Diabetes & Metabolic Syndrome: Clinical Research & Reviews 16 (2022) 102661

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

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

Cardiorenal disease management in type 2 diabetes: An expert consensus

Viswanathan Mohan [a,*], Awadhesh Kumar Singh [b], Abdul Hamid Zargar [c], Alan Almeida [d], Anil Kumar Bhalla [e], Jagadish Chander Mohan [f], Jamshed Dalal [g], Manisha Sahay [h], Padhinhare P. Mohanan [i], Sanjay Maitra [j], Sujoy Ghosh [k], Tarun Jeloka [l], Upendra Kaul [m], Vinay Sakhuja [n], Mrinal Kanti Das [o]

[a] Madras Diabetes Research Foundation & Dr.Mohan's Diabetes Specialities Centre, Chennai, India
[b] Department of Endocrinology, G.D. Hospital and Diabetes Institute, Kolkata, India
[c] Centre for Diabetes and Endocrine Care, Srinagar, India
[d] Department of Nephrology, P. D. Hinduja Hospital and Medical Research Centre, Mumbai, India
[e] Department of Nephrology, Sir Gangaram Hospital, New Delhi, India
[f] Department of Cardiology, Jaipur Golden Hospital, New Delhi, India
[g] Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Mumbai, India
[h] Department of Nephrology, Osmania General Hospital & Osmania Medical College, Hyderabad, India
[i] Department of Cardiology, Westfort Hi-Tech Hospital, Thrissur, India
[j] Department of Nephrology, Apollo Hospitals, Hyderabad, India
[k] Department of Endocrinology, IPGME&R and SSKM Hospital, Kolkata, India
[l] Aditya Birla Memorial Hospital, Pune, India
[m] Max Healthcare, Mohali, Punjab, India
[n] Department of Cardiology and Dean, Academics and Research, Batra Hospital and Medical Research Center, New Delhi, India
[o] Department of Cardiology, C.K. Birla Hospitals (BMB/CMRI), Kolkata, India

ARTICLE INFO

Article history:
Received 16 February 2022
Received in revised form
28 September 2022
Accepted 29 October 2022

Keywords:
SGLT2i
Dapagliflozin
Indian phenotype
CV risk Assessment
GLP-1 agonists

ABSTRACT

Background and aim: The interplay between cardiovascular disease (CVD), chronic kidney disease (CKD) and type 2 diabetes (T2D) is well established. We aim at providing an evidence-based expert opinion regarding the prevention and treatment of both heart failure (HF) and renal complications in people with T2D.

Method: ology: The consensus recommendations were developed by subject experts in endocrinology, cardiology, and nephrology. The criteria for consensus were set to statements with ≥80% of agreement among clinicians specialized in endocrinology, cardiology, and nephrology. Key expert opinions were formulated based on scientific evidence and clinical judgment.

Results: Assessing the risk factors of CVD or CKD in people with diabetes and taking measures to prevent HF or kidney disease are essential. Known CVD or CKD among people with diabetes confers a very high risk for recurrent CVD. Metformin plus lifestyle modification should be the first-line therapy (unless contraindicated) for the management of T2D. Glucagon-like peptide 1 (GLP-1) agonists can be preferred in people with atherosclerotic cardiovascular disease (ASCVD) or with high-risk indicators, along with sodium–glucose cotransporter-2 inhibitors (SGLT2i), whereas SGLT2i are the first choice in HF and CKD. The GLP-1 agonists can be used in people with CKD if SGLT2i are not tolerated.

Conclusion: Current **e**vidence suggests SGLT2i as preferred agents among people with T2D and HF, and for those with T2D and ASCVD. SGLT2i and GLP-1RA also lower CV outcomes in those with diabetes and ASCVD, and the treatment choice should depend on the patient profile.

1. Introduction

The burden of type 2 diabetes (T2D) is very high in India. In

* Corresponding author., Dr.Mohan's Diabetes Specialities Centre, President and Chief of Diabetes Research, Madras Diabetes Research Foundation, IDF Centre of Excellence in Diabetes Care and ICMR Centre for Advanced Research on Diabetes No 4, Conran Smith Road, Gopalapuram, Chennai, 600 086. India.,
URL: http://www.drmohans.com, http://www.mdrf.in

https://doi.org/10.1016/j.dsx.2022.102661
1871-4021/

2019, India reported the second-highest prevalence of diabetes in the world, with 77 million individuals living with diabetes. This figure is estimated to increase to >130 million by 2045 [1]. Earlier studies have reported that most adults with diabetes in India have at least one comorbid condition, including a high prevalence of major cardiovascular (CV) risk factors such as hypertension, dyslipidemia, and body mass index ≥25 kg/m^2 [2].

1.1. Pathophysiology of cardiorenal disease in T2D

Several studies have established an independent association of cardiovascular disease (CVD) and chronic kidney disease (CKD) with T2D. Consequently, individuals with these risk factors tend to develop cardiorenal syndrome (CRS) with acute or chronic organ dysfunction of one organ influencing the function of the other. The pathophysiology of CRS constitutes an interplay of multifaceted dysfunctional cardiac and renal factors, including insulin resistance, hypertension, and dyslipidemia. The overlapping of these two distinct processes results in subsequent heart failure (HF) associated with diastolic dysfunction, HF with preserved ejection fraction (HFpEF), HF with reduced ejection fraction (HFrEF), left ventricular hypertrophy, and kidney failure associated with acute injury and CKD [3,4].

Hyperfiltration, characterized by a gradual loss of kidney function and an increase in albuminuria, is a critical process in the pathogenesis of kidney disease in people with diabetes [5]. Further, both hyperglycemia and hypertension have an additive effect on the progression of diabetic nephropathy, driven by oxidative stress, inflammation, and fibrosis.

Acute and chronic CV events increase the risk of acute kidney injury and end-stage renal disease (ESRD), and conversely, acute and chronic renal events increase the risk of new CV events, at least in people with T2D. As these two processes share a common pathophysiologic mechanism, they can be considered under a "single CRS" umbrella. Diabetes management is hence considered complex for both the patient and healthcare providers [6].

1.2. Indian phenotype with T2D

Indians usually develop diabetes at a much younger age compared to Western population. Indians have a "thin–fat" phenotype characterized by low lean body mass and high abdominal and hepatic fat. This phenotype together with glucose and lipid dysregulation accentuates the susceptibility to insulin resistance among Indians. Indians also tend to have early pancreatic beta-cell dysfunction that precipitates diabetes faster in them [7,8]. Additionally, while the risk of microvascular complications is lower, the risk of coronary artery disease is higher among Indians compared to the Western population [7]. Further, in the INSPIRED study involving 19,084 Indian individuals with T2D, four clusters with distinct phenotypes and varied disease outcomes have been identified: cluster 1 (severe insulin-deficient diabetes [SIDD]); cluster 2 (insulin-resistant obese diabetes [IROD]); cluster 3 (combined insulin-resistant and deficient diabetes [CIRDD]); and cluster 4 (mild age-related diabetes [MARD]). Two of these clusters, IROD and CIRDD, were unique to the Asian Indian population [9].

