventing wider adoption of these agents in real world [30]. Barriers include mounting cost, inconvenience of administration (GLP1-RAs) and a range of rare but evidently serious side effects (SGLT2is) [31]. Furthermore, the scientific evidence of specific benefits on CV/total mortality has proved increasingly inconsistent as shown by the negative findings of recent SGLT2is trials (VERTIS-CV, EMPEROR-REDUCED trials) [32,33]. Finally, patients' adherence to glucose-lowering medications is a real clinical obstacle encountered among patients in Middle Eastern countries including Saudi Arabia [34]. Poor adherence to diabetes medications is estimated to reach 68% in parts of the Middle East [35,36]. Reasons for this include heightened fear of adverse effects, use of alternative herbal remedies, unease about injectable therapies, complexity of treatment regimens, inadequate socio-economic support, and a firm belief amongst many patients that divine intervention, not medications can prevent adverse diabetes complications [34,35,37].

3. Selecting a glucose-lowering medication in Saudis with T2D

Our approach to selecting a glucose-lowering agent takes into account patient- and drug-specific factors of direct relevance to Saudis with T2D. We refer to this as the "SAUDI ARABIA" approach for diabetes management. It advocates clinical consideration of the following key factors prior to selecting a glucose-lowering agent: **S**ymptoms of hyperglycemia, **A**dherence to medications, **U**nwanted effects of medications, **D**uration of diabetes, **I**ndividual patient preference and needs, **A**1C level, **R**enal function, **A**ge, **B**udget, **I**ndividual circumstances, and **A**SCVD or heart failure. Details about how each of these factors should guide the selection of treatment in Saudis with T2D are described below and summarized in Table 2. A simplified algorithm scheme on medications management of Saudis with T2D is provided in Fig. 1.

1) Symptoms of Hyperglycemia and osmosis:

In addition to lifestyle interventions and initiation of metformin, we recommend the addition of either SU or basal insulin in the presence of symptoms of hyperglycemia, particularly weight loss,

Table 2
Patient- and drug-specific factors to consider when selecting a glucose-lowering medication in Saudis with T2D.

S	*Symptomatic from hyperglycemia and osmosis?*	Initiate metformin & (SUs or insulin) in patients with symptomatic hyperglycemia, catabolism, or weight loss.
A	***Adherence to medications***	Assess the patient's adherence to therapy in the past, identify patient-specific barriers and facilitators of adherence, evaluate patient's perception of illness goals of treatment, and work with the patient on selecting a therapeutic regimen that takes into consideration all these factors and maximizes the likelihood of patient's adherence to therapy.
U	***Unwanted effects of medications***	- Exercise precaution when prescribing medications that increase the risk of weight gain (e.g. SU and insulin) to individuals with obesity; fluid retention (e.g. pioglitazone) to patients with heart failure; fracture (e.g. pioglitazone and SGLT-2 I) to patients with low bone-mineral density; GI side effects (e.g. metformin and GLP-1 agonists) to patients with troublesome GI symptoms or severe gastroparesis. - Avoid pioglitazone if the patient has bladder cancer or uninvestigated macroscopic hematuria. - Exercise precaution when prescribing SGLT-2 inhibitors to patients with recurrent UTI or GU infections; and counsel them regarding the risk, symptoms, and signs of diabetic ketoacidosis. - Exercise precaution when prescribing SGLT-2 inhibitors (particularly canagliflozin) to patients with peripheral vascular disease, diabetic foot, or history of amputation. - Whenever possible, agents with low risk of hypoglycemia should be prioritized over hypoglycemia-inducing agents, such as old-generation SUs and insulin, in patients at high risk of hypoglycemia (e.g. those with history of cognitive disorder, recurrent hypoglycemia, or hypoglycemia unawareness) or if the consequences of hypoglycemia are significant (e.g. drivers of heavy vehicles or public transportation vehicles such as buses or taxis, or individuals with ischemic heart disease
D	***Duration of Diabetes***	Intensive glucose control is recommended when duration of DM is less than 5–10 years; whereas less aggressive control is recommended for those with a long duration of diabetes
I	***Individual preference and needs***	Consider the patient's preference and needs [e.g. injectables vs non-injectables, health literacy, beliefs (e.g. fatalism); and adherence to therapy in the past (e.g. combination pills vs single pills)
A	***HbA1C***	Assess the current and target hemoglobin HbA1C levels and select medication(s) that can achieve the desired change in HbA1C. Generally, the glucose-lowering efficacy is the highest for injectable therapies (such as insulin and GLP-1 agonists). Among the oral glucose-lowering agents, SU and TZD have the highest efficacy in lowering HbA1C; whereas DPP4is, SGLT2is, and meglitinide have a moderate efficacy, and AGI has the lowest efficacy.
R	***Renal function***	- Adjust all medications doses for renal function, whenever appropriate - Some medications (e.g. repaglinide & linagliptin) can be used across all stages of CKD. - Use of long-acting and old-generation SUs should be minimized in patients with low eGFR. - Insulin is the safest and most effective glucose-lowering medication in ESRD - When available, SGLT-2 inhibitor is a favorable add-on medication to metformin in patients with CKD
A	***Age***	***Consider the following when treating older adults with T2D:*** - The long-term benefit from glucose lowering may be reduced in these individuals. - Be more flexible & consider the patients' broader health and social needs. - They usually have comorbidities and are at higher risk of falls and frailty. - Risk of hypoglycemia should be minimized. - Pioglitazone is less preferred in post-menopausal women due to higher risk of low bone density.
B	***Budget***	- Metformin, SU, and alpha-glucosidase inhibitors have the lowest cost - GLP-1 & SGLT-2I have the highest cost - When two medications from the same class are appropriate, prescribe the one that has the lower cost
I	***Individual Circumstances***	- Consider occupational implications of using insulin - Insulin might be the least favorable in patients with blindness, inability to inject, or those who spend most of their time outdoor and cannot properly store insulin. - Patients with NASH or severe insulin resistance may benefit from pioglitazone
A	***ASCVD and Heart Failure***	- When available, GLP1 agonist is a favorable add-on medication to metformin in patients with history of ASCVD - When available, SGLT-2 inhibitor is a favorable add-on medication to metformin in patients with history of HF

