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Review Article

PHARMACOLOGICAL MANAGEMENT OF PATIENTS WITH TYPE 2 DIABETES AND CARDIOVASCULAR DISEASE: A REVIEW

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ABSTRACT

The global incidence and prevalence of type 2 diabetes have been escalating in recent decades. Patients with type 2 diabetes have an increased risk of atherosclerotic cardiovascular disease (ASCVD). About two-thirds of deaths in type 2 diabetes are due to ASCVD, including 40% from coronary heart disease (CHD), 15% from heart failure (HF), and 10% from stroke. The association between hyperglycemia and elevated CV risk has been demonstrated in multiple cohort studies. However, clinical trials of intensive glucose reduction did not significantly reduce macrovascular outcomes. This review article provides a Pharmacological Management of Patients with Type 2 Diabetes and CV Diseases. The consensus is comprised of 5 major parts: 1) Treatment of diabetes in patients with hypertension, 2) Treatment of diabetes in patients with CHD, 3) Treatment of diabetes in patients with stage 3 chronic kidney disease, 4) Treatment of diabetes in patients with a history of stroke, and 5) Treatment of diabetes in patients with HF. The members of the consensus group comprehensively reviewed all the evidence, mainly RCTs, and also included meta-analyses, cohort studies, and studies using claim data. The treatment targets of HbA1c were provided. The anti-diabetic agents were ranked according to their clinical evidence.

Keywords: Anti-diabetic agents, chronic kidney disease, Coronary heart disease, Heart failure, Hypertension; Stroke, Type 2 diabetes.

INTRODUCTION

The coexistence of cardiovascular disease and type 2 diabetes mellitus is a common and has a strong impact on clinical management and prognosis. Atherosclerotic cardiovascular disease (ASCVD) is the major cause of death and disability in patients with type 2 diabetes [1]. About two-thirds of causes of death in type-2 diabetes are due to ASCVD, including 40% from coronary heart disease (CHD), 15% from heart failure (HF), and 10% from stroke [2]. Given that many macrovascular complications develop even 10 to 15 years before the clinical diagnosis of diabetes, management of diabetes and the associated ASCVD become even more difficult [3]. A plethora of evidence supports the association between hyperglycemia and elevated cardiovascular (CV) risk. In the United Kingdom Prospective Diabetes Study (UKPDS), for each 1% reduction in mean glycated hemoglobin (HbA1c) there are reductions in diabetes-related death and in myocardial infarction (MI) by 21% and 14%, respectively [4]. In the Emerging Risk Factors Collaboration group, every 1 mmol/L (18 mg/dL) increase in fasting glucose is associated with a 12% increase in the risk of ASCVD [5]. However, clinical trials of intensive glucose reduction did not significantly reduce macrovascular outcomes in four major randomized controlled [6]. With a much safer profile of the new generations of anti-diabetic agents, including dipeptidyl peptidase-4 (DPP-4) inhibitors (DPP-4 i), glucagon like peptide (GLP)-1 receptor agonists (GLP-1 RA), and sodium/glucose co-transporter 2 (SGLT-2) inhibitors (SGLT-2i), a more favorable effect on CV outcomes can be anticipated.

This review article comprised of 5 major parts: 1) Treatment of diabetes in patients with hypertension. 2) Treatment of diabetes in patients with CHD. 3) Treatment of diabetes in patients with chronic kidney disease. 4) Treatment of diabetes in patients with a history of stroke, and 5) Treatment of diabetes in patients with History of stroke.

Treatment of diabetes in patients with hypertension:

Hypertension is the most common co-morbidity in patients with diabetes. The estimated prevalence is 40 to 50% in general Diabetic populations [7]. The prevalence of hypertension is even higher (70%) in placebo controlled drug trials, because they usually enrolled high risk patients [8]. There has been no trial specifically designed to examine the HbA1c target or the CV effect of anti-diabetic agents in diabetic patients with hypertension. The target office BP is < 130/80 mmHg is recommended for diabetic hypertensive patients.

Target of HbA1c:

The benefits of glucose lowering depend on duration of therapy, the degree of the HbA1c reduction and choice of drugs. The HbA1c level of 6.5 % or lower will provide the vascular benefits [9, 10]. The meta-analysis demonstrated that reducing HbA1c down to 6.4 % was associated with significant reduction in non-fatal myocardial infarction [11]. The HbA1c recommended is < 7 % for diabetic patients with hypertension.

