Overview of diabetes agents in cardiovascular disease: it takes an orchestra to play Tchaikovsky in symphony

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Purpose of review
The aim of this review was to discuss the use and concerns of diabetes agents, clinical targets, and key aspects to be considered in the management of patients with type 2 diabetes mellitus (T2DM), and at high risk or established cardiovascular disease (CVD).

Recent findings
The recent European and American guidelines recommended SGLT2 inhibitors and GLP-1 receptor agonists as the preferred first-line diabetes agents in patients with T2DM and CVD. This is a paradigm shift from using metformin as first-line therapy. Amid their widespread use, however, there are also concerns about their side effects. With the rapidly growing diabetes regimens available, questions arise about how best to approach the management of patients with T2DM and CVD.

Summary
To reduce CVD morbidity and mortality in patients with T2DM and at high or very high risk for CVD, the two key diabetes agents SGLT2i and/or GLP1-based therapies should be offered. Although lacking cardiovascular benefit, other diabetes agents remain necessary for many patients with T2DM for their glucocentric effects; Metformin and pioglitazone are useful in severe insulin resistance, while insulin therapy is often necessary in advanced diabetes; GLP1-RA is cautioned in patients with active gastrointestinal and mental health conditions, while DPP4 inhibitor is likely a well tolerated option in a challenging psychosocial setting. Other important aspects that should be considered include obesity, chronic kidney disease, women's cardiovascular health, and psychosocial factors.

Keywords
antidiabetic medications, atherosclerotic cardiovascular disease, cardiovascular disease, diabetes in cardiovascular disease, glucose-lowering agents, type 2 diabetes

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease that is rapidly escalating over the last century in terms of prevalence with an estimated 537 million people worldwide as of the year 2021 [1]. Diabetes, particularly type 2 diabetes mellitus (T2DM) is a major risk factor for cardiovascular disease (CVD), the leading cause of global disease burden for morbidity and mortality [1].

The flurry of publications of positive cardiovascular and renal outcome trials investigating newer therapeutic diabetes agents in the field of CVD has led to recommendations from recent European and American guidelines for two preferred classes of medications to be first-line medications in patients with T2DM and with concomitant or at a high risk for atherosclerotic CVD: these are the sodium-glucose co-transporter-2 inhibitors (SGLT2i) and the glucagon-like peptide-1 receptor agonists (GLP1-RA) [2▪▪–4▪▪,5]. However, there are also observational data highlighting concerns of their potential side effects, for example bowel obstruction and suicidality associated with GLP1-RA [6▪,7], and euglycaemic diabetic ketoacidosis (DKA) with SGLT2i [8].

In this review, we discuss the use and concern of currently available diabetes agents in the management of patients of T2DM with CVD, taking into consideration the efficacy, safety, tolerability, and

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Curr Opin Endocrinol Diabetes Obes 2025, 32:3–11
DOI:10.1097/MED.0000000000000892

KEY POINTS

- As recommended by recent American and European guidelines, SGLT2i and GLP1-based therapies should be offered to patients with T2DM and CVD because of their cardiovascular-metabolic-renal-obesity protective traits.
- Diabetes agents lacking in cardioprotective benefits are still important for their glucocentric effects to achieve glycaemic control and targets that lower microvascular complications.
- The vast expansion of diabetes agent formulary allows for four important clinical purposes to be served:
  - To achieve near-normoglycaemia with minimal hypoglycaemia,
  - To manage hyperglycaemic emergencies,
  - To promote early and long-term cardio-metabolic-renal protection, and
  - To bring us nearer to the ultimate goal of inducing diabetes remission safely.
- Practicing personalized medicine in the management of T2DM with CVD requires considerations of patient factors (including comorbidities, women's health, and psychosocial) as well the medication factors (efficacy, safety, tolerability, and affordability), yet minimizing the two commonest iatrogenic consequences: polypharmacy and hypoglycaemia.

affordability of these medications. A PubMed online search was carried out in these fields: diabetes, obesity, and/or cardiovascular guidelines; management of diabetes and CVD, heart failure or chronic kidney disease (CKD); side effects of each class of diabetes agents; semaglutide and/or tirzepatide studies; reviews and meta-analysis of specific diabetes agents.