Abbreviations: AGI, Alpha-glucosidase inhibitor; SU, Sulphonylurea; TZD, thiazolidinediones; SGLT-2, Sodium-glucose Cotransporter-2; DPP-4i, dipeptidyl peptidase-4 inhibitors, GLP-1, Glucagon-like peptide-1; ASCVD, Atherosclerotic cardiovascular disease; CKD, Chronic Kidney Disease.

catabolism, or osmosis. Data have shown that the use of SU alone as the initial therapy in cases of severe hyperglycemia is as effective as the use of both SU and basal insulin in improving both blood glucose levels and beta-cell function in individuals with T2D [38]. This offers a safe and effective alternative to insulin injections that many Saudis with T2D dread to take from the outset of the disease. It is important to emphasize however, that, insulin therapy is the only treatment option recommended whenever the diagnosis of T1D is clinically suspected.

2) Adherence to medications:

The most effective glucose-lowering medication is the one that the patient ends up taking as prescribed. Therefore, it is essential to assess patient's adherence to therapy a priori, discuss treatment goals and preempt likely barriers of adherence to therapy. A glucose-lowering agent that the patient is likely to accept and adhere to is more important than the designated place of the agent in the cascade of treatment options. Patient's adherence to medications is more important to clinical outcome than physician's adherence to random formal guidelines. Expense and inconvenience of use of diabetes medication are key factors known to impede patient's adherence to therapy.

3) Unwanted effects of medications:

It is not uncommon for patients with T2D to discontinue medications because of an actual encounter or subjective fear (real or perceived) of adverse effects [39]. It is essential that patients with T2D are counseled about the frequency and severity of potential side effects of glucose-lowering agents. Only glucose-lowering medications with likely benefits outweighing potential risks should be offered to patients with T2D. What might be considered as a low risk or dismissed as "mild" adverse effect by the treating physician may prove emotionally taxing and physically burdensome to the patient and their families. Insulin and old-generation SU are associated with a significant risk of hypoglycemia. The use of these medications should be minimized in individuals with hypoglycemia unawareness, recurrent severe hypoglycemia, and older people with T2D. It is worth noting that newer-generation

