

Dose Modification of Antidiabetic Agents in Patients with Type 2 Diabetes Mellitus and Heart Failure

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Abstract

Heart failure is the most common comorbidity of diabetes. The incidence of heart failure in patients with diabetes is about 9%–22%, which is four times higher than that in patients without diabetes. Heart failure and diabetes are collectively associated with increased morbidity and mortality compared to either condition alone. Several epidemiological studies have demonstrated an increased risk of heart failure in patients with diabetes; moreover, poor glycemic control accounts for the increased risk of heart failure. At present, several oral (metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, etc.) as well as injectable (insulins, glucagon-like peptide 1 receptor agonists) antidiabetic agents are available. However, optimal treatment strategy to achieve adequate glycemic control in patients with type 2 diabetes mellitus (T2DM) and heart failure has not been well studied. In the view of rising prevalence of heart failure in patients with diabetes mellitus, clinicians need to understand the potential implications of antidiabetic agents in patients with heart failure. A group of experts from across India were involved in a consensus meeting in Pondicherry during the National Insulin Summit in November 2015. They evaluated agents currently available for the treatment of diabetes looking at existing scientific evidence relevant to each class of therapy. In addition, the existing guidelines and prescribing literature available with all these agents were also reviewed. Findings from the expert evaluations were then factored into the national context incorporating personal experience and common clinical practices in India. The purpose of this consensus document is to assist the clinicians while treating patients with T2DM and heart failure.

Keywords: Antidiabetic agents, heart failure, type 2 diabetes mellitus

INTRODUCTION

The Framingham study, long ago, established the association of heart failure with type 2 diabetes mellitus (T2DM).^[1] The incidence of heart failure in diabetic patients is about 9%–22%, which is four times higher than nondiabetic population.^[2–4] Type 2 diabetes frequently coexists with other cardiovascular (CV) risk factors, such as hypertension, dyslipidemia, smoking, and obesity, which in combination could result in atherosclerosis, ischemic heart disease, and left ventricular (LV) dysfunction. LV dysfunction can be clinically quiet or may manifest with the typical clinical signs and symptoms of heart failure (e.g., peripheral edema, shortness of breath, fatigue) although the elderly may have atypical symptoms.^[5] Heart failure could be a manifestation of coronary artery disease; other possible causes include hypertension and nonischemic cardiomyopathy. The presence of diabetic cardiomyopathy may increase the risk of heart

failure.^[6] Diabetes mellitus is associated with a large increase in the risk of mortality, independently of age, sex, body mass index, renal function, comorbidity, ejection fraction, and year of heart failure. This underscores the importance of aggressive evaluation and management of diabetes mellitus in heart failure.^[7]

In addition, factors associated with diabetes such as poor glycemic control,^[8] insulin resistance,^[9] hypertension,^[10,11] microalbuminuria,^[12–14] end-stage renal disease,^[10,11] and duration of diabetes^[11] are risk factors for heart failure. The coexistence of diabetes and heart failure leads to poor prognosis. Indeed, studies have witnessed hospitalizations for

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heart failure (hHF) nearly double for patients with diabetes compared to patients without diabetes.^[15,16] Further, several clinical studies have shown an increased mortality of patients with T2DM and heart failure.^[7,10,17,18]

Clinicians, who commonly encounter patients with T2DM and heart failure in their daily practice, currently face dilemmas due to the lack of a clear consensus.

To facilitate and draw the attention of physician community toward optimal dose modification of antidiabetics for T2DM heart failure patients, a group of experts from across the India held a consensus meeting during the National Insulin Summit in Pondicherry, India, on November 8, 2015.

The objectives of the meeting were to:

- Examine the position of antidiabetic therapies in algorithms published as part of established treatment guidelines from globally recognized professional bodies such as American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE), and International Diabetes Federation (IDF) as well as those published within India
- Examine the published evidence and prescribing information on dose modifications of each antidiabetic agent
- Frame consensus recommendations for dose modifications of commonly used agents based on published guidelines, evidence, and own experience.

METHODS

New York Heart Association (NYHA) functional classification on heart failure was the basis for the recommendations [Table 1].^[19] The expert group identified the following classes of drugs for patients with T2DM and heart failure and proposed recommendations on consensus: biguanides (metformin), sulfonylureas (SUs) (glipizide, glimepiride, glyburide, gliclazide), thiazolidinediones (pioglitazone), alpha-glucosidase inhibitors (AGIs) (acarbose, miglitol), dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, saxagliptin, vildagliptin, linagliptin), sodium-glucose cotransporter 2 (SGLT2) inhibitors (dapagliflozin, canagliflozin, empagliflozin), glucagon-like peptide-1 receptor agonists (GLP1 RAs) (liraglutide, exenatide, dulaglutide), and various types of insulin products.

Each class of drugs was subsequently evaluated for relevant and published clinical and epidemiological evidence as well as defined place in guidelines/algorithms from national and global professional associations. These evaluations were then factored into the national context based on personal experience and common therapy practices in India. The final proposed consensus recommendations captured the collective outcome of the above process in easily implementable steps under each therapeutic drug class.

The global and national guidelines that were considered include position statement of the ADA and EASD (written henceforth

Table 1: The New York Heart Association classification system

Class	New York Heart Association (NYHA) functional classification
I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain
IV	Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

as ADA-EASD position statement), AACE-ACE clinical practice guidelines (written as AACE-ACE guidelines), global guideline for type 2 diabetes, and IDF treatment algorithm for patients with type 2 diabetes (written as IDF guidelines).^[20-25]

Glycemic targets

Glycemic goals need to be individualized, and the choice of pharmacotherapy should address challenges of hypoglycemia and weight gain.