Considering the aforementioned literature views, this manuscript aims at reviewing strategies for the prevention and treatment of both HF/renal complications in T2D by stratifying the risk of patients. The experts' statements are presented in this article.

2. Methodology

The consensus recommendations were formed by experts from three different specialties (five each from endocrinology, cardiology, and nephrology). These experts then formulated key opinions based on scientific evidence and clinical judgment. Based on the agreed statements, supporting data were extracted from multiple databases including PubMed/MEDLINE, Embase, Cochrane, and Google Scholar. The criteria for consensus were set to statements with ≥80% of agreement among experts.

3. Risk stratification

Currently, the American College of Cardiology and the American Heart Association guidelines recommend the stratification of people with diabetes with risk calculators. Stratification is essential as it enables individual treatment for cardiac or renal disease prevention. Further, risk stratification is useful for decision-making in assigning specific treatment for diabetes control and prevention and or management of risk factors [10]. As much of the evidence appraised in the guidelines is from the West, the recommendations may not always be suitable for the Indian population. Moreover, considering the peculiarities of diabetes among Indians as shown by the clustering studies of Anjana et al. [9], risk stratification followed in the West may not correlate with Indian settings [11].

Therefore, patients in the low-risk category in the West may be considered to be at intermediate risk in India, whereas those at intermediate risk may be categorized to be at high risk. In a real-world analysis of CVD risk in asymptomatic people with T2D in India, more than half of the patients had a 10-year CVD risk of >20%. Individuals with T2D aged 25–44 years had a fivefold higher CVD risk compared to the healthy cohort. Females aged 55–64 years had a mean high-CVD risk of >20% contrary to males who had a similar risk a decade earlier [12]. Given the vulnerability of the Indian phenotype, people with T2D qualify for the high-risk approach of atherosclerotic cardiovascular disease (ASCVD). According to European Society of Cardiology and European Association for the Study of Diabetes (ESC/EASD) guidelines [13], men <35 years and women <45 years, with a duration of diabetes of <10 years, without other risk factors or established CVD, are considered at medium risk. Target organ damage or the presence of two additional major CV risk factors is considered very high risk. Also, patients above the age of 50 years are considered to be at high risk of HF (Table 1). Similar stratification of people with diabetes in India is needed. Verma et al. apprised the predictors of HF in people with T2D. Diabetes-specific risk factors include chronic hyperglycemia, insulin resistance, mitochondrial dysfunction, abnormal calcium management, autonomic dysfunction, abnormal extracellular matrix remodeling, and enhanced renin-angiotensin-aldosterone system (RAAS) dysfunction that is attributed to the increased risk of HF development [14]. The presence of albuminuria in T2D is considered high risk as it predicts HF and other CVD events, independent of other risk factors. Traditional CV risk factors such as hypertension, obesity, and history of CVD also contribute to the development of HF. Additionally, age and presence of obstructive sleep apnea among people with T2D render them at a high risk of developing HF [14]. Also, people with T2D without CVD but with increased N-terminal pro-brain natriuretic peptides are at high risk of incident HF [15]. A meta-analysis of 21 studies (N = 1,111,569, including 507,637 people with T2D) has shown that CAD (hazards ratio [HR], 1.77), $Hb_{A1c} \geq 10\%$ (HR, 1.66), insulin use (HR, 1.43), Hb_{A1c} 9.0%–10.0% (HR, 1.31), fasting glucose (HR, 1.27), and 5-year increase in age (HR, 1.26) were associated with a significant increase in HF development [16]. Albuminuria and high serum creatinine levels are early indicators of CKD. People with T2D and clinical predictors of CKD are at a high risk of diabetic neuropathy [13].

The expert recommendations regarding the CVD and CKD risk in people with T2D are presented in Box 1.

Table 1
Cardiovascular risk categories in people with diabetes [16].

Very high risk	People with diabetes with established CVD or target organ damage or two or more major risk factors such as age, hypertension, dyslipidemia, smoking, and obesity or patients aged 50 years and more with more than one risk factor.
High risk	People with a duration of diabetes for more than 10 years without target organ damage and more than one risk factor.
Moderate risk	Men aged <35 and women aged <45, with a duration of diabetes for <10 years and without any other risk factor or absence of CVD.

CVD: Cardiovascular disease.

4. Management of T2D

As T2D is a lifestyle-related disease, the initial therapeutic approach should target lifestyle management and weight management. The Look AHEAD trial has shown that intense lifestyle interventions, including dietary restrictions and weight loss, were associated with clinically significant improvements in glycemic control over a longer period. However, no benefits on CV mortality were observed [17].

Several clinical trials have shown the safety, efficacy, and tolerability of metformin (850–2000 mg daily) monotherapy or combination therapy in controlling glycemic levels and providing CV protection in people with T2D [18,19]. Based on these findings, guidelines published by national and international diabetes associations, such as the American Diabetes Association (ADA), EASD, and Research Society for the Study of Diabetes in India (RSSDI), have clearly defined the use of metformin as the first-line therapy along with lifestyle changes for the management of T2D [20–22].

Sodium–glucose cotransporter-2 inhibitors (SGLT2i) are the new class of antidiabetics with a different mode of action from other classes of antidiabetics—largely due to their insulin-independent function—thus maintaining the effectiveness of these drugs at all stages of T2D. These drugs promote reduced renal glucose reabsorption by directly blocking SGLT2, increasing the urinary excretion of glucose, and efficiently lowering hyperglycemia. Further, SGLT2i seem to have added benefits, including lowering of BP, body weight, and serum urate levels, with protective effects on cardiac as well as renal systems [23]. The recent ADA and EASD consensus report recommend the use of SGLT2i in people with T2D with CKD or HFrEF and ASCVD. They can also be primarily used to minimize weight gain or promote weight loss along with hypoglycemia in people with T2D irrespective of baseline CVD or CKD [21]. The RSSDI also suggested the use of SGLT2i for people with established ASCVD, HF, and DKD or those in need of weight reduction [22].

Based on available evidence from literature and the consensus agreement, the expert panel put forward the following recommendations for the management of T2D (Box 2).

Box 1
Risk stratification of people with T2D

- People with T2D and established CVD or CKD should be considered to be at "very high CV risk."
- People aged above 50 years with T2D and the presence of one or more risk factors for CVD should be considered to be at "very high CV risk.".
- People with T2D for >10 years without target organ damage and more than one risk factor should be considered to be at "high CV risk."
- Albuminuria and high serum creatinine levels indicate a high risk of CKD due to the distinct CIRDD phenotype among Indians with diabetes. The presence of albuminuria in T2D is considered a high risk factor for CVD.