THE EXPANSION OF DIABETES AGENT FORMULARY: INSTRUMENTS WITH DIFFERENT MUSICAL CAPABILITIES

With the advancement of therapeutic agents in the field of T2DM, there are now 13 classes of diabetes medications with various glucose-lowering effects ranging from weak (e.g. DPP4 inhibitors, acarbose, bromocriptine) to highly effective (e.g. insulin therapy, GLP1-RA based therapies) as well as their side effect profile, summarized in Table 1 [3▪▪,9]. Given the heterogeneity of effectiveness in glucose-lowering and cardiovascular profiles between different classes of T2DM medications, 'diabetes agents' rather than 'glucose-lowering agents' or 'antihyperglycaemic agents' is the preferred term used in this review.

The expansion of diabetes medication formulary has allowed diabetes agent(s) to serve four important clinical purposes: firstly, to achieve near-normoglycaemia state with minimal hypoglycaemia, a critically important purpose to prevent microvascular complications; secondly, to avoid and manage acute hyperglycaemic emergencies, that is DKA and hyperglycaemic hyperosmolar state; thirdly, to potentiate early and long-term cardiovascular, metabolic, and reno-protective benefits in patients with T2DM; and finally, to have an ideal diabetes agent(s) that can successfully induce and maintain diabetes mellitus remission after cessation of the diabetes medication.

The advent of strong evidence supporting SGLT2i and GLP1-RA based therapies has led to clinical recommendations for a paradigm shift in the management of a patient with both T2DM and CVD from a target-based approach (HbA1c and time-in-range) towards integrating disease-based approach early in the management of T2DM, regardless of the underlying glucose control [2▪▪–4▪▪,5].

The benefits of GLP-1 RA based therapies

The class GLP-1 RA was initially developed based on its hormonal mechanism of action that stimulates insulin secretion in a glucose-dependent manner, suppresses glucagon secretion in hyperglycaemia or euglycaemia, decreasing appetite, and delaying gastric emptying [10]. Apart from its antihyperglycaemic, antiobesity, and for disease-modifying potential to induce remission ('antidiabetes'), GLP-1 RAs also reduce risks of cardiovascular and renal events in patients with and without T2DM [11,12▪]. A meta-analysis in 2021 of eight GLP1-RA randomized controlled cardiovascular outcome trials (CVOT) of 60 080 patients with T2DM reported that GLP1-RA compared with placebo reduced major adverse cardiovascular event rate (MACE) by 14%, reduced all-cause mortality by 12%, heart failure hospital admission by 11%, and composite kidney outcome by 21% [11]. The cardiovascular benefit of GLP-1 RA was similar whether injected subcutaneously weekly or daily, or orally (semaglutide), and appeared to be strongest in reducing risk of stroke (fatal or nonfatal), followed by cardiovascular death and myocardial infarction (fatal and nonfatal) [11]. The number needed to treat of 65 patients to prevent one major adverse cardiovascular outcome (MACE) over 3 years [11]. Reassuringly, this meta-analysis showed that GLP-1 RA did not increase the risk of severe hypoglycaemia, retinopathy, pancreatitis, or pancreatic cancer [11].