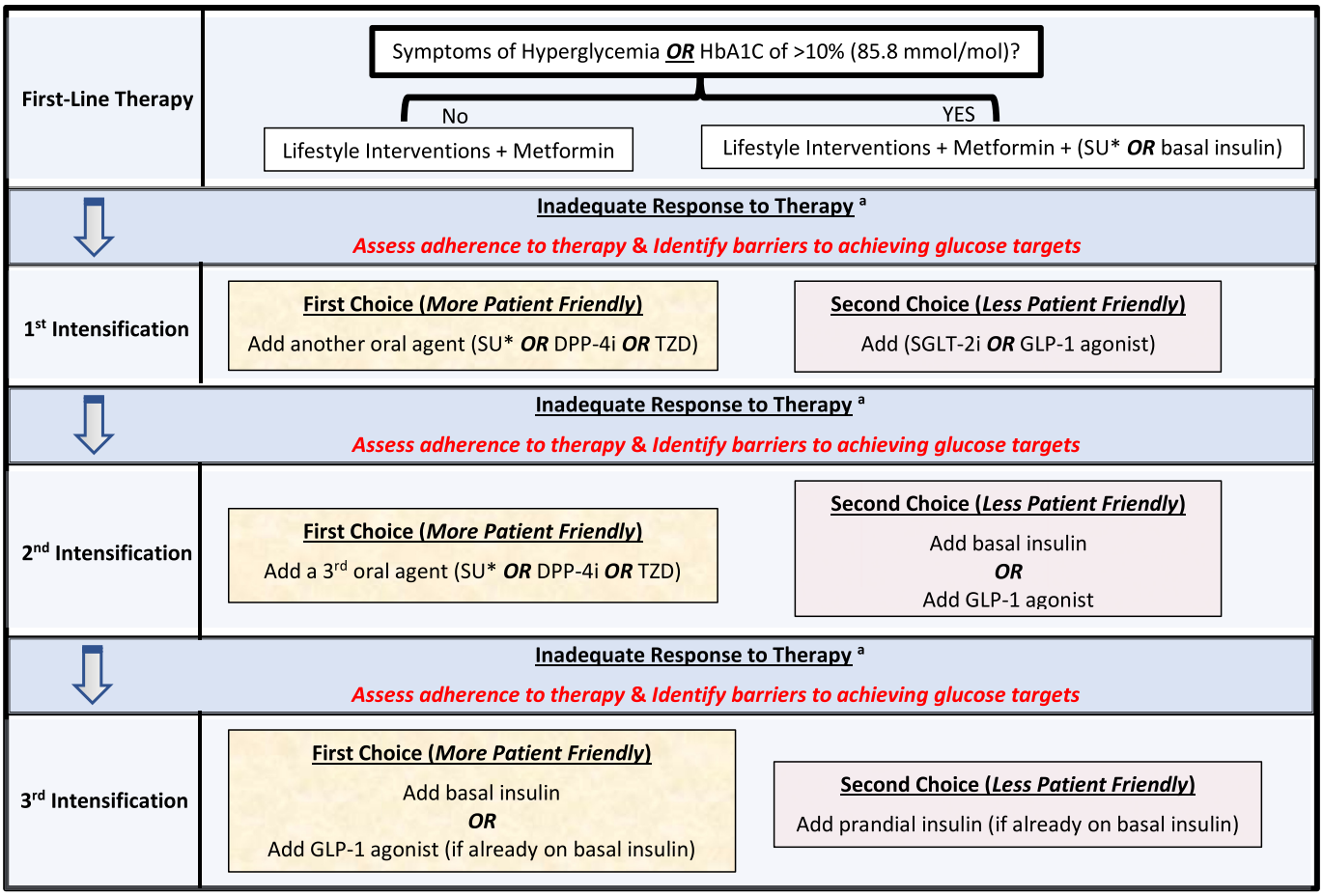

Fig. 1. Approach to selecting glucose-lowering medications in patients with type 2 diabetes in Saudi Arabia. Abbreviations: SU, Sulfonylurea; DPP-4i, dipeptidyl peptidase-4 inhibitors; TZD, thiazolidinediones; GLP-1, Glucagon-like peptide-1.

SUs are associated with a lower risk of hypoglycemia and reassuring cardiovascular safety; which along with their wide availability and affordability make SU as useful treatment option for patients with T2D and health-care systems alike [40,41]. Table 2 highlights unwanted (adverse) effects of glucose-lowering medications.