4.1. Management of T2D in people with risk/history of CVD and/or CKD

4.1.1. Cardiovascular outcome trial (CVOT) with SGLT2i

SGLT2i have multiple glycemic advantages beyond regulation of body weight, BP, and lipid levels, viz. lowering the risk of CV events and renal protection. The first SGLT2i CVOT trial, the EMPA-REG OUTCOME [24], focused on empagliflozin, which established better glycemic control and improved CV mortality and renal outcomes in the T2D population at CVD risk and mild-to-moderate kidney dysfunction at baseline. The primary composite CV endpoint of MACE was observed in 10.5% of people with empagliflozin vs. 12.1% of people with placebo (rate per 1000 patient-years: 37.4 vs. 43.9; HR = 0.86; 95% confidence interval [CI], 0.74–0.99; p = 0.04). Hospitalization for HF (hHF) or CV death occurred in 5.7% vs. 8.5% (empagliflozin vs. placebo; rate per 1000 patient-years: 19.7 vs. 30.1; HR = 0.66; 95% CI, 0.55–0.79; p < 0.001). In a subgroup analysis among Asian patients, empagliflozin was associated with a reduced risk of the composite endpoint of doubling of serum creatinine, initiation of renal replacement therapy or renal death (HR, 0.48; 95% CI, 0.25–0.92), incidence or worsening of nephropathy (HR, 0.64; 95% CI, 0.49–0.83), and progression to macroalbuminuria (HR, 0.64; 95% CI, 0.49–0.85) [25].

The CANVAS program [26] included participants with T2D at high CVD risk and mild-to-moderate kidney dysfunction at baseline. The composite CV endpoint (CV death, nonfatal MI, or nonfatal stroke) rate per 1000 patient-years was 26.9 with canagliflozin vs. 31.5 with placebo (HR = 0.86; 95% CI, 0.75–0.97; p < 0.001 for noninferiority; p = 0.02 for superiority). The hHF rate per 1000 patient-years was 5.5 vs. 8.7 with canagliflozin vs. placebo (HR = 0.67; 95% CI, 0.52–0.87; p = 0.02). The hHF or CV death rate per 1000 patient-years was 16.3 vs. 20.8 (HR = 0.78; 95% CI, 0.67–0.91; p = 0.0015). The composite renal outcome of a 40% decrease in estimated glomerular filtration rate (eGFR), death

Box 2
Consensus recommendations for the management of T2D

- Physical inactivity should be avoided, and physical fitness is advisable for people with T2D with concomitant CVD.
- Moderation of dietary intake, especially reducing carbohydrates, increasing plant protein intake, and accommodating medical nutritional therapy depending on the risks or history of CVD, is recommended.
- In line with several international and national guidelines, we recommend metformin plus lifestyle modification as the first-line therapy, unless contraindicated, for the management of T2D.
- SGLT2i can be alternatively used due to their insulin-independent action and additional benefits, including promoting weight loss and reducing BP.

resulting from kidney disease, or kidney replacement therapy requirement was reduced with canagliflozin vs. placebo (HR = 0.60; 95% CI, 0.47–0.77). Further, the progression of albuminuria was low with canagliflozin vs. placebo (HR = 0.73; 95% CI, 0.67–0.79) [27]. These benefits were seen across all eGFR subgroups as well. In a prespecified analysis, canagliflozin was associated with a reduction in doubling of serum creatinine, end stage kidney disease (ESKD), and kidney disease–related death (HR = 0.53; 95% CI, 0.33–0.84) [28].

The DECLARE–TIMI 58 trial [29] evaluated the safety of dapagliflozin in people with T2D and either established CVD (40% with ASCVD) or multiple risk factors (60%), unlike the EMPA-REG trial that included only people with ASCVD. After a median follow-up of 4.2 years, CV death or hHF was significantly reduced with dapagliflozin compared to placebo (4.9% vs. 5.8%; HR = 0.83; 95% CI, 0.73–0.95; p = 0.005). This finding was mainly driven by a reduction in hHF (HR = 0.73; 95% CI, 0.61–0.88). Dapagliflozin was found to be noninferior to placebo for major adverse cardiovascular events (MACE) (p < 0.001 for noninferiority) [30]. Further, dapagliflozin greatly reduced CV death or hHF in people with HFrEF (HR = 0.62; 95% CI, 0.45–0.86), but not in people without HFrEF (HR = 0.88; 95% CI, 0.66–1.17 and HR = 0.88; 95% CI, 0.76–1.02, respectively). It also significantly reduced cardiac and all-cause mortality in people with HFrEF, but not in those without HF. Further, dapagliflozin significantly reduced MACE in people with a history of myocardial infarction (MI) (HR = 0.84; 95% CI, 0.72–0.99) vs. those without a history of MI (HR = 1.00; 95% CI, 0.88–1.13) [31]. The composite cardiorenal outcomes of a 40% decrease in eGFR, ESKD, or death caused by kidney or CV disease were in favor of dapagliflozin vs. placebo (HR = 0·76; 95% CI, 0·67–0.87; p < 0·0001) in people with T2D, with and without established ASCVD and preserved renal function [30].

The VERTIS-CV trial [32] evaluated the effects of ertugliflozin in 8246 patients aged ≥40 years with T2D and established ASCVD. The mean follow-up time was 3.5 years. Noninferiority of ertugliflozin over placebo for MACE (HR = 0.97; 95.6% CI, 0.85–1.11; p < 0.001 for noninferiority) was noted. Further, there was no significant difference between the groups for composite endpoint of CV death or hHF (HR = 0.88; 95.8% CI, 0.75–1.03; p = 0.11 for superiority) or CV death (HR = 0.92; 95.8% CI, 0.77–1.11; p = 0.39). However, ertugliflozin lowered the risk of hHF by 30% (HR = 0.70; 95.8% CI, 0.54–0.90; p = 0.006). No significant difference was found for kidney composite outcome (renal death, ESKD, and doubling of serum creatinine) [32] but in people with eGFR <60 mL/min/1.73 m^2 and those with micro- and macroalbuminuria, HF-related events were reduced greatly [33].

The SCORED trial determined the effect of sotagliflozin in 10,584 people with T2D with CKD, with or without albuminuria (eGFR, 25–60 mL/min/1.73 m^2). The modified primary endpoint of the total number of deaths from CV causes, hHF, and urgent visits for HF was significantly reduced with sotagliflozin vs. placebo (HR, 0.74; 95% CI, 0.63–0.88; p < 0.001), driven primarily by HF events. There was no significant reduction in CV death alone. The original primary endpoint of time to first MACE was also reduced with sotagliflozin (HR, 0.84; 95% CI, 0.72–0.99) as well as time to first CV death or hHF (HR, 0.77; 95% CI, 0.66–0.91; p < 0.001) [34].

The SOLOIST-WHF trial [35] determined the effect of sotagliflozin (SGLT2i and SGLT1i) in either people with hHF or recently discharged people with T2D (N = 1222). The new primary composite endpoint of the total number of deaths from CV causes, hHF, and urgent visits for HF was significantly reduced with sotagliflozin vs. placebo (HR = 0.67; 95% CI, 0.52–0.85; p < 0.001). Treatment benefits were similar in people with both reduced LVEF, that is, <50% (HR = 0.72; 95% CI, 0.56–0.94), and preserved LVEF, that is, >50% (HR = 0.48; 95% CI, 0.27–0.86).

According to the meta-analysis by McGuire et al., which evaluated six trials (involving 46,969 people with T2D), the largest benefit noted with SGLT2i was reduced risk of hHF and kidney disease progression among people with diabetes. Notably, the findings were consistent across the trials [36].