Published scientific evidence

Optimal glycemic control has been considered to be a prime factor for combating vascular complications associated with diabetes. Indeed, studies have clearly confirmed that reducing hyperglycemia decreases the onset and progression of microvascular complications, but its effect on CV diseases (CVDs) is uncertain.^[26-29] However, conflicting results of the contemporary clinical trials in the recent years have produced confusion amid concerns that tight glycemic control, in some circumstances, could even be unfavorable. The Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) and Veterans Affairs Diabetes Trial studies found no effect of intensive glucose control on major cardiovascular events (MACEs).^[30,31]

Moreover, the Action to Control Cardiovascular Disease in Diabetes (ACCORD) study recognized an increased risk for death from CV causes and total mortality with intensive glucose control.^[32] In this context, a meta-analysis reported that intensive glycemic control reduced the risk for CVDs (relative risk [RR], 0.90; 95% confidence interval [CI], 0.83–0.98) but did not reduce the risk for all-cause mortality (RR, 0.98; 95% CI, 0.84–1.15), CV mortality (RR, 0.97; 95% CI, 0.76–1.24), or stroke (RR, 0.98, 95% CI, 0.86–1.11).^[33] Another meta-analysis reported that intensive glycemic control reduced the risk for major CVD (hazard ratio [HR], 0.91; 95% CI, 0.84–0.99),

mainly because of a 15% reduced risk of myocardial infarction (HR, 0.85; 95% CI, 0.76–0.94), but did not reduce the risk for all-cause mortality (HR, 1.04; 95% CI, 0.90–1.20), CV mortality (HR, 1.10; 95% CI, 0.84–1.42), stroke (HR, 0.96; 95% CI, 0.83–1.1), or hospitalized/fatal heart failure (HR, 1.00; 95% CI, 0.86–1.16).^[34] Furthermore, the relationship between glycosylated hemoglobin (HbA1c) and consequences seems more complex in patients with T2DM and heart failure. Some studies demonstrated a probable “U-shaped” or an inverse relationship between HbA1c and mortality.^[35-37]

In a study of 5815 ambulatory heart failure patients receiving medical treatment for diabetes, individuals with modest glycemic control (HbA1c >7.1%–7.8%) had lower mortality compared with HbA1c levels that were either higher or lower.^[36] Conversely, a meta-analysis indicated that intensive glycemic (HbA1c level below 7.0%) control has CV benefits and does not increase all-cause mortality.^[38] In addition, in 2412 participants (of which 907 participants had known diabetes) enrolled in Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity study, increasing levels of HbA1c was associated with increased risk of total mortality, hHF, and a composite outcome of CV death or hHF.^[38] In the view of these findings, further studies are warranted before a conclusion can be drawn on the impact of intensive glycemic control in patients with diabetes and heart failure.^[38,39]

Current place in guidelines/recommendations

ADA recommends less stringent HbA1c goals (such as < 8% [64 mmol/mol]) for patients with advanced microvascular or macrovascular complications.^[40] AACE/American College of Endocrinology guidelines recommends that HbA1c target should be individualized based on numerous factors, such as age, life expectancy, comorbid conditions, duration of diabetes, and risk of hypoglycemia or adverse consequences from hypoglycemia, patient motivation, and adherence.^[25] Further, an HbA1c ≤6.5% is considered optimal if it can be achieved in a safe and affordable manner, but higher targets may be appropriate for certain individuals and may change for a given individual over time.^[25] Similarly, ADA-EASD position statement recommends for personalization of the treatment, while balancing the benefits of glycemic control with its potential risks, taking into account the adverse effects of glucose-lowering medications (particularly hypoglycemia), the patient’s age and health status, among other concerns.^[24]

Oral antidiabetic agents

Biguanides: Metformin

Metformin may be used in low doses. It may lead to lactic acidosis in unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia [Table 2].

Published scientific evidence

Formally, metformin was contraindicated in patients with heart failure as it causes lactic acidosis.^[41,42] However, a recent systematic review of observational studies witnessed that metformin compared to control group is associated

Table 2: Published literature and prescribing information on use of metformin in patients with diabetes and heart failure

Agent	Suggestion from published literature	Prescribing Information
Metformin	Limited data. Marginal improvement in 1 year mortality	To be Avoided

with lower rate of all-cause mortality (23% vs. 37%, pooled adjusted risk estimates 0.80, 0.74–0.87, $P = 15%$, $P < 0.001$) and all-cause hospitalizations (35% vs. 64%, pooled adjusted risk estimate 0.93, 0.89–0.98, $P = 0%$, $P = 0.01$) in patients with T2DM and heart failure. Metformin did not increase the risk of lactic acidosis in the patients with reduced LV ejection fraction and patients with heart failure and chronic kidney disease.^[43] Thus, the review concluded that metformin can be considered for the treatment of patients with T2DM and heart failure.^[43]

Further, a study which compared heart failure patients with or without metformin therapy reported that metformin was associated with lower mortality (HR 0.85; 95% CI, 0.82–0.88), mostly due to a less CV death (HR 0.78; 0.74–0.82), and with decreased hospitalization rate (HR 0.81; 0.79–0.84).^[44] Moreover, a cohort study reported that metformin alone or combination with SU was associated with fewer deaths compared to the SU monotherapy at 1 year (HR 0.59; 95% CI, 0.36–0.96) and over long-term follow-up (HR 0.67; 95% CI, 0.51–0.88) in chronic heart failure (CHF) patients.^[45] Further, a couple of recent observational studies also suggested that metformin can be a safe and effective alternative drug for the management of diabetes with concomitant heart failure.^[46,47]

Current place in guidelines/recommendations

ADA recommends use of metformin in stable CHF patients with the absence of renal impairment and restricts its usage in unstable and hospitalized patients.^[40]

The European Society of Cardiology (ESC) guidelines recommends metformin in patients with heart failure without other comorbidities such as liver or renal dysfunction.^[48] The Australian Diabetes Society does not recommend metformin in patients with severe cardiac failure.^[49] IDF does not recommend metformin in elderly patients with CHF. Similarly, Indian Council of Medical Research (ICMR) also does not recommend metformin in patients with CHF.^[50] The consensus by an independent group from Germany recommends metformin in NYHA class I and II heart failure but not in NYHA class III or IV.^[51]

Prescribing information

Prescribing information of metformin does not recommend use in patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure. Moreover, caution should be taken while using metformin in the patients with acute congestive heart failure.^[52]

Sulfonylureas

SUs should be considered only if metformin is contraindicated or when given in combination with metformin [Table 3].