A recently published meta-analysis in 2024 of 13 CVOTs in patients with and without T2DM reported that GLP1-RA conferred MACE reduction of 14%,

Table 1. A summary of the mechanism of action, clinical utility, and practicality of different classes of diabetes agents in the management of patients with both type 2 diabetes mellitus and established or at a high risk for cardiovascular disease [3▪▪,9,10,45]

	Class of diabetes agents	Mechanism of action [10,45]	Glucose-lowering	Cardiovascular, renal, and metabolic benefits		Safety, tolerability, and affordability
1	SGLT2 inhibitors e.g. Empagliflozin, Dapagliflozin	Reduce glucose reabsorption at proximal renal tubules; Off-target benefits at heart and kidneys	++	ASCVD: HF: CKD: Obesity: NAFLD:	Benefit Benefit Benefit Benefit Possible benefit	Caution use: critical illness, prolong fasting, severe insulinopenia S/e: rarely DKA, genitourinary infection, Fournier's gangrene Cost: $$$
2	GLP-1 RA e.g.. Semaglutide, Liraglutide, Dulaglutide	Stimulates insulin secretion (glucose-dependent), suppresses glucagon secretion (when hyperglycaemia), decrease appetite, delay gastric emptying.	+++	ASCVD: HF: CKD: Obesity: NAFLD:	Benefit Benefit Benefit Benefit Benefit	Caution: medullary thyroid cancer, MEN2 syndrome, active GI issues, severe untreated mental health disorders, pancreatitis (but causality not established)
3	Dual GLP1 and GIP- RA (Tirzepatide)		+++	ASCVD: HF: CKD: Obesity: NAFLD:	Benefit Benefit Benefit Benefit Benefit	S/e: GI side effects including nausea, constipation, bowel pseudo-obstruction. Headache. Cost: $$$
4	Biguanides (Metformin)	Insulin sensitizer by activating AMP-kinase, decrease hepatic glucose production	++	ASCVD: HF: CKD: Obesity: NAFLD:	Neutral Neutral Neutral Slight benefit Neutral	Caution: GFR<30 ml/min S/e: potentially vitamin B12 deficiency, GI side effects Cost: $
5	Sulfonylureas (e.g. Glipizide, Gliclazide, Glimepiride)	Insulin secretagogue by closing K_{ATP} channels on β-cell	++	ASCVD: HF: CKD: Obesity: NAFLD:	Possible increased Possible increased Hypoglycaemia Weight gain Neutral	Caution: patients at a high risk for hypoglycaemia S/e: hypoglycaemia, weight gain Cost: $
6	Thiazolidinedione (Pioglitazone)	Insulin sensitizer by activating the nuclear transcription factor PPAR-γ	++	ASCVD: HF: CKD: Obesity: NAFLD:	Likely benefit Worsen HF Neutral Weight gain Benefit	Caution: congestive heart failure, osteoporosis, severe CKD S/e: fluid retention, weight gain, risk of bone fractures Cost: $
7	DPP4 inhibitor	Inhibits DPP-4 activity to increase postprandial incretin (GLP-1, GIP)	+	Neutral for CVD except for saxagliptin (HF risk), Neutral for other aspects		Caution: bullous pemphigoid S/e: rare athralgia or myalgia Cost: $ or $$

Table 1 (*Continued*)

	Class of diabetes agents	Mechanism of action [10,45]	Glucose-lowering	Cardiovascular, renal, and metabolic benefits	Safety, tolerability, and affordability
8	α glucosidase inhibitor (acarbosemiglitol)	Inhibits intestinal alpha-glucosidase to slow carbohydrate absorption	+	Neutral but insufficient evidence for ASCVD.	Caution: bowel obstruction S/e: moderate GI symptoms Cost: $ or $$
9	Meglitinides (Nateglinide, repaglinide)	Insulin secretagogue by closing K_{ATP} channels on β-cell	+	Neutral for mentioned aspects	Caution: severe liver dysfunction S/e: hypoglycaemia, joint pain Cost: $ or $$
10	Bile acid sequestrant (Colesevelam)	Possibly reduce hepatic glucose production	+	Neutral for mentioned aspects Lowers LDL-C	Caution: bowel obstruction S/e: GI, interfere drug absorption Cost: $$$
11	Dopamine agonist (Bromocriptine)	Insulin sensitizer, hypothalamic metabolism	+	Neutral/well tolerated for the mentioned aspects	Caution: severe hypertension, fibrotic or valvular disorder S/e: moderate GI symptoms Cost: $$$
12	Amylin mimetic (pramlintide)	Decrease glucagon, slows gastric emptying, increase satiety	+	ASCVD, HF: Insufficient evidence Obesity: Slight benefit NAFLD: Benefit	Caution: gastroperesis S/e: moderate GI symptoms Cost: $$$
13	Insulin therapies	Increase glucose disposal, Decrease hepatic glucose production	+++	ASCVD and HF: Neutral Obesity: Weight gain Decrease microvascular risk	S/e: hypoglycaemia, weight gain, injection-site lipohypertrophy Cost: variable from $ to $$$