4.1.2. Real-world studies with SGLT2i

The CVD-REAL study [37] compared the range of CV outcomes in people with T2D at high CV risk (n = 154,528) initiated on SGLT2i vs. other glucose-lowering drugs (OGLDs). The SGLT2i were associated with a significant reduction in hHF (pooled HR = 0.61; 95% CI, 0.51–0.73; p < 0.001) and all-cause death (pooled HR = 0.49; 95% CI, 0.41–0.57; p < 0.001) compared to OGLDs. Further, the CVD-REAL2 study [38] reported significant reduction in the risk of mortality (HR = 0.51; 95% CI, 0.37–0.70; p < 0.001), hHF (HR = 0.64; 95% CI, 0.50–0.82; p < 0.001), CV death or hHF (HR = 0.60; 95% CI, 0.47–0.76; p < 0.001), MI (HR = 0.81; 95% CI, 0.74–0.88; p < 0.001), and stroke (HR = 0.68; 95% CI, 0.55–0.84; p < 0.001) with SGLT2i compared to OGLDs. According to the CVD-REAL 3 study [39] the between-group difference in the rate of eGFR decline was 1.53 mL/min/1.73 m^2 per year favoring SGLT2i over OGLDs (p < 0.0001). Further, SGLT2i were associated with a lower risk of ESKD alone compared to OGLDs (HR = 0.33; 95% CI, 0.16–0.68; p = 0.0024).

The EMPRISE study compared the efficacy and safety of empagliflozin with dipeptidyl peptidase-4 inhibitors (DPP4i) in people with T2D based on the data collected from US healthcare databases. Empagliflozin decreased the risk of hHF-specific by 50% (HR = 0.50; 95% CI, 0.28–0.91) and the risk of hHF-broad by 49% (HR = 0.51; 95% CI, 0.39–0.68) compared to sitagliptin [40]. According to the OBSERVE 4-D study new users of canagliflozin were associated with a lower risk of hHF in the on-treatment (HR = 0.39; 95% CI, 0.26–0.60) and intent-to-treat analyses (HR = 0.58; 95% CI, 0.42–0.80) compared to new DPP4i or GLP-1 receptor agonists [41].

4.1.3. CVOT trials with GLP-1 receptor agonists

GLP-1 receptor agonists are the other class of diabetes medication with beneficial CV outcomes. ELIXA was the first CVOT involving a GLP-1 agonist, lixisenatide. The composite primary outcome of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina was found to be noninferior to placebo (HR = 1.02; 95% CI, 0.89–1.17). After adjusting for baseline Hb_{A1c}, a change in the urinary albumin-to-creatinine ratio was comparable to the placebo group [42]. In the high-risk CV patients of the LEADER trial [43], the primary composite outcome of CV death, nonfatal MI, or nonfatal stroke was significantly low with liraglutide compared to placebo (HR = 0.87; 95% CI, 0.78–0.97; p < 0.001 for noninferiority; p = 0.01 for superiority). The lower CV risk was due to a significant reduction in CV death (HR = 0.78; 95% CI, 0.66–0.93; p = 0.007). Additionally, liraglutide was associated with a low incidence of new-onset macroalbuminuria compared to placebo. Semaglutide in the SUSTAIN-6 trial [44] demonstrated noninferiority to placebo with a 26% reduction in the primary composite outcome of CV death, nonfatal MI, or nonfatal stroke (HR = 0.74; 95% CI, 0.58–0.95; p < 0.001 for noninferiority; p = 0.02 for superiority). In contrast, nonfatal stroke (HR = 0.61; 95% CI, 0.38–0.99; p = 0.04) was significantly reduced with semaglutide compared to placebo. In the EXSCEL study [45], once-weekly exenatide significantly reduced composite primary outcomes (HR = 0.91; 95% CI, 0.83–1.00; p < 0.001 for noninferiority). In the REWIND trial [46] once-weekly dulaglutide demonstrated a significant reduction in the primary endpoint (HR = 0.88; 95% CI, 0.79–0.99; p = 0.026).

According to a meta-analysis by Sattar et al., which evaluated eight trials involving 60,080 people with T2D, GLP-1 receptor

agonists were associated with a reduction in MACE by 14%, all-cause mortality by 12%, hHF by 11%, and composite kidney outcome by 21% [47]. The important outcomes noted in these trials have been enumerated in Table 3 [47].

4.1.4. Trials with a focus on HFrEF, irrespective of diabetes status

The DAPA-HF trial [48] evaluated the safety and efficacy of dapagliflozin in people with HF with reduced LVEF (defined as LVEF ≤40%) regardless of T2D status (N = 4744). About 45% of patients had T2D at baseline. The primary endpoint (a composite of death from CV causes or worsening HF, which was defined as an unplanned hospitalization or an urgent visit requiring intravenous therapy for HF) was significantly reduced in the dapagliflozin group vs. the placebo group (16.3% vs. 21.2%; HR = 0.74; 95% CI, 0.65–0.85; p < 0.001). The CV improvements were also seen in people with diabetes (n = 215 in the dapagliflozin group and n = 271 in the placebo group) or people without diabetes (n = 163 and 213) with no difference between the groups (HR = 0.75; 95% CI, 0.63–0.90 vs HR = 0.73; 95% CI, 0.60–0.88; p for interaction = 0.80). The CV mortality was low in the dapagliflozin group vs. placebo group (9.6% vs. 11.6%; HR = 0.82; 95% CI, 0.69–0.98). The hHF or CV mortality was also lower in the dapagliflozin group compared to the placebo group (16.1% vs. 20.9%; HR = 0.75; 95% CI, 0.65–0.85; p < 0.001).

The EMPEROR-Reduced trial [49] evaluated the safety and efficacy of empagliflozin in people with chronic HF and a reduced ejection fraction (with or without diabetes). About 50% of the study population had diabetes at baseline. After a median of 16 months, the primary outcome event occurred in 19.4% in the empagliflozin group compared to 24.7% in the placebo group (HR for CV death or hHF, 0.75; 95% CI, 0.65–0.86; p < 0.001). The CV improvements were also seen in people with diabetes (n = 200 events in the empagliflozin group and n = 265 events in the placebo group) and without diabetes (n = 161 and 197 events, respectively) with no difference between the groups (HR = 0.72; 95% CI, 0.60–0.87) vs HR = 0.78; 95% CI, 0.64–0.97). According to the similarly designed EMPEROR-Preserved trial [50], empagliflozin was associated with a reduction in the combined risk of CV mortality or hHF in patients with HFpEF, irrespective of diabetes status.

The DELIVER trial [50] evaluated the effect of dapagliflozin 10 mg on CV death reduction or heart failure worsening among patients with HFpEF (n = 6263). According to the recently published results, dapagliflozin administration was associated with lower total events and symptom burden compared to placebo (composite of worsening heart failure: 16.4% vs 19.5%; worsening heart failure: 11.8% vs 14.5%; CV death: 7.4% vs 8.3%; in dapagliflozin vs placebo groups, respectively). The results were similar among patients with mildly reduced or preserved ejection fraction and with or without diabetes.