Published scientific evidence

To achieve optimal glycemic targets, SUs have emerged as alternative treatment options to metformin.^[53] Currently, there is a paucity of data with regard to the use of SU in patients with T2DM and heart failure. A retrospective cohort study compared SU against metformin in 12,272 diabetic patients and CHF. Over 2.5 years of follow-up, SU monotherapy was associated with higher mortality (52% vs. 33%) and hospitalizations (70% vs. 69%) compared to metformin monotherapy.^[54]

Further, a systematic review and meta-analysis reported a higher risk of heart failure with SUs compared to metformin (RR 1.17, 95% CI, 1.06–1.29, $I^2 = 24\%$).^[55] An observational study compared the long-term mortality of SUs in patients with diabetes and CHF. The study found similar HR for mortality with glimepiride (1.10, 95% CI, 0.92–1.33), glibenclamide (1.12, 0.93–1.34), and glipizide (1.14 [0.93–1.38]).^[56] In addition, a dose–response analysis concluded that high-dose SU (median daily dose of >4 mg for glyburide) was associated with more episodes of heart failure than high-dose metformin (adjusted HR 1.24; 95% CI, 1.01–1.54) and low-dose SU (HR 1.38; 95% CI, 1.20–1.60). The study concludes that physicians should carefully weigh benefits versus risks while prescribing high-dose SUs in diabetic patients with CHF.^[57]

Gliclazide has been suggested as a better SU agent for patients with T2DM and CV risk. Indeed, the ADVANCE study found that rigorous glucose control with gliclazide has no significant effect on major macrovascular events.^[30,58] In addition, recent studies have documented lower risk of CV events and mortality with gliclazide.^[59,60] In contrast, another study found that metformin demonstrated its superiority over gliclazide in terms of CV safety.^[61]

Current place in guidelines/recommendations

No specific guidelines are available pertaining to SU.

Prescribing information

The prescribing information of glipizide, glimepiride, and glyburide mentions that there is an increased risk of CV mortality with SU. Therefore, these agents may be avoided in patients with CV risk.^[62-64]

Thiazolidinediones

Pioglitazone is contraindicated in patients with symptomatic heart failure New York Heart Association Class III or IV. Caution is also advised while their use in patients with New York Heart Association Class I or II heart failure [Table 4].

Published scientific evidence

The peroxisome proliferator-activated receptor- γ -activating thiazolidinediones are known to cause sodium retention and plasma volume expansion.^[65,66] Fluid retention may aggravate heart failure and lead to increased number of hospitalizations.^[66,67] The PROactive trial compared pioglitazone against placebo in

T2DM patients with preexisting CVDs. The study reported more cases of serious heart failure with pioglitazone (5.7%) than the placebo group (4.1%) ($P = 0.007$). However, death due to heart failure was comparable for pioglitazone (0.96%) and placebo (0.84%) ($P = 0.639$).^[68] Further, a double-blind randomized controlled trial (RCT) compared pioglitazone with glyburide in NYHA functional class I heart failure patients. Pioglitazone was associated with more incidence of heart failure (10 vs. 7 patients), edema (21.2% vs. 12.8%), and weight gain (2.565 vs. 0.864 kg) as compared to glyburide.^[69] Similarly, another RCT examined the safety of pioglitazone and glyburide with or without insulin in NYHA Class II and III heart failure patients. The study reported that pioglitazone as compared to glyburide was associated with a higher incidence of heart failure (30 vs. 15 patients).^[70] A systematic review and meta-analysis compared pioglitazone with other oral hypoglycemic agents in patients with T2DM. Pioglitazone reported higher risk of heart failure as compared to metformin (RR: 1.14; 95% CI, 0.86–1.50) and SU (RR: 1.30; 95% CI, 0.90–1.87).^[55]

Current place in guidelines/recommendations

Several guidelines restrict use of thiazolidinediones in patients with diabetes and heart failure. The ADA guidelines recommend restricting the usage of thiazolidinediones in symptomatic CHF patients.^[40] Similarly, European Society of Cardiology (ESC) comments that thiazolidinediones should not to be used in T2DM with heart failure patients since water retention may deteriorate or aggravate heart failure.^[71] ICMR guidelines also recommend to avoid thiazolidinediones in patients with a history of CHF.^[50] Consensus by an independent group from Germany recommend to not use pioglitazone in all NYHA class of heart failure as it elevates cardiac decompensation.^[51]

Prescribing information

Pioglitazone prescribing information recommends avoiding its use in patients with symptomatic heart failure and in patients with NYHA Class III or IV heart failure.^[72]

Table 3: Published literature and prescribing information on use of sulphonylureas in patients with diabetes and heart failure

Agent	Published literature	Prescribing Information
Glipizide	Should only be considered if metformin is contraindicated or when given in combination with metformin	Not available
Glimepiride		Not Available
Glyburide		Not Available
Gliclazide		Not Available

Table 4: Published literature and prescribing information on use of thiazolidinediones in diabetic patients with heart failure

Agent	Published Literature	Prescribing Information
Pioglitazone	Fluid retention may aggravate heart failure and lead to increased number of hospitalizations	Not to be used in NYHA III, IV

Alpha-glucosidase inhibitors

There is limited data available with AGIs that examine their beneficial and/or harmful effects in patients with diabetes and heart failure. Thus, we recommend its use with caution [Table 5].

Published scientific evidence

AGIs have emerged as an alternative first-line therapy in old-aged DM patients due to low risk of hypoglycemia and better postprandial glycemic control.^[53] A few studies have examined the CV safety of AGIs. For instance, acarbose in an RCT, Study to Prevent Non-insulin Dependent Diabetes Mellitus displayed a 34% RRR of hypertension and a 49% RRR of CV events, as well as a 36% RRR of developing T2DM in patients with impaired tolerance to glucose.^[73,74] A meta-analysis demonstrated that acarbose reduced CV events in patients with T2DM (HR 0.65; 95% CI, 0.48–0.88, $P = 0.0061$).^[75]

The gluco VIP trial, a multinational, observational study investigated the efficacy, safety, and tolerability of acarbose as add-on or monotherapy in a large cohort of Asian patients with or without CV morbidities. The results indicate that acarbose was effective and safe with a good tolerability profile regardless of the presence of CV comorbidities or diabetes-related complications.^[76] However, an intension-to-treat cohort study reported that acarbose was associated with higher risk of CV events (HR 1.05; 95% CI, 1.01–1.09), heart failure (HR 1.08; 95% CI, 1.00–1.16), and ischemic stroke (HR 1.05; 95% CI, 1.00–1.10) compared to metformin as first-line therapy in T2DM.^[77] So far, the data are limited and further studies are warranted. The Acarbose Cardiovascular Evaluation (ACE) trial is underway involving patients with impaired glucose tolerance and established coronary heart disease. The trial examines the impact of acarbose on CV-related morbidity and mortality.^[78]

Current place in guidelines/recommendations

There are no guidelines specific to use of AGIs in patients with heart failure.