Choice of drugs:

The glucose lowering agents for diabetic patients with HT, the relative efficacy in CV protection should be first priority, followed by relative efficacy in BP lowering effects. The metformin is the first lines glucose

lowering agent for diabetic patients with hypertension [12] followed by SGLT2 inhibitors as second lines glucose lowering agents. The third lines agent includes GLP-1, RADs, TZDs, DPP-4 inhibitors, sulfonylurea, glinides, and alpha-glucosidase inhibitors. The Bp lowering efficacy of glucose lowering agents should be (from top to bottom) SGLT-2, GLP-1, RAs/DPP-4 inhibitors/TZDs and metformin/Sulfonylurea/alpha-glucosidase inhibitors/glinides [13].

Target HbA1c:	<7%		
Monotherapy:	Metformin		
Dual therapy:	Metformin + SGLT-2 i		
Triple therapy:	Metformin + SGLT-2 i +GLP-1 RA	Metformin + SGLT-2 i +TZDs	Metformin + SGLT-2 i +DPP-4 i
Insulin therapy	Basal insulin or premixed insulin or basal bolus insulin, plus oral agents		

Table 1: Treatment algorithm in diabetic patients with hypertension

CHD = coronary heart disease, GLP-1 RA = glucagon-like peptide-1 receptor agonist, SGLT-2 i = sodium glucose co-transporter 2 inhibitor, TZD =Thiazolidinedione.

Treatment of diabetes in patients with coronary heart disease:

Diabetes is a CHD equivalent [14]. More than 70% of the diabetic patients died of CV diseases [2]. The risk of CHD correlated with the baseline HbA1c [4]. For every 1% increase inHbA1c, the risk of fatal and non-fatal MI increased by 14% [4]. Two meta-analyses showed a significant reduction in non-fatal MI with intensive glucose control [15].

Target HbA1c level:

The risk of CVD and total mortality has a linear relationship with the level of HbA1c [16]. The risk of MI starts to increase from the level of HbA1cof 6 % or above [4]. The recommended HbA1c level is less than 7 % as a treatment target for diabetic patients with CHD. However, an HbA1c level less than 6.5 % may be considered in selected patients who are younger, highly educated and highly motivated.

Choice of drugs:

Following are the choice of drugs for treatment of diabetes with coronary heart disease.

a) Metformin:

The metformin therapy is the first line therapy for patients with diabetes and CHD. Meta regression suggested that metformin monotherapy was marginally associated with an improved survival [17]. The treatment with metformin in overweight diabetes patients was associated with a decreased risk of CV mortality and risk of MI compared with any other anti-diabetic agents [18]. The metformin monotherapy together with lifestyle recommendations was associated with 33% reduction in CHD [19]. However metformin didn't decrease the carotid intima thickness in CHD patients who didn't have diabetes [20].

Lactic acidosis is an uncommon but potential lethal complication of metformin [21]. Metformin should not be used in patients with stage 4 and 5 CKD that is GFR < 30 mL/min/1.73m^2 [22].

b) Sulfonylurea:

There are controversies in CV safety of sulfonylurea. The first and second generation sulfonylurea (including glimepiride and gliclazide) increased total mortality when compared with metformin [23]. The risk of MI was also higher with sulfonylurea compared with metformin [23]. Hypoglycemic episodes are more common than other new agents. Sulfonylurea increased body weight compared with metformin. The most intriguing effect of sulfonylureas is their interference with the protective mechanism in ischemic preconditioning, due to blockade of mitochondrial K_{ATP}. This may account for the increase in MI and CV mortality observed in many meta-analyses. Sulfonylurea is a low priority of drugs in treatment of diabetes with coronary heart disease

c) Alpha-glucosidase inhibitors:

Gastrointestinal side effect was more common with in the acarbose group [24]. The Acarbose group of drugs has a low priority in diabetic patients with coronary heart disease.

d) Thiazolidinedione:

The risk of death, MI and stroke was reduced, if treated with pioglitazone. There is an increase in chance of heart failure but heart failure mortality is not increased [25]. The carotid intima-medial thickness in type 2 diabetic patients treated with pioglitazone did not progress whereas those treated with glimepiride showed progression [26]. In the PERISCOPE study, atheroma volume progressed with glimepiride but not with pioglitazone [27]. The pioglitazone is put on high priority in treatment of diabetes patients with coronary heart disease.

e) Insulin:

The insulin is not given in high priority in initial therapy in diabetes patients with coronary heart disease because insulin/sulfonylurea therapy had a similar risk of MI compared with patients on conventional diet therapy [6].

f) DPP-4 inhibitors:

The DPP-4 Inhibitors is not commonly used in diabetes patients with coronary heart disease.

g) GLP- 1 receptor agonists:

The GLP-4 Inhibitors receptors agonists group of drugs put on high priority in treatment of diabetes patients with coronary heart because mortality rate was significantly reduced [28].

h) SGLT-2 Inhibitors:

The SGLT-2 Inhibitors groups of drugs (empagliflozin), put on high priority in treatment of diabetes patients with coronary heart disease because it reduce the cardiovascular mortality and all causes mortality with no differences seen for 10 or 25 mg doses [29]. Dapagliflozin reduced the risk of MI in diabetes patients [30].