Table 2 summarizes the CV outcomes of various CVOTs by SGLT2i.

The expert recommendations for the prevention and management of T2D with the risk of CVD and or CKD are presented in Box 3.

4.1.5. Trials with a focus on CKD, irrespective of diabetes status

The CREDENCE trial [51] showed renal benefits of canagliflozin among people with T2D with moderate-to-advanced renal impairment (eGFR, 30 to <90 mL/min/1.73 m^2). The primary composite renal endpoint of doubling of serum creatinine from baseline (up to 30 days), ESRD, or occurrence of renal/CV death was seen in 11.1% with canagliflozin compared to 15.4% with placebo (rate per 1000 patient-years, 43.2 vs. 61.2 for canagliflozin vs. placebo; HR = 0.70; 95% CI, 0.59–0.82; p < 0.001). The incidence of CV death, nonfatal MI, or nonfatal stroke was 9.9% with canagliflozin vs. 12.2% with placebo (rate per 1000 patient-years, 38.7 vs. 48.7; HR = 0.80; 95% CI, 0.67–0.95; p = 0.01); hHF was observed in 4.0% with canagliflozin compared to 6.4% with placebo (rate per 1000 patient-years, 15.7 vs. 25.3; HR = 0.61; 95% CI, 0.47–0.80; p < 0.001); about 8.1% of patients in the canagliflozin group had hHF or CV death compared to 11.5% in the placebo group (rate per 1000 patient-years, 31.5 vs. 45.4; HR = 0.69; 95% CI, 0.57–0.83; p < 0.001).

The DAPA-CKD trial [52] evaluated the effects of the SGLT2i dapagliflozin on CV and renal events in CKD with or without concomitant T2D. The study included people with mild, mild-to-moderate, moderate-to-severe, and severe reduction in eGFR and severe increase in urine albumin-creatinine ratio (uACR) The primary composite endpoint events of worsening of renal function, defined as a composite of an eGFR decline of at least 50%, onset of end-stage kidney disease, and death from a CV or renal cause, were less with dapagliflozin compared with placebo (HR = 0.61; 95% CI, 0.51–0.72; p < 0.001). The all-cause mortality with dapagliflozin was consistent across prespecified subgroups with a relative risk reduction of 31% (HR = 0.69; 95% CI, 0.53–0.88; p = 0.003). This effect was driven primarily by a 46% relative risk reduction of non-CV death (HR = 0.54; 95% CI, 0.36–0.82). Further, dapagliflozin also reduced worsening renal function or death from kidney failure when compared to placebo (HR = 0.56; 95% CI, 0.45–0.68; p < 0.001) [37]. In a prespecified analysis, dapagliflozin reduced the risk of kidney failure, CV-related death or hHF, and prolonged survival in people with CKD with or without T2D, irrespective of concomitant CVD.

In the DAPA-HF trial, the composite renal outcome (sustained ≥50% reduction in eGFR, ESRD, or death from renal causes) was not reduced by dapagliflozin (HR = 0.71; 95% CI, 0.44–1.16; p = 0.17). However, the rate of decline in eGFR between day 14 and 720 was less with dapagliflozin (HR = −1.09; 95% CI, −1.41 to −0.78) when compared to placebo (HR = −2.87, 95% CI, −3.19 to −2.55) mL/min/1.73 m^2 per year; p < 0.001). This benefit was observed in those with and without T2D (p for interaction = 0.92) [53].

Similarly, in the EMPEROR-Reduced trial [49], the annual rate of decline in the eGFR rate was slower in the empagliflozin group than in the placebo group (−0.55 vs. −2.28 mL/min/1.73 m^2 of body surface area per year; p < 0.001) and was associated with a lower risk of serious renal outcomes. Table 4 summarizes the renal outcomes of various randomized controlled trials related to SGLT2i.

The exploratory analysis of the REWIND trial determined the long-term effect of dulaglutide on renal outcomes in people with T2D with previous CV events or CV risk factors. The incidence of renal outcomes (development of macroalbuminuria [uACR >33.9 mg/mmol in people with a lower baseline concentration] and a sustained 30% or greater decline in eGFR) was significantly low in the dulaglutide group vs. the placebo group (HR = 0.85; 95% CI, 0.77–0.93; p = 0.0004). Compared to placebo, the reduced incidence of new macroalbuminuria (HR = 0.77; 95% CI, 0.68–0.87; p < 0.0001), sustained decline in eGFR of ≥30% (HR = 0.89; 95% CI, 0.78–1.01; p = 0.066), and chronic renal replacement therapy (HR = 0.75, 0.39–1.44; p = 0.39) are in favor of dulaglutide treatment [54]. The expert recommendations for the prevention and management of T2D with the risk of CKD are presented in Box 4.

5. Conclusion

This article is a conglomeration of the existing evidence and the clinical experience of experts from three different specialties of medicine. The consensus statements have been formed accordingly based on the available scientific evidence and clinical judgment of the experts.

It is evident that for people with T2D, SGLT2i can be used in the presence of ASCVD or high-risk indicators and HF. Besides, SGLT2i also reduce the risk of ESRD events, including the occurrence of

Table 2
Composite cardiovascular outcomes with SGLT2i.

MACE outcomes						
Study	Drug	Patients enrolled	Events (%) SGLT2i	Placebo	HR 95% CI	p-Value
EMPA-REG OUTCOME [24]	Empagliflozin (10 and 25 mg)	7020 T2D: ALL CVD: 99%	10.5	12.1	0.86 (0.74–0.99)	0.04
DECLARE–TIMI 58 [29]	Dapagliflozin	17,160 T2D: ALL CVD: 40%	8.8	9.4	0.93 (0.84–1.03)	0.17
CANVAS [26]	Canagliflozin (100 and 300 mg)	10,142 T2D: ALL CVD: 65%	10.1	9.9	0.86 (0.75–1.30)	0.02
CANVAS with multiple risk factors [26]			15.7		2.36 (2.03–2.74)	<0.001
CANVAS with eCVD [26]			36.9			
Cardiovascular death outcomes						
Study	Drug	Patients enrolled	Events (%) SGLT2i	Placebo	HR 95% CI	p-Value
EMPA-REG OUTCOME [24]	Empagliflozin (10 and 25 mg)	7020 T2D: ALL CVD: 99%	3.7	5.9	0.62 (0.49–0.77)	<0.001
DECLARE–TIMI 58 [29]	Dapagliflozin	17,160 T2D: ALL CVD: 40%	2.9	2.9	0.98 (0.82–1.17)	–
CANVAS [26]	Canagliflozin (100 and 300 mg)	10,142 T2D: ALL CVD: 65%	4.6	4.3	0.87 (0.72–1.06)	–
DELIVER [50]	Dapagliflozin 10 mg	6263 HF and LVEF> 40%	7.4	8.3	0.88 (0.74–1.05)	–
Hospitalization for heart failure outcomes						
Study	Drug	Patients enrolled	Events (%) SGLT2i	Placebo	HR 95% CI	p-Value
EMPA-REG OUTCOME [24]	Empagliflozin	7020 T2D: ALL CVD: 99%	2.7	4.1	0.65 (0.50–0.85)	0.002
DECLARE–TIMI 58 [29]	Dapagliflozin	17,160 T2D: ALL CVD: 40%	2.5	3.3	0.73 (0.61–0.88)	–
DECLARE–TIMI with multiple risk factors [29]			1.2	1.9	0.64 (0.46–0.88)	0.30
DECLARE–TIMI 58 with eCVD [29]			4.3	5.5	0.78 (0.63–0.97)	
CANVAS [26]	Canagliflozin	10,142 T2D: ALL CVD: 65%	5.5	8.7	0.67 (0.52–0.87)	0.002
CANVAS with multiple risk factors [26]			3.2		2.64 (1.90–3.65)	<0.001
CANVAS with eCVD [26]			8.9			