Prescribing information

The prescribing information of acarbose did not comment on use in patients with CHF.

Dipeptidyl peptidase-4 inhibitors

Data with DPP4 inhibitors in New York Heart Association Class III–IV is still limited. We recommend its use with caution.

Published scientific evidence

Dipeptidyl-peptidase-4 inhibitors are considered as a second-line therapy after metformin in the treatment of T2DM.^[79] Several studies have been conducted to establish

the CV safety of DPP-4 inhibitors. The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) examined and confirmed the noninferiority of sitagliptin compared to placebo, in terms of primary composite CV outcome (HR, 0.98; 95% CI, 0.88–1.09; $P < 0.001$) and hHF (HR, 1.00; 95% CI, 0.83–1.20; $P = 0.98$).^[80] In addition, the trial showed no difference in total hHF between the sitagliptin and placebo groups (unadjusted HR, 1.00; 95% CI, 0.80–1.25). Rates of CV death (22.4% vs. 23.1%) and post-hHF all-cause death (29.8% vs. 28.8%) were also similar between groups.^[80] Therefore, the TECOS study concludes that sitagliptin may be used safely in patients with T2DM at high CV risk.^[81]

The EXAMINE study evaluated alogliptin (25, 12.5, and 6.25 mg QD dose) compared to placebo for CV safety over a median follow-up period of 1.5 years. The study reported more hHF in the alogliptin group compared to placebo (3.1 vs. 2.9%, HR, 1.07; 95% CI, 0.79–1.46) within the composite endpoint. In addition, alogliptin did not induce new onset of heart failure and did not worsen heart failure outcomes in patients with a history of heart failure.^[82] Subsequent reports from the EXAMINE study indicate that alogliptin in patients with type 2 diabetes and recent acute coronary syndromes does not show any effect on composite events of CV death and hHF in the *post hoc* analysis (HR, 1.00; 95% CI, 0.82–1.21).^[83]

Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction (TIMI) 53 trial was conducted in diabetic patients with existing CVDs comparing saxagliptin (5 mg/day) versus standard of care. The study reported higher rate of hHF (3.5% vs. 2.8%, HR, 1.27; 95% CI, 1.07–1.51; $P = 0.007$) in saxagliptin group compared to placebo group.^[84] Subsequent reports reported 27% higher RR of hHF with saxagliptin [Table 6]. In addition, the increased hHF was highest among the patients with elevated levels of natriuretic peptides, prior heart failure, or chronic kidney disease [Table 7].^[85]

The Vildagliptin in Ventricular Dysfunction Diabetes trial included patients with NYHA Class I to III heart failure. The trial reported more CV deaths in the treatment arm than in the placebo arm.^[86] In addition, there was a statistically considerable increase in LV end-diastolic volume and a propensity toward increased LV end-systolic volume within the vildagliptin arm.^[86]

A comprehensive patient-level pooled analysis of 19 double-blinded RCTs of linagliptin versus placebo in patients with T2DM reported all-cause mortality (13 vs. 11 patients; HR, 0.81; 95% CI, 0.36–1.81) and hospitalization for CHF (12 vs. 9 events; HR, 1.04; 95% CI, 0.43–2.47). The study concluded that linagliptin is not associated with increased CV risk versus active comparators (glimepiride and voglibose) or placebo.^[87] The Cardiovascular and Renal Microvascular Outcome Study with linagliptin trial is presently ongoing.^[88]

Table 5: Published literature and prescribing information on use of alpha-glucosidase inhibitors in diabetic patients with heart failure

Agent	Published Literature	Prescribing Information
Acarbose	No evidence of benefits/harm	Not Available
Miglitol	No evidence of benefits/harm	Not Available

Table 6: Evidence from the cardiovascular outcome studies for DPP-4 Inhibitors

Outcome	SAVOR TIMI	EXAMINE	TECOS
Primary end point	Neutral	Neutral	Neutral
All-cause mortality	Neutral	Neutral	Neutral
CV Death	Neutral	Neutral	Neutral
Hospitalization due to HF	27% increased risk	Neutral	Neutral
Stroke	Neutral	Neutral	Neutral
Unstable angina	Neutral	Neutral	Neutral

Table 7: Published literature and prescribing information on use of DPP-4 inhibitors in patients with diabetes and heart failure

Agent	Published Literature	Prescribing Information
Sitagliptin	CVOT results from SAVOR TIMI and TECOS available	Not Available
Saxagliptin		Not Available
Vildagliptin		Not Available
Linagliptin		Not Available

Current place in guidelines/recommendations

There are no specific guidelines pertaining to the use of DPP-4 inhibitors in patients with heart failure.

Prescribing information

Prescribing information recommend to evaluate risks and benefits of saxagliptin before initiating treatment in patients at a higher risk for heart failure^[89] and to avoid vildagliptin in patients with NYHA functional class IV heart failure.^[90]

Sodium glucose cotransporter-2 inhibitors

There are limited data available with SGLT2 inhibitors in heart failure. They may be useful due to their mild diuretic effect. We recommend using SGLT2 inhibitors cautiously.

Published scientific evidence

SGLT2 inhibitor could be an attractive drug for patients with T2DM and chronic Heart Failure with Reduced Ejection Fraction as a part of the SGLT2 inhibitor mechanism includes diuresis, which leads to a preload reduction. At present, canagliflozin, dapagliflozin, and empagliflozin are the three SGLT2 inhibitors approved for the treatment of T2DM by the US Food and Drug Administration and European Medicines Agency.^[91-94]

A systematic review and meta-analysis of RCTs pertaining to SGLT2 inhibitors revealed that dapagliflozin (odds ratio [OR] 0.73; 95% CI, 0.46–1.16) and canagliflozin (OR 0.95; 95% CI, 0.71–1.26) or the two agents pooled together (OR 0.89; 95% CI, 0.70–1.14) did not show significant effect on CV events. Similarly, no variance in all-cause mortality was seen between the SGLT2 inhibitors and control (OR 0.90; 95% CI, 0.72–1.13).^[95]

A recent meta-analysis compared dapagliflozin (2.5–10 mg) with control in T2DM patients. Dapagliflozin reported CV

beneficial effect for both overall population (HR 0.77; 95% CI, 0.54, 1.10 for MACE) and in patients with a history of CVD (HR 0.80; 0.53, 1.22). In addition, hHF with dapagliflozin was lower compared to control (event rate/100 patient years 0.15 vs. 0.41, HR 0.361; 95% CI, 0.156–0.838).^[96] The CV effects of dapagliflozin are being tested in the ongoing DECLARE-TIMI58 study.^[97]