ASCVD, atherosclerotic cardiovascular benefits, including MACE, CVD, and stroke risk reduction; GFR, estimated glomerular filtration rate; GI, gastrointestinal; HF, heart failure; LDL-C, low-density lipoprotein cholesterol concentration; S/e, side effects.

all-cause mortality of 13%, as well as stroke, coronary revascularization, and composite kidney outcome [13]. The cardioprotective effects of GLP-1 RA extended to patients independent of their CVD history, BMI (above or below 30 kg/m^2), kidney function, and sex [13]. In a recently published RCT named FLOW study, the use of semaglutide (subcutaneously 1 mg/week) compared with placebo reduced major kidney disease events by 24%, kidney failure, and death from cardiovascular causes in patients with T2DM and CKD [14▪]. The authors postulated that the renal benefits of semaglutide were attributed to the reduction of inflammation, oxidative stress, and fibrotic effects on the kidneys via GLP-1 receptors, and unlikely attributable to weight changes alone (difference of 4 kg weight loss between treatment groups) [14▪]. Semaglutide has also been shown to improve nonalcoholic hepatic steatosis, as well as reduce the risk of hepatocellular carcinoma in patients with T2DM [15–17].

Tirzepatide is a dual receptor agonist of the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 approved for T2DM management as well as obesity. Under hyperglycaemic conditions, GIP agonism stimulates insulin release lowering glucagon concentrations [18]. GIP acts on the adipose tissue improving insulin sensitivity and postprandial lipid regulation [18]. In the SURPASS-II study, an open-label phase 3 trials of 1879 patients with T2DM, once-weekly tirzepatide (subcutaneously 10 mg/week) was superior to semaglutide (subcutaneously 1 mg/week) with superiority in HbA1c-lowering (−2.2 versus −1.86%, respectively) and weight loss (treatment difference was -3.6 to 5.5 kg) [19]. In a retrospective review of a US healthcare database of 41 222 patients with obesity of whom 67% had T2DM, tirzepatide was found to be superior to semaglutide for weight loss (difference of -6.9% at 12 months) [20]. The gastrointestinal side effects of tirzepatide compared with semaglutide were similarly high at approximately 20% [19,20].

The success of GLP1-RA in diabetes and metabolic aspects have spurred further combination GLP-1RA based therapies in the pipeline [21]. Retatrutide, a triple gut hormone receptors agonist (GIP, GLP-1, and glucagon), was shown in phase 2 trial to be more effective than placebo and dulaglutide to reduce HbA1c and weight [22]. Multiple other combinations using GLP1-RA as the anchor (e.g. amylin RA, glucagon agonist, PYY agonist) are also currently under investigation [21].