CANVAS: Canagliflozin Cardiovascular Assessment Study; CI: Confidence interval; CVD: Cardiovascular disease; DECLARE-TIMI: Dapagliflozin effect on cardiovascular events; DELIVER: Dapagliflozin Evaluation to Improve the LIVEs of Patients With Preserved Ejection Fraction Heart Failure; eCVD: established CVD; EMPA-REG OUTCOME: Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients Removing Excess Glucose; HR: Hazards ratio; MACE: Major adverse cardiac events; SGLT2i: Sodium–glucose cotransporter-2 inhibitors; T2D: Type 2 diabetes mellitus.

Table 3
Risk of MACE, all cause mortality, hHF, composite kidney outcome and worsening of kidney outcome with GLP-1RA in different trials [47].

	ELIXA (n = 6068)	LEADER (n = 9340)	SUSTAIN-6 (n = 3297)	EXSCEL (n = 14752)	Harmony Outcomes (n = 9463)	REWIND (n = 9901)	PIONEER 6 (n = 3183)	AMPLITUDE-O (n = 4076)
Three point MACE	400/3034 (13%)	608/4668 (13%)	108/1648 (7%)	839/7356 (11%)	338/4731 (7%)	594/4949 (12%)	61/1591 (4%)	189/2717 (7%)
All cause mortality	211/3034 (7%)	381/4668 (8%)	62/1648 (4%)	507/7356 (7%)	196/4731 (4%)	536/4949 (11%)	23/1591 (1%)	111/2717 (4%)
hHF	122/3034 (4%)	218/4668 (5%	59/1648 (4%)	219/7356 (3%)	79/4731 (2%)	213/4949 (4%)	21/1591 (1%)	40/2717 (1%)
Composite kidney outcome	172/2647 (6%)	268/4668 (6%)	62/1648 (4%)	366/6256 (6%)	NA	848/4949 (17%)	NA	353/2717 (13%)
Worsening of kidney outcome	41/3031 (1%)	87/4668 (2%)	18/1648 (1%)	246/6456 (4%)	NA	169/4949 (3%)	NA	7/2717 (<1%)

AMPLITUDE-O: Effect of Efpeglenatide on Cardiovascular Outcomes; ELIXA: Evaluation of Lixisenatide in Acute Coronary Syndrome; EXSCEL: Exenatide Study of Cardiovascular Event Lowering; Harmony Outcomes: Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease; hHF: Hospitalization for heart failure; LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MACE: Major adverse cardiac events; PIONEER 6: Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes; REWIND: Dulaglutide and cardiovascular outcomes in type 2 diabetes; SUSTAIN-6: Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes.

renal death and the need for renal replacement therapy. Both SGLT2i and GLP-1RA reduce CV risk among patients with T2D and ASCVD; the treatment choice should be individualized based on the patient profile. The experts opined that endocrinologists should

Box 3
Consensus recommendations for the prevention and management of people with T2D with the risk of CVD.

- SGLT2i should be used for the first-line treatment of people with T2D with known CVD.
- For people with high-risk ASCVD (prior MI, ischemic stroke, unstable angina with electrocardiography changes, myocardial ischemia on imaging or stress test, or revascularization of coronary, carotid, or peripheral arteries), GLP-1 agonists are preferred.
- SGLT2i are also recommended for T2D people with HFrEF/HfpEF to reduce hHF, MACE, and CV mortality.
- In patients who are already on metformin, SGLT2i or GLP-1 agonists should be added.

consider evaluating the risk of HF and CKD among people with T2D based on the suggested risk stratification while planning the treatment. They also suggested the need for multidisciplinary academic meetings involving endocrinologists, cardiologists, and nephrologists for better management of people with T2D.

Summary

The association between cardiovascular disease (CVD) and chronic kidney disease (CKD) in type 2 diabetes (T2D) is well known. Hence, the management of T2D among individuals with these comorbidities needs careful evaluation. Key expert opinions were accordingly formulated based on scientific evidence and clinical judgment. The use of glucagon-like peptide 1 (GLP-1) agonists is suggested in individuals with atherosclerotic CVD or high-risk indicators, along with sodium–glucose cotransporter-2 inhibitors (SGLT2i), whereas SGLT2i are the first choice in HF and CKD. SGLT2i are becoming the drugs of choice in individuals with T2D and CKD.

Box 4
Consensus recommendations for the prevention and management of people with T2D with the risk of CKD.

- SGLT2i are preferred in people with CKD progression.
- In people with established CVD and CKD, SGLT2i may be preferred.
- Similarly, in people without established CVD but with CKD or at risk of HF, SGLT2i can be used.

Funding

AstraZeneca Pharma India Limited.

Author contributions

All co-authors were involved in the review of the literature and actively participated in forming the consensus recommendations as well as in the writing of the manuscript.

Declaration of competing interest

Dr. V. Mohan has served as a consultant and speaker and received research or educational grants from Astra Zeneca, Novo Nordisk, MSD, Novartis, Boehringer Ingelheim, USV, Dr. Reddy's Laboratories, Eli Lilly, Lifescan J & J, Sanofi-Aventis, Roche

Table 4
Composite renal outcomes with SGLT2i.