For the treatment of diabetes in patients with CHD, the target of HbA1c is <7%. Metformin should be the first-line therapy in diabetes patients with coronary heart disease mainly based on the finding from the UKPDS Trial [12], 2 Meta analyses [18], 1 observational study [19] and its effect on the reduction in CAC severity [31]. For dual therapy, we in diabetic patients with CHD, mainly based on the findings from the UKPDS trial, [9], 2 meta-recommend metformin plus TZDs (pioglitazone only), followed by metformin plus SGLT-2 inhibitors, and then metformin plus GLP-1 RAs. The Proactive trial [31] an important meta-analysis [25] and 2 image studies (CHICAGO and PERISCOPE)[27] provided strong evidence to support the role of pioglitazone. The ranking of SGLT-2 inhibitors is a little bit higher than GLP-1 RAs mainly because of a more convenient oral administration of the former. The EMPA-REG OUTCOME trial [29], the CANVAS program [32] and the CVD-REAL Nordic study [33], gave a rationale for the use of SGLT-2 inhibitors. The LEADER trial [34] and the SUSTAIN-6 trial [35] gave a rationale for the use of GLP-1 RAs. If the fourth drug is to be added, DPP-4 inhibitors are recommended due to their neutral effects and safety. Glinides and acarbose have low priority due to lack of any supporting evidence [36].

Target HbA1c: < 7%
Monotherapy: Metformin
Dual therapy: Metformin + TZD Metformin + SGLT-2 i Metformin + GLP-1 RA
Triple therapy: Metformin + TZD + SGLT-2 i Metformin+ TZD + GLP-1 RAs Metformin + SGLT-2 i + GLP-1 RAs
Insulin therapy: Basal insulin or premixed insulin or basal bolus insulin, plus oral agents.

Table 2: Treatments algorithm in diabetic patients with CHD

CHD = coronary heart disease, GLP-1 RA = glucagon-like peptide-1 receptor agonist, SGLT-2 i = sodium glucose co-transporter 2 inhibitor, TZD =Thiazolidinedione.

Treatment of diabetes in patients with stage 3 chronic kidney disease:

Diabetes-related CKD is a very common complication for patients with type 2 diabetes. It leads to end-stage renal disease (ESRD, defined as the need for dialysis or kidney transplantation, or death due to kidney disease), accounting for approximately 50% of cases in the developed world [37]. According to a cross-sectional study of 6251 adult diabetic patients participating in the US National Health and Nutrition Examination Surveys in 2009-2014, the prevalence of albuminuria (albumin creatinine ration [ACR] >30 mg/gm) is 15.9%, and the prevalence of reduced eGFR (eGFR <60 mL/min/1.73 m2) is 14.1%, while 26.2% have either[38]. Of note, diabetes with concomitant CKD leads to a marked increase in CVD risk [[39]. The prevalence of diabetic nephropathy increased from 13.32 % in 2000 to 15.42% in 2009[40].

Any factors involving the development of CHD contribute to the development of CKD in diabetes, including hyperglycemia, hypertension, dyslipidemia, smoking, ethnicity, sex, age, and a long diabetes duration. Good glycemic control is the mainstay for preventing microvascular complications, including CKD, in patients with diabetes [[37]. The American Diabetes Association (ADA) guideline suggests a general HbA1c goal of <7%

to prevent or delay the progression of albuminuria and other microvascular complications in diabetes. It should be noted that in these studies most subjects had an eGFR ≥ 60 mL/min/1.73 m2 (or CKD stage 1 and 2) and only about 10-25% had CKD stage 3, while patients with CKD stage 4 and 5 were excluded[41].The impact of glycemic control in patients with stage 4 and 5 CKD remains unclear.