The benefits of SGLT2 inhibitors

The SGLT2i class was initially developed with the knowledge of its hormonal mechanism of action as a glucosuric agent. The SGLT2i works by inhibiting SGLT2 transporter-mediated-glucose reabsorption at proximal renal tubules, leading to a modest glucose-lowering effect (HbA1c lowering of 0.5–1%) and a small amount of weight loss [23]. A meta-analysis in 2021 of six RCT CVOT of SGLT2i with T2DM analysed 46 969 patients with T2DM (66% with ASCVD), and reported that SGLT2i reduced MACE (hazard ratio 0.90), with largest benefit seen in reducing risk of hospitalization for heart failure (hazard ratio 0.68) and kidney composite outcomes (hazard ratio 0.62) [24]. However, there was significant heterogeneity in the effects of different SGLT2i agents on cardiovascular death and MACE; only empagliflozin was associated with reduction in cardiovascular mortality risk, while both empagliflozin and canagliflozin had reduction in MACE when compared with placebo [24]. Hence, the American and European consensus recommended the use of SGLT2i as first-line diabetes agents for patients with T2DM and heart failure [2▪▪,9]. SGLT2i with proven cardiovascular benefit is preferred in patients with T2DM and ASCVD; use of empagliflozin, canagliflozin, dapagliflozin, and sotagliflozin was associated with cardiovascular benefit while ertugliflozin was cardiovascular neutral [2▪▪]. In patients with T2DM and CKD, SGLT2i namely empagliflozin, dapagliflozin, or canagliflozin, should be initiated to reduce cardiovascular and kidney failure risk [2▪▪].

However, the glucosuric effect of SGLT2i could not fully account for the cardio-renal-metabolic protective benefit that was disproportional to the amount of glucosuria, mild blood pressuring and albuminuria reduction, or natriuresis put together [25]. Postulations include off-target effects of SGLT2i to inhibit sodium hydrogen exchanger 1 (NHE-1) in the heart and kidneys, stabilizing cardiomyocytes and reducing cardiomyocytes injury [24,25]. This is because an increased expression of NHE-1 in T2DM and heart failure may increase intracellular calcium resulting in cardiomyocyte dysfunction [25].

THE PRACTICAL QUESTIONS ABOUT DIABETES AGENTS IN CLINICAL PRACTICE: *HOW THE MUSIC SHOULD BE PLAYED*

When is the best time to initiate GLP-1 RA and which patients are not suitable?

There appears to be lack of data to support the initiation of GLP-1 RA in the acutely unwell clinical setting including acute coronary syndrome. Among the eight different GLP-1 RA RCTs in patients with T2DM, only the ELIXA RCT (lixisenatide) was tested in acute coronary syndrome patient population, whereas the

other RCTs were in stable CVD, or with cardiovascular risk factors [26]. The ELIXA study randomized 6068 patients with T2DM with recent myocardial infarction or hospitalization for unstable angina (within 180 days) to lixisenatide versus placebo and found no reduction in cardiovascular outcomes [26].

Furthermore, there is concern about the associated increased risk of gastrointestinal complications with GLP-1 RA based therapies; a retrospective study of 5411 individuals in a US health claims database reported that the use of GLP1-RA for weight loss (liraglutide, semaglutide) was associated with increased risk of bowel obstruction (hazard ratio 4.22), gastroparesis (hazard ratio 3.67), and pancreatitis (hazard ratio 9.09) [6▪]. There have been conflicting opinions that GLP-1 RA dose should be omitted prior to elective procedure or surgery or not [27–29]. Reassuringly, a retrospective study of a large claims database reported that the use of GLP1-RA in 15 119 patients compared with 14 407 DPP4i patients for T2DM did not detect an increased risk of pulmonary complications after upper endoscopy [30]. The additional gastric emptying delay by 36 min is unlikely to be clinically significant, as the fasting period preanaesthesia typically entails at least an 8-h solid-food fast and a 2-h liquid fast [31].

Additionally, there is concern related to increased signal of suicidal ideation particularly with semaglutide as reported in a case–control study using WHO database [7]. However, a recent retrospective study of approximately 300 000 patients with T2DM, published reassuring data that there was no increased suicidality, self-harm, depression, or anxiety when comparing the use of GLP-1 RA and SGLT2i [32].