Study	Drug	Patients enrolled	Outcomes (vs. placebo)	
			Kidney	CVD
CREDENCE [51] Criteria: 30≤eGFR <90 plus uACR>300 Mean eGFR, 56.2	Canagliflozin	4401 T2D: ALL CVD: 50%	Composite of ESKD, doubling of creatinine, kidney or CV-related death HR = 0.70 (95% CI, 0.59–0.82); p < 0.001	Reduction in CV death, MI, stroke HR = 0.80 (95% CI, 0.67–0.95) Reduction in HF hospitalizations HR = 0.61 (95% CI, 0.47–0.80)
DAPA-HF [48] Criteria: eGFR≥30 Mean eGFR, 66	Dapagliflozin	4744 T2D: 42% CVD: ALL	Composite of >50 reductions in eGFR, ESKD, or kidney-related death HR = 0.71 (95% CI, 0.44–1.16)	Composite of CV death or HF hospitalization HR = 0.75 (95% CI, 0.65–1.85)
DAPA-CKD [52] Criteria: eGFR ≥25 but ≤75 mL/min/1.73 m2 and uACR ≥200 mg/g but ≤5000 mg/g (≥22.6 to ≤565 mg/mmol)	Dapagliflozin	4304 T2D: 67.6%	Composite of >50 reductions in eGFR, ESKD, kidney or CV-related death HR = 0.61 (95% CI, 0.51–0.72); p < 0.001	CV death/HF hospitalization: 4.6% vs. 6.4% (p < 0.001)
EMPA-REG OUTCOME [24] Criteria: eGFR ≥30 Mean eGFR, 74.1	Empagliflozin	7020	Composite of ≤45 reductions in eGFR, doubling of creatinine, need for a transplant, kidney-related death HR = 0.54 (95% CI, 0.40–0.75)	Discussed in Table 1
DECLARE–TIMI 58 [29] Criteria: eGFR ≥30 Mean eGFR, 74.1	Dapagliflozin	7020	Composite of ≤40 reductions in eGFR, to <60, ESKD, kidney-related death HR = 0·76; (95% CI, 0·67–0.87; p < 0·0001)	Discussed in Table 1
CANVAS [26] Criteria: eGFR ≥30 Mean eGFR, 76.5	Canagliflozin	10142	Progression of albuminuria HR = 0.73 (95% CI, 0.67–0.79) Composite of ≤40 reductions in eGFR, doubling of creatinine, need for KRT, kidney-related death HR = 0.60 (95% CI, 0.47–0.77)	Discussed in Table 1

CANVAS: Canagliflozin Cardiovascular Assessment Study; CREDENCE: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CVD: Cardiovascular disease; DAPA-CKD: Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DECLARE-TIMI: Dapagliflozin effect on cardiovascular events; DAPA-HF: Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; eGFR: Estimated glomerular filtration rate; EMPA-REG OUTCOME: Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients Removing Excess Glucose; ESKD: End-stage kidney disease; HF: Heart failure; HR: Hazards ratio; KRT: Kidney replacement therapy; MI: Myocardial infarction; SGLT2i: Sodium-glucose cotransporter-2 inhibitors; T2D: Type 2 diabetes mellitus; uACR: Urine abumin-to-creatinine ratio.

Diagnostics, Abbott, and several Indian pharmaceutical companies.Dr. A.K. Singh has no conflicts of interest to declare. Dr. A.H. Zargar was a speaker/advisor for Boehringer Ingelheim, AstraZeneca, and Johnson and Johnson and has received honoraria for his professional services. Dr. Alan Almeida has served as a consultant and speaker for Abbott, AstraZeneca, Bayer, and Dr. Reddy's Laboratories and has received honoraria for the same. Dr. A.K. Bhalla has been a speaker/advisor for Dr. Reddy 's, Zydus, La Renon Healthcare, Fresenius Kabi, Boehringer Ingelheim, AstraZeneca, Novartis, Pfizer, Abbott, Bayer, Boston Scientific, GE, and Siemens and has received honoraria for his professional services from them. He has been part of trials sponsored by Zydus, Baxter, Siemens, GE, Abbott, AstraZeneca, and PPD as a principal investigator (PI).Dr. J.C. Mohan has been a speaker/advisor for Johnson and Johnson, Boehringer Ingelheim, AstraZeneca, Novartis, Pfizer, Abbott, Bayer, Boston Scientific, GE, Siemens, Toshiba Health Systems and has received honoraria for his professional services from them. He has been part of the ATTR-ACT trial of Pfizer as a PI.Dr. Jamshed Dalal has received speaker honoraria from Astra Zeneca Pharma India Limited and Boehringer Ingelheim, India. Dr. Manisha Sahay has received speaker honoraria from AstraZeneca and Johnson and Johnson. Dr. P.P. Mohanan has received an honorarium from AstraZeneca for academic purposes. Dr. Sanjay Maitra has been a speaker/advisor for Johnson and Johnson, Boehringer Ingelheim, and AstraZeneca, Dr. Sujoy Ghosh has served as a consultant and speaker and received research or educational grants from Astra Zeneca, Novo Nordisk, MSD, Novartis, Boehringer Ingelheim, Glenmark, USV, Dr. Reddy's Laboratories, Eli Lilly, Lifescan J & J, Sanofi-Aventis, Roche Diagnostics, Abbott, and several Indian pharmaceutical companies. Dr. Tarun Jeloka has been a speaker/advisor for AstraZeneca and Zydus and has received honoraria for his professional services from them. Dr. Upendra Kaul has been a speaker/advisor for Boehringer Ingelheim, AstraZeneca, Novartis, Pfizer, Abbott, Bayer, Medtronic, Boston Scientific, and GE and has received honoraria for his professional services from them. He has been associated with PARAGON-HF, EMPEROR-Reduced, and EMPEROR-Preserved trials as a PI. Dr. Vinay Sakhuja has no conflicts of interest to declare. Dr. M.K. Das has no conflicts of interest to declare.

Acknowledgement

The authors thank Dr. Ranjini Sen, Medical Advisor, AstraZeneca Pharma India Limited, for providing medical writing assistance in the development of this manuscript, in collaboration with BioQuest Solutions and in accordance with GPP3 guidelines (http://www.ismpp.org/gpp3).