Target HbA1c level:

Glycemic control in patients with CKD has special challenges, considering that the risk of severe hypoglycemia is doubled when the eGFR is less than 60 mL/min/1.73 m^2 [42]. In other words, glucose management in diabetic patients with CKD should be a balance between glycemic control to reduce the progression of kidney disease and the avoidance of hypoglycemia. The recommended HbA1c less than 7.0% as the treatment target for patients with diabetes and stage 3 CKD. The risk of hypoglycemia should be carefully monitored. An observational study of non-dialyzing CKD patients with diabetes has demonstrated a U-shaped relationship between HbA1c level and mortality, with increased mortality in patients with HbA1c levels above 8.0% or below 6.5% [43].

Choice of drugs:

There are no specific trials testing the efficacy and safety in CV events of anti-diabetic agents in patients with CKD.

a) Thiazolidinedione:

Pioglitazone significantly decreased all causes of death, MI and stroke in patients with CKD (GFR < 60 mL/Min/1.73m^2 [44]. The Thiazolidinedione is very important drug for control of glucose in patients with diabetes and CKD.

b) DPP-4 inhibitors:

Sitagliptin therapy is not associated with a reduction in CV outcome in any stage of GFR stage. This group of drugs has neutral position in patients with diabetes and stage 3CKD.

c) GLP-1 receptors agonists:

These groups of drugs have a high priority in patients with diabetes and CKD.

d) SGLT-2 inhibitors:

The use of empagliflozin reduces the rates of CV mortality and all causes of mortality. There is also decrease in the progression to microalbuminuria [45]. These groups of drugs have a high priority in patients with diabetes and mild to moderate CKD (eGFR ≥30 mL/min/1.73 m2).

The treatments of diabetes in patients with stage 3 CKD, metformin should be the first line therapy in diabetic patients with CKD stage 3 because it has long-standing evidence for efficacy and safety, and is inexpensive, though a dosage reduction is necessary. For dual therapy, we recommend metformin plus SGLT-2inhibitors. The use of SGLT-2 inhibitors is compelling based on their effects in reducing 3-point MACE and renal endpoints in the EMPA-REG OUTCOME trial [45] and the CANVAS Program. They can be used as the first line therapy if metformin cannot be tolerated. For the triple therapy on top of metformin/SGLT-2 inhibitors,

we recommend GLP-1 RAs, followed by TZD, and DPP-4 inhibitors. The role of GLP-1 RAs was supported by the LEADER trial in which the patients with CKD stage 3 had better CV outcomes and the renal endpoints were significantly reduced [46]. The benefits in the renal events by semaglutideb in the SUSTAIN-6 trial also support a higher ranking ofGLP-1 RAs. The role of TZD was supported by the posthoc analysis of the Proactive trial in which patients with stage 3 CKD had benefits in the secondary CV endpoints. DPP-4 inhibitors have neutral effect in CV and renal endpoints. Sulfonylureas and glinides have hypoglycemic risk in diabetics with stage 3 CKD. Acarbose has gastrointestinal side effects (bloating, diarrhea). For these reasons, they were ranked in a lower tier, and should be reserved for patients who cannot tolerate nor have contraindication for GLP-1 RAs, TZD, or DPP-4 inhibitors.

Target HbA1c:	<7%
Monotherapy:	Metformin
Dual therapy:	Metformin + SGLT-2 i
Triple therapy:	Metformin + SGLT-2 i + GLP-1 RA Metformin + SGLT-2 i+ TZD Metformin + SGLT-2 i+ DPP-4 I Metformin + SGLT-2 i+ SU or Glinides or AGI
Insulin therapy	Basal insulin or premixed insulin or basal bolus insulin, plus oral agents

Table 3: Treatment algorithm in diabetic patients with stage 3 CKD

AGI= alpha glucosidase inhibitors. CKD= chronic kidney disease. DPP-4 i= dipeptidyl peptidase 4 inhibitor. GLP-1 RA = glucagon-like peptide-1 receptor agonist, SGLT-2 i = sodium glucose co-transporter 2 inhibitor, TZD =Thiazolidinedione. SU= sulfonylurea.

Treatment of diabetes in patients with a history of stroke:

Diabetes is associated with a higher risk of ischemic stroke [2]. The prevalence of diabetes is high both in patients with ischemic stroke/TIA (45.4%) and in patients with hemorrhagic stroke (37%). In patients with stroke, the presence of diabetes confers a much worse outcome compared with patients without diabetes. Furthermore, stroke increases subsequent functional disability and psychiatric disorders, such as depression, and leads to an enormous economic burden and impact on quality of life]. Several risk factors for stroke in patients with diabetes are potentially modifiable, including blood sugar [47]. Because there are only limited data for patients with a history of hemorrhagic stroke, the content of this section is mainly focused in patients with a history of ischemic stroke.