Therefore, prior to initiation of GLP-1 RA based therapies, patients should also be assessed for risk of bowel obstruction, depression, and suicidality. GLP-1 RA should not be initiated until the gastrointestinal issues and mental health disorders have been addressed. In the author's opinion, GLP-1 RA use is not advisable in patients with moderate-severe gastrointestinal symptoms, gastrointestinal disease (e.g. bowel stricture, severe reflux [33▪], motility issues), gastrointestinal malignancy, cancer cachexia, and uncontrolled severe depression. In summary, generally, the initiation of GLP-1 RA is likely more tolerable when initiated when well in outpatient setting rather than when acutely unwell (e.g. acute coronary syndrome, acute decompensated heart failure, sepsis, or nausea).

Are the side effects of SGLT2i still of concern?

Unlike type 1 diabetes wherein SGLT2i is associated with an increased risk of euglycaemic DKA [34], the use of SGLT2i in patients with T2DM is generally well tolerated [24,35]. The risk factors for SGLT2i-associated DKA are severe insulin deficiency from any cause (autoimmune, pancreatectomy, or advanced T2DM), and Asian patients with T2DM may be at a higher risk due to a higher predisposition to beta-cell dysfunction [36]. The common precipitants of SGLT2i-associated DKA are infection, myocardial infarction, stroke, surgery, intensive exercise, and reduction of doses of insulin or insulin secretagogues [8]. SGLT2i promotes ketonemia because of reduction of insulin doses, increase in glucagon levels, and less renal clearance. Thus, patients should be advised to omit SGLT2i on days of illness and decreased oral intake with monitoring of capillary blood ketone level [9].

It remains unclear whether the slight increased risk of amputation with canagliflozin in the CANVAS trial was a causative association or spurious finding, as there were no other SGLT2i that were associated with increased risk of amputations [24]. SGLT2i adverse effect profile includes an increased risk of genital infections (two-fold compared with DPP4 inhibitor) [37] and rarely Fournier's gangrene (an increase of one case per 10 000 men treated) [38].

What considerations are there in using diabetes therapies alone or in combination?

Combination therapy is often required in many patients with T2DM due to the nature of progressive beta-cell dysfunction in T2DM. The traditional default choice of metformin as first-line therapy in patients with T2DM and high risk for ASCVD is now changed to either SGLT2i or GLP1-RA or combination of both [2▪▪–4▪▪,5]. However, there is a lack of trials to confirm the most effective algorithm of add-on medications that would achieve diabetes targets (HbA1c and time-in-range). ESC 2023 guideline recommend metformin and pioglitazone to be considered as second-tier medications after SGLT2i or GLP-1 RA [2▪▪], but there are still many permutations possible thereafter including premixed insulin-GLP-1 RA therapies [9]. The GRADE trial of 5047 patients with T2DM found that patients with higher baseline HbA1c had a greater benefit with glargine, liraglutide, and glimepiride than with sitagliptin, when added on as second-line agent to metformin [39]. Pioglitazone has been found to reduce MACE in patients with T2DM and ASCVD as a secondary endpoint (PROactive CVOT) [40], but should be avoided in heart failure, CKD, and osteoporosis [2▪▪]. While on GLP-1 RA based therapies, DPP4 inhibitors should be stopped because both classes target the same incretin pathway [3▪▪].

The add-on diabetes agents should be decided on their predicted effectiveness, and the distance of

the patient's HbA1c level from the individualized goal, their comorbidities, along with the tolerability, practicality, and cost of each medication, Table 1 [3▪▪,9,10,23]. In patients at a very high risk of hypoglycaemia such as CKD and elderly with variable food intake, sulphonylureas should be avoided. In adults with T2DM and advanced CKD (GFR <30 ml/min), a GLP-1 RA is preferred to sulphonylurea [9]. Importantly, in adults with T2DM with evidence of ongoing catabolism, initiation of insulin should be strongly considered to avoid an acute hyperglycaemic emergency [9]. Markers of ongoing catabolism or severe insulinopaenia in T2DM include unexpected weight loss, hyperglycaemic osmotic symptoms (thirst, polyuria) especially paired with elevated HbA1c more than 10%, and random glucose of at least 16.7 mmol/l [9]. In this regard, the initiation insulin should not be delayed because of noninsulin agents (including SGLT2i) owing to the increased risk of DKA. To compare the effectiveness of SGLT2i and GLP-1 RA in reducing cardiovascular and kidney outcomes, a randomized controlled trial PRECIDENTD (NCT05390892) in patients with T2DM and ASCVD is ongoing.