References

[1] International Diabetes Federation. IDF diabetes atlas. ninth ed. Brussels, Belgium: International Diabetes Federation; 2019.
[2] Vijayakumar G, Manghat S, Vijayakumar R, Simon L, Scaria LM, Vijayakumar A, et al. Incidence of type 2 diabetes mellitus and prediabetes in Kerala, India: results from a 10-year prospective cohort. BMC Publ Health 2019;19(1):14.
[3] Banerjee S, Panas R. Diabetes and cardiorenal syndrome: understanding the "triple threat. Hellenic J Cardiol 2017;58(5):342–7.
[4] Whaley-Connell A, Sowers JR. Basic science: pathophysiology: the cardiorenal metabolic syndrome. J Am Soc Hypertens 2014;8(8):604–6.
[5] Rangaswami J, Bhalla V, de Boer IH, Staruschenko A, Sharp JA, Singh RR, et al. Cardiorenal protection with the newer antidiabetic agents in patients with diabetes and chronic kidney disease: a scientific statement from the American heart association. Circulation 2020;142(17):e265–86.
[6] Rodríguez E, Arias-Cabrales C, Pascual J. Diabetes mellitus: a single cardiorenal syndrome umbrella. Clin Kidney J 2019;13(1):14–6.
[7] Unnikrishnan R, Anjana RM, Mohan V. Diabetes mellitus and its complications in India. Nat Rev Endocrinol 2016 Jun;12(6):357–70.
[8] Gujral UP, Pradeepa R, Weber MB, Narayan KM, Mohan V. Type 2 diabetes in South Asians: similarities and differences with white Caucasian and other populations. Ann N Y Acad Sci 2013;1281(1):51–63.
[9] Anjana RM, Baskar V, Nair ATN, Jebarani S, Siddiqui MK, Pradeepa R, et al. Novel subgroups of type 2 diabetes and their association with microvascular outcomes in an Asian Indian population: a data-driven cluster analysis – the INSPIRED STUDY. BMJ Open Diabetes Research Care 2020;8:e001506.
[10] Bertoluci MC, Rocha VZ. Cardiovascular risk assessment in patients with diabetes. Diabetol Metab Syndrome 2017;9:25.
[11] Unnikrishnan R, Gupta PK, Mohan V. Diabetes in South Asians: phenotype, clinical presentation, and natural history. Curr Diabetes Rep 2018;18(6):30.
[12] Ghosal S, Sinha B, Ved J, Biswas M. Quantitative measure of asymptomatic cardiovascular disease risk in Type 2 diabetes: evidence from Indian outpatient setting. Indian Heart J 2020;72(2):119–22.
[13] Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2019;41(2). 2020 Jan 7, 255-23.
[14] Verma S, Sharma A, Kanumilli N, Butler J. Predictors of heart failure development in type 2 diabetes: a practical approach. Curr Opin Cardiol 2019;34(5):578–83.
[15] Huelsmann M, Neuhold S, Resl M, Strunk G, Brath H, Francesconi C, et al. PONTIAC (NT-proBNP Selected PreventiOn of cardiac eveNts in a populaTion of dIabetic patients without A history of Cardiac disease): a prospective randomized controlled trial. J Am Coll Cardiol 2013;62:1365–72.
[16] Wang Y, Negishi T, Negishi K, Marwick TH. Prediction of heart failure in patients with type 2 diabetes mellitus- a systematic review and meta-analysis. Diabetes Res Clin Pract 2015;108(1):55–66.
[17] Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369(2):145–54.
[18] Chakraborty A, Chowdhury S, Bhattacharyya M. Effect of metformin on oxidative stress, nitrosative stress and inflammatory biomarkers in type 2 diabetes patients. Diabetes Res Clin Pract 2011;93(1):56–62.
[19] UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;12(9131):854–65. 352.
[20] American Diabetes Association. 9. Pharmacologic Approaches to glycemic treatment: Standards of medical care in diabetes-2019. Diabetes Care 2019;42(Suppl 1). S90-02.
[21] Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Get al Mingrone. A consensus report by the American diabetes association (ADA) and the European association for the study of diabetes (EASD). Management of Hyperglycemia in Type 2 Diabetes, 2018 Diabetes Care 2018;41. 2669-01.
[22] Chawla R, Madhu SV, Makkar BM, Ghosh S, Saboo B, Kalra S, et al. RSSDI-ESI clinical practice recommendations for the management of type 2 diabetes mellitus 2020. Int J Diabetes Dev Ctries 2020;40:1–122.
[23] Neuen BL, Young T, Heerspink HJL, Neal B, Perkovic V, Billot L, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis Lancet Diabetes. Endocrinol 2019;7: 845–54.
[24] Zinman B, Lachin JM, Inzucchi SE. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2016;374(11):1094.
[25] Kadowaki T, Nangaku M, Hantel S, Okamura T, von Eynatten M, Wanner C, et al. Empagliflozin and kidney outcomes in Asian patients with type 2 diabetes and established cardiovascular disease: results from the EMPA-REG OUTCOME® trial. J Diabetes Investig 2019;10(3):760–70.
[26] Neal B, Perkovic V, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377(21):2099.
[27] Neuen BL, Ohkuma T, Neal B, Matthews DR, Zeeuw D, Mahaffey KW, et al. Cardiovascular and renal outcomes with canagliflozin according to baseline kidney function. Circulation 2018 Oct 9;138(15):1537–50.
[28] Perkovic V, de Zeeuw D, Mahaffey KW, Fulcher G, Erondu N, Shaw W, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. Lancet Diabetes Endocrinol 2018;6(9). 691-04.
[29] Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019 Jan 24;380(4):347–57.
[30] Mosenzon O, Wiviott SD, Cahn A, Rozenberg A, Yanuv I, Goodrich EL, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. Lancet Diabetes Endocrinol 2019;7(8):606–17.
[31] Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RHM, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation 2019;139(22):2528–36.
[32] Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med 2020;383(15):1425–35.
[33] Cosentino F, Cannon CP, Cherney DZI, Masiukiewicz U, Pratley R, Dagogo-Jack S, et al. Efficacy of ertugliflozin on heart failure-related events in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease: results of the VERTIS CV trial. Circulation 2020;142(23):2205–15.
[34] Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. N Engl J Med 2020;384:129–39.
[35] Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med 2020;384:117–28.
[36] McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S,

et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. JAMA Cardiol 2021;6(2):148–58.
[37] Kosiborod M, Gause-Nilsson I, Xu J, Sonesson C, Johnsson E. Efficacy and safety of dapagliflozin in patients with type 2 diabetes and concomitant heart failure. J Diabet Complicat 2017;31(7):1215–21.
[38] Kosiborod M, Lam CSP, Kohsaka S, Kim DJ, Karasik A, Shaw J, et al. Cardiovascular events associated with SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL 2 study. J Am Coll Cardiol 2018;71(23):2628–39.
[39] Heerspink HJL, Karasik A, Thuresson M, Melzer-Cohen C, et al. Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. Lancet Diabetes Endocrinol 2020;8(1):27–35.
[40] Patorno E, Pawar A, Franklin JM, Najafzadeh M, Déruaz-Luyet A, Brodovicz KG, et al. Empagliflozin and the risk of heart failure hospitalization in routine clinical care. Circulation 2019;139(25):2822–30.
[41] Ryan PB, Buse JB, Schuemie MJ, Defalco F, Yuan Z, Stang PE, et al. Comparative effectiveness of canagliflozin, SGLT2 inhibitors and non-SGLT2 inhibitors on the risk of hospitalization for heart failure and amputation in patients with type 2 diabetes mellitus: a real-world meta-analysis of 4 observational databases (OBSERVE-4D). Diabetes Obes Metabol 2018;20(11):2585–97.
[42] Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373(23):2247–57.
[43] Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375(4):311–22.
[44] Marso SP, Holst AG, Vilsbøll T. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2017;376(9):891–2.
[45] Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377(13):1228–39.
[46] Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394(10193):121–30.
[47] Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol 2021;9(10):653–62.
[48] McMurray JJV, Solomon SD, Inzucchi SE, DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381(21). 1995-08.
[49] Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383(15):1413–24.
[50] Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med 2022 Aug 27. https://doi.org/10.1056/NEJMoa2206286. Online ahead of print.
[51] Perkovic V, Jardine MJ, Neal B. CREDENCE trial investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380(24). 2295-06.
[52] Heerspink HJL, Stefansson BV, Chertow GM, Investigators Dapa-Ckd. Rationale and protocol of the dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) randomized controlled trial. Nephrol Dial Transplant 2020;35(2):274–82.
[53] Jhund SP, Solomom SD, Docherty KF, Heerspink HJL, Anand IS, Bohm M, et al. Efficacy of dapagliflozin on renal function and outcomes in patients with heart failure with reduced ejection fraction: results of DAPA-HF. Circulation 2020. https://doi.org/10.1161/CIRCULATIONAHA.120.050391.
[54] Gerstein HC, Colhoun HM, Dagenais GR, Daiz R, Lakshmanan M, Pais P, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. Lancet 2019;394(10193):131–8.