Intensive glycemic control did not reduce the risk of CV mortality or non-fatal stroke [48]. However, one should be aware of the hypoglycemic risk because symptomatic hypoglycemia is associated with significant risk of death [49]. With newer anti-diabetic drugs with lower risk of hypoglycemia, such as TZDs, GLP-1 RA, DPP-4 inhibitors, GLT-2 inhibitors, and the effect of glucose control on the stroke risk might be different. For instance, pioglitazone in the IRIS trial decreased stroke and MI in patients with ischemic stroke/TIA.

Target of HbA1c:

Although diabetes is associated with an increased risk of stroke and a worse post-stroke outcome, Intensive glycemic control using more traditional antidiabetic agents has a neutral effect on recurrent stroke.

The target HbA1c to be less than 7.0% in diabetic patients with a history of stroke, however, one should balance the benefits of glycemic control with the risk of hypoglycemia, particularly when sulfonylureas, glinides and insulin are administrated.

Choice of drugs:

a) Metformin:

In the UKPDS trial, metformin therapy was associated with a non-significant reduction in the risk of stroke compared with conventional lifestyle therapy in overweight patients. Metformin monotherapy together with lifestyle recommendations was associated with a 25% reduction in the risk of stroke compared with lifestyle [19]. Patients who took metformin prior to stroke onset had a reduced neurological severity and milder neurological symptoms, compared with those who had not taken metformin [50]. Therefore, metformin is the first line therapy for patients with diabetes and a history of stroke.

b) Sulfonylureas:

The sulfonylurea did not decrease the risk of stroke [6]. So sulfonylureas have a low priority in treatment of patients with diabetes and strokes.

c) Alpha-glucosidase inhibitors:

The acarbose has no effect on ischemic stroke when compared with metformin [51]. Gastrointestinal side effect is more common in acarbose group [24]. Therefore, Acarbose group of drug is not used in treatment of diabetes with stroke due to gastrointestinal side effects.

d) Thiazolidinedione:

Among patients with a history of stroke who entered the Proactive trial, pioglitazone therapy was associated with a 47% relative risk reduction in recurrent stroke [52]. Pioglitazone is associated with lower risk of recurrence stroke in patients with insulin resistance, pre-diabetes, and diabetes mellitus. There was no effect on all-cause mortality and heart failure [[53]. The pioglitazone has high priority in the treatment of diabetes in patients with a history of stroke.

e) Insulin:

The insulin therapy didn't decrease the risk of CVD in patients with diabetes and stroke, so insulin didn't have high priority as an initial therapy in diabetes patients with a history of strokes.

f) DPP-4 inhibitors:

The DPP-4 inhibitors groups of drugs have neutral position in diabetes patients with history of stroke because it didn't decrease the risk of CVD.

g) GLP-1 receptor agonist:

There is a reduction in risk of stroke in diabetes patients by using this group of drugs, so GLP-1 has a high priority in diabetes patient with history of stroke.

h) SGLT-2 inhibitors:

The use of SGLT-2 inhibitors was associated with a decreased risk of CV mortality, so this group of drugs has moderate priority in treatment of diabetes with a history of stroke.

Metformin should be the first-line therapy in diabetic patients with a history of stroke, mainly based on the findings from the UKPDS trial and several observational studies in Taiwan and Asia. For dual therapy, we recommend metformin plus TZDs, followed by metformin plus GLP-1 RAs, and then metformin þ SGLT-2 inhibitors. The Proactive trial, the IRIS trial, and an important meta-analysis provided strong evidence to support the role of TZDs. The SUSTAIN-6 trial and the LEADER trial gave a rationale for the use of GLP-1 RAs. The CANVAS program gave some support to use SGLT-2 inhibitors. If the fourth drug is to be added, DPP-4 inhibitors are recommended due to their neutral effects and safety. Sulfonylurea did not have any positive trial to support and a Taiwanese cohort showed a worse outcome. In addition, the risk of hypoglycemia is well-known. Glinides and acarbose have low priority due to lack of any supporting evidence.