Apart from cardiovascular disease risk reduction and type 2 diabetes mellitus control, what does a holistic approach entail?

A patient-centred approach with interdisciplinary input remains the fundamental component in the care of patients with T2DM and CVD, to achieve the major clinical targets, Fig. 1 [2▪▪]. Other important aspects to be considered include obesity, CKD, women's cardiovascular health, psychosocial factors, and patient's preferences in financial, behavioural, and cultural aspects, as summarized in Fig. 1. In this figure, the conductor refers to the doctor's role in an interdisciplinary team to coordinate and provide patient-centred care to achieve key clinical targets while taking into consideration of multidimensional aspects that may exist in the management of T2DM. The recent AHA scientific statement on

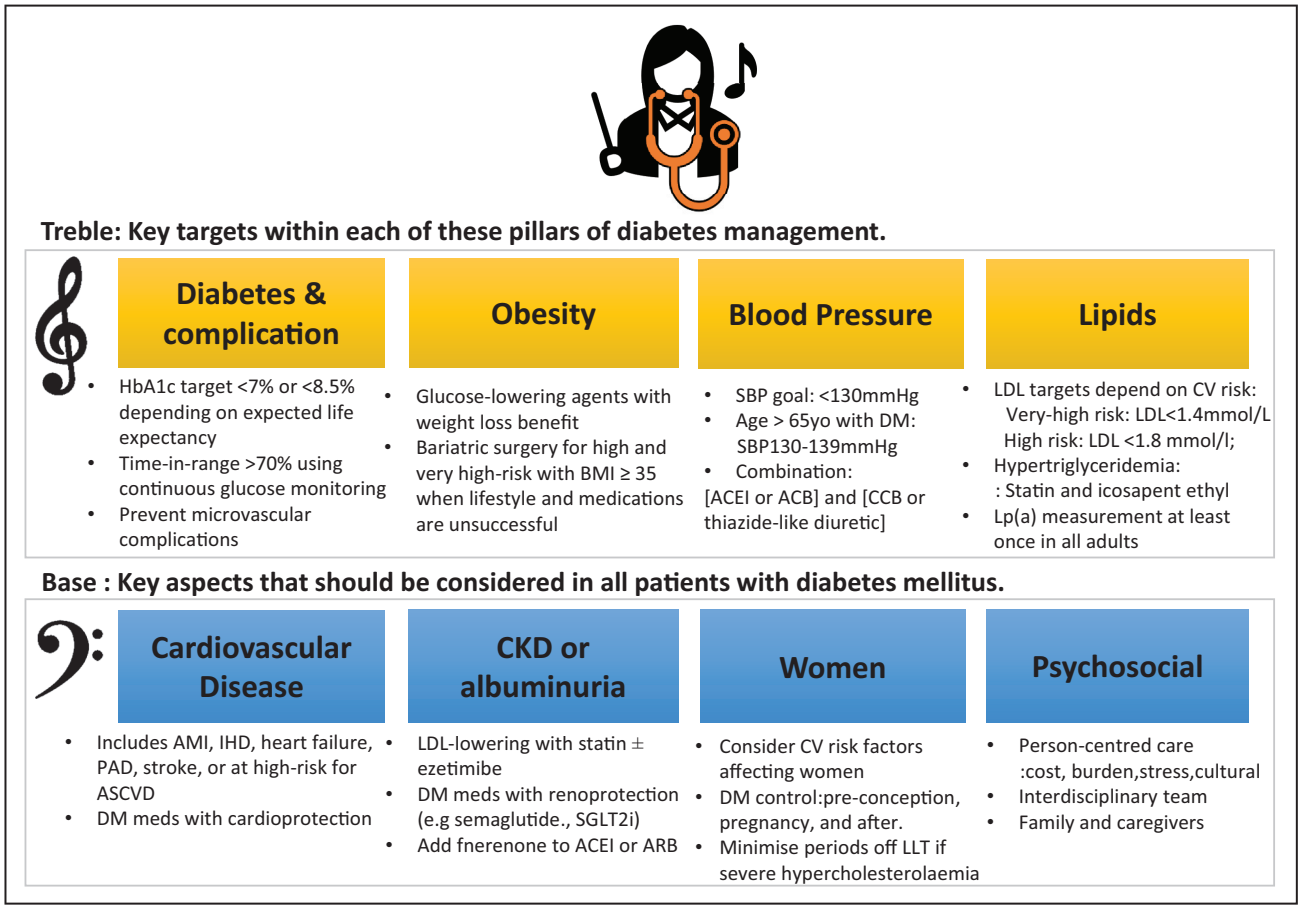

FIGURE 1. An overview of the major targets [2▪▪,46] and aspects that should be considered in the management of patients with T2DM and established or at a high risk of cardiovascular disease. AMI, acute myocardial infarction; CKD, chronic kidney disease; CV, cardiovascular; DM, diabetes mellitus; HbA1c, glycated haemoglobin: IHD, ischaemic heart disease; LDL, low-density lipoprotein cholesterol concentration; LLT, lipid-lowering therapies; Lp(a), lipoprotein(a); PAD, peripheral artery disease.

cardiovascular-kidney-metabolic (CKM) syndrome highlights the core pathophysiology is the underlying dysregulation of insulin resistance and inflammation fuelled by adiposity [41▪▪]. As obesity always accompanies T2DM at least in the early phase, it is important to consider antiobesity therapies, for example GLP-1 RA based therapies, bariatric surgery, meal replacements, selective appetite suppressants except phentermine in CVD, on the background of diet and lifestyle changes. In patients with T2DM and CKD, finerenone is recommended to reduce cardiovascular events and CKD progression [2▪▪,4▪▪].