4) Duration of Diabetes:

A tighter glycemic control is advocated for in patients with new onset or short duration of T2D to minimize the risk of long-term micro- and macrovascular complications. As the duration of diabetes increases, the task of maintaining glucose control becomes clinically challenging necessitating use of multiple oral glucose-lowering medications or the addition of insulin therapy. The decision to initiate injectable glucose-lowering medications, particularly insulin, should not be delayed when clinically indicated after proper discussion with the patient.

5) Individual Preferences and Needs:

The most effective glucose-lowering medication is the one that the patient will take as prescribed. Therefore, patient's preference and needs should be prioritized when selecting a glucose-lowering agent. These preferences and needs may differ from community to another and from patients to another within the same community. For example, patients with T2D generally prefer oral medications over injectable therapies; however, a drug with weight loss benefit may appeal to some patients regardless of route of administration (or prohibitive cost) [42,43]. Similarly, some patients may prefer to take two-drug combination over taking the same drugs separately. Others may prefer a diabetes medication that can be taken specifically at meal ingestion time to counteract the postprandial rise in blood glucose (otherwise, no meal, no medication) and accordingly may find glinide therapy (eg Repaglinide) a desirable treatment option. Patient's choice should always be probed and respected. The role of health care provider is not to "sell" any product but rather help the patient make an informed personal decision. Considering the current gap in diabetes knowledge and awareness among Saudis with T2D, the role of structured diabetes education programs in improving patients' health literacy, debunking myths, and ultimately guiding patients' choices of medications cannot be overemphasized [44]. For example, the unwillingness to commence insulin therapy when clinically indicated, a common issue among Saudis with T2D, can sometimes be due to myths surrounding the use of insulin [45]. The implementation of diabetes education programs and adoption of an integrated care approach can be of tremendous value in promoting patients' acceptance of insulin and early initiation of insulin therapy when indicated [46].

6) A1C

Some glucose-lowering medications are known to be more efficacious in lowering HbA1C levels than others (Table 2). Involving patients in the discussion about the current and target HbA1C levels can help deciding which, and how many, glucose-lowering medications are most appropriate therapy for the

Table 3
Cost estimates of common glucose-lowering agents (excluding insulin) in Saudi Arabia.

CLASS	MONTHLY COST US $ (SAR*)	ANNUAL COST US $ (SAR*)	RELATIVE TO METFORMIN COST
Metformin	$ 4.13 (SAR 15.5)	$ 49.6 (SAR 186)	Ref (1)
Sulfonylurea	$ 6.4 (SAR 24)	$ 76.8 (SAR 288)	1.5
Thiazolidinedione	$ 22.1 (SAR 83)	$ 265.6 (SAR 996)	5
DDP4	$ 29 (SAR 109)	$ 348.8 (SAR 1308)	7
SGLT2	$ 36.4 (SAR 136.5)	$ 436.8 (SAR 1638)	9
GLP1	$ 219.4 (SAR 823)	$ 2633.6 (SAR 9876)	53

Estimated published prices in 2020.
*SAR = 0.266 US$.

patient. In addition to lifestyle interventions and metformin, patients with T2D and HbA1C >10% (>85.8 mml/mol) should be offered the option to start basal insulin or SU to effectively lower the glucose levels and resolve the glucose toxicity state. De-escalation of therapy is always an option after achieving an acceptable glucose control.

7) Renal Function:

Renal function should be considered prior to prescribing a glucose-lowering medication for two main reasons: First, some medications are renally cleared and are either clinically contra-indicated or require specific dose adjustment based on estimated glomerular filtration rate (eGFR). Second, most SGLT2 inhibitors and some GLP-1 agonists have been shown to improve indices of renal function and accordingly are considered to be of particular value in patients with CKD. The use of hypoglycemia-inducing agents, such as old-generation SUs, should be avoided or replaced with safer agents (newer generations or glinides) in patients with T2D and CKD or end-stage renal disease (ESRD) due to the increased risk of hypoglycemia.

8) Age:

Patient age is an important factor in determining the desired HbA1C target level and choice of diabetes medication preferred. Younger individuals with no comorbidities can be advised to target HbA1C level of 7% (53 mmol/mol) or less; strict control in such patients is feasible and worthwhile, representing a good long term “investment” to preventing chronic diabetes complications; on the other hand, a less stringent HbA1C goal is advisable in older adults with co-morbid conditions in whom personal safety and quality of life take precedence over any longterm benefits of strict control. Therapeutic regimens should always be simplified and treatment de-intensified in elderly patients to avert unnecessary harm (e.g. hypoglycemia), stress or inconvenience [47,48].