The EMPA-REG outcome trial evaluated empagliflozin (10 or 25 mg OD) in high-risk CVD patients for a median duration of 3.1 years [Table 8]. Empagliflozin compared to placebo group reported 38% and 35% RRR for CV death (3.7 vs. 5.9%, HR 0.62; 95% CI, 0.49–0.77, $P < 0.001$) and hHF (2.7 vs. 4.1%, HR 0.65; 95% CI, 0.50–0.85, $P = 0.002$), respectively. In addition, empagliflozin was also associated with 32% RRR of death from all causes than placebo.^[98] Recent reports from the trial show that empagliflozin reduced hHF and CV death in all patients irrespective of history of heart failure.^[99] This response could be due to inhibition of renal sodium and glucose reabsorption.

Canagliflozin proved its safety and efficacy in a wide range of patients with T2DM,^[100,101] but CV effects still remain uncertain. At present, according to the interim analysis of the CANagliflozin cardioVascular Assessment Study (CANVAS) study, canagliflozin may not increase the overall CV risk.^[102] The ongoing CANDLE trial in patients with T2DM and CHF (NYHA I–III class) evaluates the clinical safety and efficacy of canagliflozin.^[103] In addition, the Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy,^[104] CANVAS,^[105] effects of Canagliflozin on Renal Endpoints (CANVAS-R)^[106] and Cardiovascular Outcomes Trial^[107] are presently ongoing.

Current place in guidelines/recommendations

Canadian guidelines recommend adding an SGLT2 inhibitor to the antihyperglycemic therapy in patients with uncontrolled hyperglycemia and a history of CVD.^[108]

Prescribing information

The prescribing information of SGLT2 inhibitors does not comment on use in patients with CHF.

Injectable antidiabetic agents

Glucagon-like peptide-1 receptor agonists

GLP1 RAs should be used with caution while managing patients with New York Heart Association Class I–II heart failure. No evidence is available with New York Heart Association Class III–IV.

Published scientific evidence

GLP1 RAs seems to have positive effects on the CV system.^[109-112] A meta-analysis of RCTs, which assessed MACE, mortality, and CV risk factors, found that of GLP1 RAs were associated with a substantial drop in the incidence of MACEs, compared with placebo and pioglitazone, and a similar effect as active comparators (SU, insulin, and DPP-4 inhibitors).^[113] In addition, a large meta-analysis of 32 trials observed a greater reduction in systolic blood pressure (SBP)

by GLP1 RAs in comparison to other active antiglycemic comparators.^[114] A large cohort study reported that the rate of hHF did not increase with the use of incretin-based drugs (GLP1 RAs) as compared with oral antidiabetic drug combinations among patients with a history of heart failure (HR, 0.86; 95% CI, 0.62–1.19) or among those without a history of heart failure (HR, 0.82; 95% CI, 0.67–1.00).^[115] A retrospective study of patients undergoing treatment for T2DM witnessed that exenatide showed a lower risk of CV events and hospitalizations (CVD-related and all-cause) than treatment with other glucose-lowering treatments, including metformin, AGIs, thiazolidinediones, SU, DPP-4 inhibitors, and insulin [Table 9].^[116]

The LEADER trial investigated effect of liraglutide (1.2 and 1.8 mg) in patients with T2DM and CV risk. It demonstrated a statistically significant reduction in CV risk (CV death, nonfatal myocardial infarction, or nonfatal stroke).^[117] A study evaluating dulaglutide in patients with T2DM on three or fewer medications for hypertension demonstrated that dulaglutide 1.5 mg resulted in significantly lower SBP (95% CI, -2.8 mmHg [-4.6, -1.0]; $P \leq 0.001$) compared to placebo.^[118] The 0.75-mg dose was shown to be noninferior to placebo.^[118] In addition, the Researching Cardiovascular Events With a Weekly Incretin in Diabetes study is presently ongoing [Table 9].^[119]

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) study was conducted to establish the CV safety of lixisenatide.^[120] The findings of ELIXA study showed no increased risk for the primary composite endpoint, lixisenatide versus placebo: 13.4% versus 13.2% (HR, 1.02; 95% CI, 0.89–1.17).^[120] There was no significant difference in the rate of hHF lixisenatide versus placebo: 4.0% versus 4.2% (HR, 0.96; 95% CI, 0.75–1.23) and rate of death (HR, 0.94; 95% CI, 0.78–1.13) between the groups [Table 10].^[120]

Exenatide Study of Cardiovascular Event Lowering trial^[121] and effects of Liraglutide in Young Adults with Type 2 Diabetes^[122] are the ongoing trials assessing the CV safety of exenatide and liraglutide, respectively.

Current place in guidelines/recommendations

There are no guidelines specific to use of GLP1 RAs in patients with heart failure.

Prescribing information

The prescribing information of GLP1 RAs did not comment on use in patients with heart failure.

Dose modification with insulins

Insulin dose should be titrated to requirements to reduce the risk of hypoglycemia.

Insulin analogs may be preferred agents in patients at risk for hypoglycemia.

Published scientific evidence

Insulin is known to contribute to arterial dilatation in skeletal muscle and is thus expected to be an attractive agent in achieving ideal glycemic control in CV patients.^[123] Insulin is a selective skeletal muscle vasodilator that leads to increased muscle perfusion primarily through redistribution of regional blood flow.^[124–126] Several studies have demonstrated the CV safety of insulins. The Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) and DIGAMI 2 studies in patients with diabetes mellitus and acute myocardial infarction showed no increase in rates of heart failure in insulin-treated groups. The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial did not find adverse effects with insulin glargine treatment in patients with T2DM and heart failure, with CV risk factors.^[127] The long-term (>6 years) follow-up of the ORIGIN study documented neutral effects of insulin glargine on CV outcomes.^[128] Further, the data analyses of a recent

Table 8: Published literature and prescribing information on use of SGLT-2 inhibitors in patients with diabetes and heart failure

Agent	Published Literature	Prescribing Information NYHA grade			
		I	II	III	IV
Dapagliflozin	May have beneficial effects	Limited Data	Limited Data	No Data	No data
Canagliflozin	CVOT underway	Not available	Not available	Not available	Not available
Empagliflozin	CVOT data from EMPA-REG available. Beneficial effects	Limited Data	Limited Data	No Data	No data