Target HbA1c:	<7%
Monotherapy:	Metformin
Dual therapy:	Metformin + TZD Metformin + GLP-1 RA Metformin + SGLT-2 i
Triple therapy:	Metformin + TZD + GLP-1 RA Metformin + TZD + SGLT-2 i Metformin + GLP-1 RA+ SGLT-2 i
Insulin therapy:	Basal insulin or premixed insulin or basal bolus insulin, plus oral agents

Table 4: Treatment algorithm in diabetic patients with a history of stroke

DPP-4 i = dipeptidyl peptidase 4 inhibitor. GLP-1 RA = glucagon-like peptide-1 receptor agonist. SGLT-2 i = sodium glucose co-transporter 2 inhibitor.

TZD = Thiazolidinedione.

Treatment of diabetes in patients with heart failure:

Diabetes is a risk factor for developing heart failure, diabetic males and females had a 2.4 fold and a 5-fold risk of HF, respectively [54]. Patients with diabetes were much more likely to develop HF than patients without diabetes, with a risk ratio of 2.5[55]. Poor glycemic control is associated with an increased risk of HF among diabetic patients [56]; each 1% increase in HbAIc is associated with an 8% increase in the risk of HF. An HbAIc ≥ 10%, relative to an HbAIc <7%, was associated with 1.56 fold greater risk of HF [56]. Several possible mechanisms account for the association between diabetes and HF: disturbance in calcium handling, endothelium dysfunction, microcirculatory dysfunction, etc [57]. Impaired LV diastolic function is a hallmark in diabetic cardiomyopathy [58] while systolic dysfunction is the terminal stage of this progressive disease. The prevalence of HF in the elderly diabetic patients was approximately 20 % [59].

Heart failure patients have a higher risk of developing diabetes. HF is an established risk factor for development diabetes [60]. In patients with HF of NYHA class III were associated with a 1.7-fold increase in the risk of new-onset diabetes [61]. In HF registries around the world, the prevalence of diabetes in HF patients is approximately 30 to 50% [62]. The 40 % of hospitalized patients with reduced ejection fraction (HFrEF) had diabetes [63]. The 40% of patients with HFrEF and 45% of patients with preserved ejection fraction (HFpEF) had diabetes [64]. There is a higher CV risk in patients with diabetes and concomitant heart failure. HF has been called “the frequent, forgotten, and often fatal” complication of diabetes [65]. Diabetic patients with pre-

existing HF had a higher CV risk compared with those without HF. Even in well-treated patients, patients with pre-existing HF had an approximately 4-fold increase in the future HF admission [66, 67].

Target of HbA1c:

The target HbA1c for patients with diabetes and HF is <8.0%.

Choice of drugs:

a) Metformin:

Metformin users had numerically lower risk of developing HF compared with conventional therapy. The use of metformin in HF patients was associated with a 20% reduction in total mortality and a 7% reduction in HF admission [68]. Therefore, metformin can be used in patients with stable HF, but should be discontinued in patients with acute congestive HF (particularly when accompanied by hypoperfusion and hypoxemia), cardiovascular collapse (shock), AMI, sepsis, and other conditions associated with hypoxemia. Therefore, metformin has a high priority in patients with diabetes and stable HF.

b) Sulfonylureas:

In the UKPDS trial, the combination of sulfonylurea and insulin did not increase the risk of HF when compared with conventional dietary-based therapy [6]. In some cohort studies, sulfonylurea generally increased the risk of HF when compared with metformin [69]. In a more recent cohort study, initiation of sulfonylurea in diabetic patients increased the risk of HF and CV compared to patients initiating metformin [70]. Sulfonylurea should be reserved for add-on therapy in patients whose blood glucose cannot be controlled by other effective or safer drugs. The sulfonylureas have neutral position in patients with diabetes and HF.

c) Glinides:

The use of repaglinide was associated with a 2-fold risk of all-cause death or hospitalization [71]. In a retrospective cohort study using the Taiwan NHIRD, the use of glinides was associated with a higher risk of HF admission compared with acarbose [72]. The glinides have a neutral position in patients with diabetes and HF.

d) Alpha-glucosidase inhibitor:

The acarbose group of drugs has a neutral position in patients with diabetes and heart failure and did not give a priority due to its gastrointestinal side effects.

e) Thiazolidinedione:

TZDs activate a sodium channel in collecting tubules and enhance sodium retention and fluid overload [73] but have no direct effect on LV function [74]. TZDs increased risk of HF and have been repetitively shown in multiple RCTs. In the Proactive trial, use of pioglitazone increased 50% of HF compared with placebo. Rosiglitazone increased the risk of HF by about 2 fold compared with metformin/sulfonylurea [75]. Therefore, TZDs should not be used in patients with symptomatic, and should be discontinued when HF appears.

f) Insulin:

Insulin has an anti-natriuretic property and may increase sodium and fluid retention in diabetic patients [76]. In the BARI-2D trial, insulin did not create any significant change in the HF risk compared with other anti-diabetic medications [77]. The used of basal insulin glargine resulted in a non-significant reduction in HF admission. In patients with diabetes and HF, there are several pieces of evidence to suggest a harmful effect of insulin on heart failure. The insulin has a neutral position in patients with diabetes and HF. The use of insulin should be reserved for patients whose blood glucose cannot be controlled by other safer drugs.

g) DPP-4 Inhibitors:

The use of saxagliptin increased HF admission. The risk factors for HF admission included the followings: prior HF, elevated base line N-terminal pro-B-type natriuretic peptide (NT-pro BNP), and CKD. The mechanism of increased HF admission with the use of saxagliptin was not completely understood. Therefore, for patients with diabetes and HF, saxagliptin and alogliptin should not be used. Therefore DPP-4 inhibitors have neutral position in patients with diabetes and HF, but did not recommend saxagliptin, alogliptin, and vildagliptin in patients with HF.

h) GLP-1 receptor agonists:

The GLP-1 RAs have a neutral effect on HF and can be used safely in patients with diabetes and HF. Therefore, GLP-1 RAs have neutral position in patients with diabetes and HF.

i) SGLT-2 inhibitors:

The use of empagliflozin significantly lowers the rates of CV death, hospitalization for HF and all causes mortality. The mechanisms are not completely understood. The first possible, and perhaps the most widely credited, mechanism that has with the positive CV and renal outcomes of SGLT-2 inhibitors relates to its effect on diuresis, both natriuresis and osmotic diuresis. Short-term empagliflozin treatment was associated with a significant reduction in LV mass index and improved diastolic function [78]. SGLT-2 inhibitor is a unique class of anti-diabetic agents that decrease HF admission in both HF and non-HF diabetic patients. Therefore SGLT-2 inhibitor groups of drugs are the first line therapy in patients with diabetes and HF.

The target of HBA1c is <8%. SGLT-2 inhibitors or metformin are the first line therapy. The use of SGLT-2inhibitors is compelling, based on their effects in reducing 3-point MACE and HF admission in the EMPA-REG OUTCOME trial [29], The CANVAS program [32] and the CVD-REAL study [79]. The use of metformin was based on 2 recent metaanalysis [68]. Metformin should not be used or should be discontinued in patients with clinical conditions associated with hypoxemia, such as acute HF, shock, or sepsis, to avoid lactic acidosis. For dual therapy, we recommended SGLT-2 inhibitors plus metformin. If a third drug is to be added, we recommended GLP-1 RAs, based on their neutral effects that have been confirmed in the LEADER trial. The ranking of DPP-4inhibitors is lower than GLP-1 RAs. Sitagliptin can be safely used, based on the finding from the TECOS trial. Saxagliptin, alogliptin, and vildagliptin should be avoided, based on the findings from the SAVOR trial.

Linagliptin can be used, but there is only a patient-level pooled analysis to support its use. Sulfonylurea, acarbose, and glinides are ranked lower than DPP-4 inhibitors.

Target HbA1c: <8%
Monotherapy: SGLT-2 i or metformin
Dual therapy: SGLT-2 i + metformin
Triple therapy: SGLT-2 i + metformin+ GLP-1 RA SGLT-2 i + metformin + DPP-4 I SGLT-2 i + metformin+ SU or AGI SGLT-2 i + metformin + Glinides.
Insulin therapy: Basal insulin or premixed insulin or basal bolus insulin, plus oral agents

Table 5: Treatment algorithm in diabetic patients with heart failure

AGI= alpha-glucosidase inhibitor. DPP-4 i= dipeptidyl peptidase 4 inhibitor. GLP-1 RA= glucagon-like peptide-1 receptor agonist. SGLT-2 i= sodium glucose co-transporter 2 inhibitor. SU=sulfonylurea. TZD= Thiazolidinedione.