9) Budget:

Medication cost is recognized by everyone involved in diabetes care (patients, physicians, and policy makers) as a major factor determining the choice of medications available for patients around the world [31,41]. Cost of medications matters everywhere, even in countries where the main health-care services are generously funded by the state, such as Saudi Arabia. Expensive medications can be a major burden on individual patients and a financial drain on healthcare resources. Affordable and cost effective medications such as metformin, SUs, TZDs, and certain DPP-4 inhibitors appeal to many healthcare providers as offering a rational alternative (to expensive drugs) in the treatment of T2D, deterring cost without compromising clinical outcome. The high cost of GLP-1 agonists and SGLT-2 inhibitors on the other hand has perturbed full utilization of these drugs despite an inherent novelty factor and proven benefits associated with these agents. Table 3 presents price list estimates of common (non-insulin) glucose-lowering agents available in Saudi Arabia to highlight the substantial disparity in cost between new and old medications.

10) Individual Circumstances:

The decision to selecting a diabetes medication can be an intricate one that often goes beyond standard medical advice or the plain wishes of the individual patient into accommodating the wider role played by the native culture and surrounding environment. Common social myths, misperception of good health, fatalistic attitudes, adherence to religious beliefs and spiritual wellbeing are additional factors encountered everyday in the management of Saudi patients with T2D. Harsh local climate manifests by formidable heat over the long summer months is a daily reality in many parts of Saudi Arabia, hindering outdoor activities and exposing participants to the risk of fluid loss and dehydration. Saudi patients often refrain from carrying insulin therapy around in case of damage to supply by heat and deliberately avoid injecting themselves in public for perceived fear of social intrusion. Another distinct circumstance in Saudi Arabia, is fasting the month of Ramadan, one of the main pillars of Islam. The vast majority of people living with T2D in Saudi Arabia devotionally elect to fast the entire month of Ramadan; and they must abstain from eating, drinking, and ingestion of oral medications from predawn till sunset. Clinically, it is not practical nor feasible to interchange diabetes medication regimen for only one calendar month of the year for the T2D population in Saudi Arabia; rather it’s better to have necessary dose adjustments made during the month of Ramadan to avoid the risk of adverse effects such as hypoglycemia or dehydration. Similarly, Hajj (the Arabic word for pilgrimage) is another Islamic ritual that involves traveling into holy sites in Saudi Arabia and walking on foot long distances. Extreme heat (particularly in summer months) can interfere with the quality of diabetes medications; high physical activities and constant mobility schedule associated with performance of rituals along with overcrowding of pilgrims can expose patients to physical exhaustion, risk of dehydration, heat stroke, and viral infections. Thus, modifying the glucose-lowering regimen to ensure safety and convenience is warranted prior to performing the Hajj pilgrimage.

11) ASCVD and HF:

The cardioprotective characteristics of several GLP1 agonists and anti-HF effects exhibited by most SGLT-2 inhibitors makes these agents of valuable use in respective targeted patients. However, as indicated earlier, the limited access, high cost, and uncertainties related to benefits on long term adherence and patient mortality make many of these medications less than desirable for use by the common patient with T2D in real world setting [30].

4. Conclusions

In this consensus statement, we propose a medication-algorithm scheme for the treatment of people with T2D in Saudi Arabia. We sought to integrate firsthand clinical experience along with strong knowledge and understanding of Saudi society and culture into the proposed scheme. In addition, the document places special emphasis on medication-cost and medication-adherence as determining factors in the choice of diabetes medications recommended. This statement aims to provide general guidance for practicing physicians and policy makers in Saudi Arabia and should be revised prospectively as local evidence emerge and international trials deliver outcome (e.g. GRADE Study) [49]. Finally, as in all consensus statements and clinical practice guidelines, our recommendations are meant solely to supplement, not substitute or replace, physician's knowledge, clinical intuition, and professional experience.

Financial Support

This consensus statement was supported by the SSEM. No financial sponsorship (direct or indirect) was received from pharmaceutical companies or other entities.

Acknowledgment

The authors would like to thank the Saudi Society for Endocrinology and Metabolism (SSEM) for the trust and support.

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