Cardiovascular health in women with T2DM requires deeper considerations in management because of the unique risk factors interplay and treatment concerns [42▪]. There are female-specific risk factors (e.g. polycystic ovarian syndrome, partial lipodystrophy syndromes), common risk factors with disproportionate adverse effect to women (e.g. diabetes, smoking, hypertension), and other risk factors affecting women more commonly (e.g. autoimmune disease, partner violence) [42▪,43▪]. The management needs to include preconception and pregnancy considerations, where insulin therapy has the safest clinical data [44]. Given the lack of safety data of lipid-lowering agents in pregnancy and breastfeeding, a common cardiovascular risk factor in young women with severe hypercholesterolemia is the prolonged duration of omission of lipid-lowering therapies [42▪].

CONCLUSION: THE EVOLVING FINALE

The complementary mechanisms of actions of different classes of diabetes agents make it easier for clinicians and patients to achieve glycaemic targets and improve microvascular and cardio-metabolic-renal outcomes. Practicing personalized medicine in T2DM requires considerations of patient factors (including obesity, women's health, comorbidities, psychosocial, cultural) as well the medication factors (efficacy, safety, tolerability, and affordability to each patient), yet minimizing the two commonest iatrogenic consequences: polypharmacy and hypoglycaemia. More studies are awaited to better delineate the treatment algorithm pathways in patients with T2DM and CVD.

After all, it takes an orchestra to play Tchaikovsky in symphony.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

The author W.J.L. declares that this manuscript was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. W.J.L. has received honoraria from Medtronic, Abbott, DKSH, Roche, Novartis, Inova, Kowa, and Amgen, but unrelated to this manuscript.

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