Adverse effect of antidiabetic agents:

Hypoglycemia and some emerging adverse effect of newer anti-diabetic agents were noted here.

a) Hypoglycemia:

Minimizing risk of both severe and non-severe hypoglycemia is a priority in the management of diabetes [80]. Hypoglycemia is common in daily practice. In a cross sectional survey in 5 Asian countries, symptomatic hypoglycemia was reported in 35.8% of overall patients and in 29.4% of Taiwanese patients, who were treated with oral antidiabetic agents [92]. There is an increasing trend in emergency department visits for hypoglycemia in patients with type 2diabetes in Taiwan from 2000 to 2010[81]. Among anti-diabetic agents, sulfonylureas, glinides, and insulin increase the risk of hypoglycemia [82]. Metformin, alpha-glucosidase inhibitor [83], TZD, and other newer anti-diabetic agents, such as DPP-4 inhibitors, GLP-1 RAs, andGLT-2 inhibitors, have lower risk of hypoglycemia. Although a modest benefit of intensive glucose control on CV events is likely to be present, it should be noted that overly aggressive glycemic control, especially in older patients with more advanced disease, may not have significant benefits but instead may produce some risks. Therefore, clinicians should balance the risk of hypoglycemia vs. CV benefit.

b) Genital tract infection:

The risk of genital tract infection (GTI) is increased by SGLT-2 inhibitors. In the EMPA-REG OUTCOME trial, the annual incidence of GTI was significantly higher with empagliflozin than with placebo group in both men and women. In the CANVAS program, the annual incidence of GTI was also higher in the canagliflozin group than in the placebo group. Therefore, personal hygiene should be emphasized in patients' receivingSGLT-2 inhibitors.

c) Acute kidney injury:

The use of SGLT-2 has a higher risk of acute kidney injury. We recommended examining several factors that may predispose patients to AKI. These factors include hypovolemia, CKD, HF, and concomitant

medications such as diuretics, ACE inhibitors, ARBs, and NSAIDs. Renal function should be evaluated prior to initiating SGLT-2 inhibitors and monitored periodically thereafter. Temporary discontinuation of SGLT-2 inhibitors should be considered in any setting of reduced oral intake such as acute illness or fasting, or with fluid losses such as gastrointestinal illness or excessive heat exposure.

d) Diabetic Ketoacidosis:

The causes of diabetic Ketoacidosis in patients with type-1 and type-2 diabetes mellitus, treated with SGLT-2 were identified. Because DKA is a potentially lethal complication, the potential triggering factors should be identified during the exposure period to SGLT-2inhibitors, which include inter-current illness, reduced food and fluid intake, reduced insulin doses, and history of alcohol intake. Symptoms of DKA, including nausea, vomiting, abdominal pain, tiredness, and shortness of breath, should be monitored. One should be aware that patients with SGLT-2 inhibitors related DKA may not have very high blood glucose level, sometimes being called "euglycemic DKA", and their plasma glucose level is usually < 300 mg/dL. In a systemic review, the average blood glucose on presentation of DKA was 265.6 mg/dL.

e) Amputation:

There was a higher risk of amputation of toes, feet, or legs with canagliflozin than with placebo. The risk of amputation of canagliflozin was higher than non-SGLT-2 inhibitors. Amputation of the toe and middle of foot were the most common; however, amputations involving the leg, below and above the knee, also occurred. Several clinical conditions may predispose patients to the risk of amputations, including a history of amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers. Physicians should remind patients of the following symptoms: new pain or tenderness, sores or ulcers, or infections in legs or feet.

f) Fracture:

Thiazolidinedione have been shown to exert detrimental effects on the skeleton and increase the risk of fracture [84]. In the recent IRIS trial, the incidence of fracture in the pioglitazone group was higher than that in the placebo group [85]. Canagliflozin decreased bone mineral density and increased the risk of fracture [86].

CONCLUSION

The prevalence of type 2 diabetes has been escalating in recent decades. The CV complications created a huge economic burden to our society. Treatment of diabetes should now be expanded from a glucose-centric concept to an event-driven strategy. Fortunately, we have many new anti-diabetic agents, proven to be effective in CV and renal protection. Just in these few years, many RCTs have demonstrated significant reductions in MI, stroke, CV death, and all-cause death, HF, and ESRD, in patients with pre-existing CVD. This review article provides treatment consensus for type 2 diabetic patients with 5 different categories of CVD, including HTN, CHD, CKD, stroke, and HF. Also provide most updated information and recommendations regarding targets of HbA1c and choice of drugs.

Abbreviations:

ASCVD: Atherosclerotic cardiovascular disease.

CHD: Coronary heart disease.

HF: Heart failure.

CV: Cardiovascular.

DM: Diabetes mellitus.

CKD: Chronic kidney disease.

MI: Myocardial infarction.

GFR: Glomerular Filtration rate.

ADA: American diabetic association.

TIA: Transient ischemic attack.

DPP-4: Dipeptidyl peptidase- 4.

ESRD: End stage renal disease.

HTN: Hypertension.

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