Table 9: Published literature and prescribing information on use of GLP-1 analogues in diabetic patients with heart failure

Agent	Published Literature	Prescribing Information NYHA grade			
		I	II	III	IV
Liraglutide	Limited data	Limited Data	Limited Data	No Data	No data
Exenatide	Limited Data	Not available	Not available	Not available	Not available
Dulaglutide	Limited data	Not available	Not available	Not available	Not available

study ACCORD showed no association of insulin with the CV mortality.^[129] Recently, an RCT in patients with T2DM and diastolic dysfunction found that the insulin analogs (insulin detemir, insulin aspart, and NPH-insulin) treatment was associated with improved diastolic cardiac function, compared to human insulin.^[130] An ongoing trial comparing CV safety of insulin Degludec Versus insulin glargine in subjects with Type 2 Diabetes at high risk of cardiovascular Events (DEVOTE) will give further insights on use of insulin analogs in patients who are at high risk of CV events [Table 11].^[131]

Current place in guidelines/recommendations

Indian National Consensus Group recommends use with caution and a swift clinical action is recommended if any deterioration in cardiac symptoms occur.^[21]

Prescribing information

Prescribing information of insulin glargine, insulin glulisine, insulin aspart 30/70, insulin degludec, and IDegAsp recommends dosage reduction or discontinuation of thiazolidinediones during concomitant use of insulins should be considered if signs and symptoms of heart failure occur [Table 11].^[132-136]

CONCLUSION

Patients with T2DM are prone to develop CV comorbidities. Patients with diabetes and heart failure pose a challenge while managing glycemic control. Most of the agents discussed in the present consensus statement do lack CV safety data. Metformin is relatively safe in treating patients with T2DM and heart failure. SUs such as glipizide, glimepiride, glibenclamide and glyburide share a similar kind of low CV safety profile.

Table 10: Evidence from cardiovascular outcome studies of GLP-1 analogues

Outcome	ELIXA
Primary end point	Neutral
All-cause mortality	NA
CV Death	Neutral
Hospitalization due to HF	Neutral
Stroke	Neutral
Unstable angina	Neutral

Table 11: Published literature and prescribing information on use of insulins in patients with diabetes and heart failure

Insulin	Published Literature	Prescribing Information
Glargine	Dilates arteries in skeletal muscle	Heart failure with concomitant use of thiazolidinediones
Detemir	Attractive option in HF	
Neutral Protamine Hagedorn (NPH)	Areas of concern could be weight gain and sodium retention	
Regular		
Aspart		
Lispro		
Glulisine		
Biphasic Insulin Aspart		
Insulin Degludec + Insulin Aspart		

Gliclazide has been found to be a safe drug among SU. Thiazolidinediones have been found to be associated with fluid retention. The CV safety profile of AGIs is also not clear due to lack of evidence. Among DPP-4 inhibitors, sitagliptin, saxagliptin and alogliptin have been evaluated for CV safety. Saxagliptin has been associated with a higher rate of hHF. Currently, CV safety of GLP1 RAs has been examined in several clinical studies; some of them are showing impressive CV safety. Recent evidence with SGLT2 inhibitors provides reassuring signals. The safety data with insulins in patients with T2DM and heart failure are evolving. Some studies have shown good CV effects with insulin analogs. Considering all this evidence, existing guidelines from various professional bodies, and personal experiences in clinics, we have formulated the present consensus statement.

This consensus has been developed with due considerations to the Indian population. The consensus was aimed at providing simple and practical recommendations on the use of antidiabetic agents in patients with T2DM and heart failure. However, the present consensus statement suffers from lack of published and robust evidence from studies among local people. This may appear surprising given the huge burden of T2DM in India. We are aware that clinical and epidemiological research in India is resource-intensive in terms of economic expenses and other resources. It is promising that some organizations have started to invest in such epidemiological studies.^[137] We believe that present consensus recommendations on antidiabetic drugs for patients with T2DM and heart failure will be a beneficial tool for physicians and their effect will be corroborated through observational studies in daily clinical practice.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: The Framingham study. *Am J Cardiol* 1974;34:29-34.
2. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: An update. *Diabetes Care* 2004;27:1879-84.

3. Dei Cas A, Fonarow GC, Gheorghiadu M, Butler J. Concomitant diabetes mellitus and heart failure. *Curr Probl Cardiol* 2015;40:7-43.
4. Shimabukuro M, Higa N, Oshiro Y, Asahi T, Takasu N. Diagnostic utility of brain-natriuretic peptide for left ventricular diastolic dysfunction in asymptomatic type 2 diabetic patients. *Diabetes Obes Metab* 2007;9:323-9.
5. Albertini JP, Cohen R, Valensi P, Sachs RN, Charniot JC. B-type natriuretic peptide, a marker of asymptomatic left ventricular dysfunction in type 2 diabetic patients. *Diabetes Metab* 2008;34(4 Pt 1):355-62.
6. Valle R, Bagolin E, Canali C, Giovinazzo P, Barro S, Aspromonte N, *et al.* The BNP assay does not identify mild left ventricular diastolic dysfunction in asymptomatic diabetic patients. *Eur J Echocardiogr* 2006;7:40-4.
7. From AM, Leibson CL, Bursi F, Redfield MM, Weston SA, Jacobsen SJ, *et al.* Diabetes in heart failure: Prevalence and impact on outcome in the population. *Am J Med* 2006;119:591-9.
8. Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S, *et al.* Glycemic control and heart failure among adult patients with diabetes. *Circulation* 2001;103:2668-73.
9. Ingelsson E, Sundström J, Arnlöv J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. *JAMA* 2005;294:334-41.
10. Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff DC Jr. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care* 2004;27:699-703.
11. Nichols GA, Koro CE, Gullion CM, Ephross SA, Brown JB. The incidence of congestive heart failure associated with antidiabetic therapies. *Diabetes Metab Res Rev* 2005;21:51-7.
12. Jarrett RJ, Viberti GC, Argyropoulos A, Hill RD, Mahmud U, Murrells TJ. Microalbuminuria predicts mortality in non-insulin-dependent diabetics. *Diabet Med* 1984;1:17-9.
13. Agewall S, Wikstrand J, Ljungman S, Fagerberg B. Usefulness of microalbuminuria in predicting cardiovascular mortality in treated hypertensive men with and without diabetes mellitus. Risk Factor Intervention Study Group. *Am J Cardiol* 1997;80:164-9.
14. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. A systematic overview of the literature. *Arch Intern Med* 1997;157:1413-8.
15. Aguilar D, Solomon SD, Køber L, Rouleau JL, Skali H, McMurray JJ, *et al.* Newly diagnosed and previously known diabetes mellitus and 1-year outcomes of acute myocardial infarction: The VALsartan In Acute myocardial infarction (VALIANT) trial. *Circulation* 2004;110:1572-8.
16. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, *et al.* Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: An analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J* 2008;29:1377-85.
17. Mosterd A, Cost B, Hoes AW, de Bruijne MC, Deckers JW, Hofman A, *et al.* The prognosis of heart failure in the general population: The Rotterdam Study. *Eur Heart J* 2001;22:1318-27.
18. Vaur L, Gueret P, Lievre M, Chabaud S, Passa P; DIABHYCAR Study Group (type DIABetes, Hypertension, *et al.* Development of congestive heart failure in type 2 diabetic patients with microalbuminuria or proteinuria: Observations from the DIABHYCAR (type 2 DIABetes, Hypertension, Cardiovascular Events and Ramipril) study. *Diabetes Care* 2003;26:855-60.
19. Raphael C, Briscoe C, Davies J, Ian Whinnett Z, Manisty C, Sutton R, *et al.* Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. *Heart* 2007;93:476-82.
20. Desai AS, Swedberg K, McMurray JJ, Granger CB, Yusuf S, Young JB, *et al.* Incidence and predictors of hyperkalemia in patients with heart failure: An analysis of the CHARM Program. *J Am Coll Cardiol* 2007;50:1959-66.
21. Das AK, Sahay BK, Seshiah V, Mohan V, Muruganathan A, Kumar A, *et al.* Indian National Consensus Group: National Guidelines on Initiation and Intensification of Insulin Therapy with Premixed Insulin Analogues. Ch. 51. API India, Medicine Update; 2013. p. 227-36. Available from: http://www.apiindia.org/medicine_update_2013/chap51.pdf. [Last accessed on 2016 Jun 28].
22. International Diabetes Federation (IDF). Clinical Guidelines Task Force. Global Guideline for Type 2 Diabetes. 2012. International Diabetes Federation; 2012.
23. Shah S, Sharma SK, Singh P, Muruganathan A, Das AK; Diabetes Consensus Group. Consensus evidence-based guidelines for insulin initiation, optimization and continuation in type 2 diabetes mellitus. *J Assoc Physicians India* 2014;62 7 Suppl: 49-54.
24. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, *et al.* Management of hyperglycemia in type 2 diabetes, 2015: A patient-centered approach: Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015;38:140-9.
25. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, *et al.* Consensus statement by the american association of clinical endocrinologists and american college of endocrinology on the comprehensive type 2 diabetes management algorithm-2016 executive summary. *Endocr Pract* 2016;22:84-113.
26. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:837-53.
27. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care* 2000;23 Suppl 2:B21-9.
28. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, *et al.* Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. *BMJ* 2000;321:405-12.
29. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577-89.
30. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, *et al.* Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560-72.
31. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, *et al.* Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360:129-39.
32. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr., Bigger JT, *et al.* Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545-59.
33. Kelly TN, Bazzano LA, Fonseca VA, Thethi TK, Reynolds K, He J. Systematic review: Glucose control and cardiovascular disease in type 2 diabetes. *Ann Intern Med* 2009;151:394-403.
34. Control Group, Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, *et al.* Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2000;52:2288-98.
35. Eshaghian S, Horwich TB, Fonarow GC. An unexpected inverse relationship between HbA1c levels and mortality in patients with diabetes and advanced systolic heart failure. *Am Heart J* 2006;151:91.
36. Aguilar D, Bozkurt B, Ramasubbu K, Deswal A. Relationship of hemoglobin A1C and mortality in heart failure patients with diabetes. *J Am Coll Cardiol* 2009;54:422-8.
37. Elder DH, Singh JS, Levin D, Donnelly LA, Choy AM, George J, *et al.* Mean HbA1c and mortality in diabetic individuals with heart failure: A population cohort study. *Eur J Heart Fail* 2016;18:94-102.
38. Wang P, Huang R, Lu S, Xia W, Sun H, Sun J, *et al.* HbA1c below 7% as the goal of glucose control fails to maximize the cardiovascular benefits: A meta-analysis. *Cardiovasc Diabetol* 2015;14:124.
39. Montori VM, Fernández-Balsells M. Glycemic control in type 2 diabetes: Time for an evidence-based about-face? *Ann Intern Med* 2009;150:803-8.
40. American Diabetes Association (ADA). Standards of medical care in diabetes-2016. *Diabetes Care* 2016;39 Suppl 1:S1-106.
41. Misbin RI, Green L, Stadel BV, Gueriguian JL, Gubbi A, Fleming GA. Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med* 1998;338:265-6.
42. Inzucchi SE, Masoudi FA, McGuire DK. Metformin in heart failure. *Diabetes Care* 2007;30:e129.
43. Eurich DT, Weir DL, Majumdar SR, Tsuyuki RT, Johnson JA,

- Tjosvold L, *et al.* Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: Systematic review of observational studies involving 34,000 patients. *Circ Heart Fail* 2013;6:395-402.
44. Romero SP, Andrey JL, Garcia-Egido A, Escobar MA, Perez V, Corzo R, *et al.* Metformin therapy and prognosis of patients with heart failure and new-onset diabetes mellitus. A propensity-matched study in the community. *Int J Cardiol* 2013;166:404-12.
 45. Evans JM, Doney AS, AlZadjali MA, Ogston SA, Petrie JR, Morris AD, *et al.* Effect of Metformin on mortality in patients with heart failure and type 2 diabetes mellitus. *Am J Cardiol* 2010;106:1006-10.
 46. Ekeruo IA, Solhpour A, Taegtmeier H. Metformin in diabetic patients with heart failure: Safe and effective? *Curr Cardiovasc Risk Rep* 2013;7:417-22.
 47. Smith AJ, Hill JD. Use of metformin in patients with diabetes and HF. *Cardiol Today* 2013. Available from: <http://www.healio.com/cardiology/diabetes/news/print/cardiology-today/%7B35b140d2-5a1f-4cbc-a6fb-b4f1114df4b4%7D/use-of-metformin-in-patients-with-diabetes-and-hf>. [Last accessed on 2017 Mar 06].
 48. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, *et al.* ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;33:1787-847.
 49. Gunton JE, Cheung NW, Davis TM, Zoungas S, Colagiuri S; Australian Diabetes Society. A new blood glucose management algorithm for type 2 diabetes: A position statement of the Australian Diabetes Society. *Med J Aust* 2014;201:650-3.
 50. Indian Council of Medical Research (ICMR). Guidelines for Management of Type 2 Diabetes. New Delhi, India: Indian Council of Medical Research; 2005. Available from: http://icmr.nic.in/guidelines_diabetes/guide_diabetes.htm. [Last accessed on 2016 Jul 06].
 51. Breuer TG, Meier JJ. Inpatient treatment of type 2 diabetes. *Dtsch Arztebl Int* 2012;109:466-74.
 52. Glucophage (Metformin hydrochloride) Tablet, Prescribing Information. Princeton, N.J.: Bristol-Myers Squibb; August, 2008. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020357s031,021202s0161bl.pdf. [Last accessed on 2016 Jul 06].
 53. International Diabetes Federation (IDF). Managing Older People with Type 2 Diabetes. IDF Diabetes Atlas. 6th ed. Brussels, Belgium: International Diabetes Federation; 2013. Available from: http://www.mtd.de/cms/images/exklusiv/14_januar/14_01-06_diabetesatlas%20s001-017.pdf. [Last accessed on 2016 Jun 28].
 54. Eurich DT, Majumdar SR, McAlister FA, Tsuyuki RT, Johnson JA. Improved clinical outcomes associated with metformin in patients with diabetes and heart failure. *Diabetes Care* 2005;28:2345-51.
 55. Varas-Lorenzo C, Margulis AV, Pladevall M, Riera-Guardia N, Calingaert B, Hazell L, *et al.* The risk of heart failure associated with the use of noninsulin blood glucose-lowering drugs: Systematic review and meta-analysis of published observational studies. *BMC Cardiovasc Disord* 2014;14:129.
 56. Andersson C, Gislason GH, Jørgensen CH, Hansen PR, Vaag A, Sørensen R, *et al.* Comparable long-term mortality risk associated with individual sulfonylureas in diabetes patients with heart failure. *Diabetes Res Clin Pract* 2011;94:119-25.
 57. McAlister FA, Eurich DT, Majumdar SR, Johnson JA. The risk of heart failure in patients with type 2 diabetes treated with oral agent monotherapy. *Eur J Heart Fail* 2008;10:703-8.
 58. Beckman JA, Creager MA. Vascular complications of diabetes. *Circ Res* 2016;118:1771-85.
 59. Zeller M, Danchin N, Simon D, Vahanian A, Lorgis L, Cottin Y, *et al.* Impact of type of preadmission sulfonylureas on mortality and cardiovascular outcomes in diabetic patients with acute myocardial infarction. *J Clin Endocrinol Metab* 2010;95:4993-5002.
 60. Schramm TK, Gislason GH, Vaag A, Rasmussen JN, Folke F, Hansen ML, *et al.* Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: A nationwide study. *Eur Heart J* 2011;32:1900-8.
 61. Hong J, Zhang Y, Lai S, Lv A, Su Q, Dong Y, *et al.* Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. *Diabetes Care* 2013;36:1304-11.
 62. Glucotrol (Glipizide) Tablet, Prescribing Information. New York: Pfizer Inc.; October, 2013. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/017783s0251bl.pdf. [Last accessed on 2016 Jul 06].
 63. Amaryl (Glimepiride) Tablet, Prescribing Information. Bridgewater, NJ: Sanofi; October, 2013. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020496s0271bl.pdf. [Last accessed on 2016 Jul 06].
 64. DiaBeta (Glyburide) Tablet, Prescribing Information. Bridgewater, NJ: Sanofi; October, 2013. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/017532Orig1s0341bl.pdf. [Last accessed on 2016 Jul 06].
 65. Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, *et al.* Thiazolidinedione use, fluid retention, and congestive heart failure: A consensus statement from the American Heart Association and American Diabetes Association. October 7, 2003. *Circulation* 2003;108:2941-8.
 66. Semenkovich CF. TZDs and diabetes: Testing the waters. *Nat Med* 2005;11:822-4.
 67. Jearath V, Vashisht R, Rustagi V, Raina S, Sharma R. Pioglitazone-induced congestive heart failure and pulmonary edema in a patient with preserved ejection fraction. *J Pharmacol Pharmacother* 2016;7:41-3.
 68. Erdmann E, Charbonnel B, Wilcox RG, Skene AM, Massi-Benedetti M, Yates J, *et al.* Pioglitazone use and heart failure in patients with type 2 diabetes and preexisting cardiovascular disease: Data from the PROactive study (PROactive 08). *Diabetes Care* 2007;30:2773-8.
 69. Giles TD, Elkayam U, Bhattacharya M, Perez A, Miller AB. Comparison of pioglitazone vs glyburide in early heart failure: Insights from a randomized controlled study of patients with type 2 diabetes and mild cardiac disease. *Congest Heart Fail* 2010;16:111-7.
 70. Giles TD, Miller AB, Elkayam U, Bhattacharya M, Perez A. Pioglitazone and heart failure: Results from a controlled study in patients with type 2 diabetes mellitus and systolic dysfunction. *J Card Fail* 2008;14:445-52.
 71. Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, *et al.* ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2013;34:3035-87.
 72. ACTOS (Pioglitazone hydrochloride) Tablet, Prescribing Information. Deerfield, IL: Takeda Pharmaceuticals; July, 2011. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021073s043s0441bl.pdf. [Last accessed on 2016 Jul 06].
 73. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: The STOP-NIDDM randomised trial. *Lancet* 2002;359:2072-7.
 74. Azimova K, San Juan Z, Mukherjee D. Cardiovascular safety profile of currently available diabetic drugs. *Ochsner J* 2014;14:616-32.
 75. Hanefeld M, Cagatay M, Petrowitsch T, Neuser D, Petzinna D, Rupp M. Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: Meta-analysis of seven long-term studies. *Eur Heart J* 2004;25:10-6.
 76. Zhang W, Kim D, Philip E, Miyan Z, Barykina I, Schmidt B, *et al.* A multinational, observational study to investigate the efficacy, safety and tolerability of acarbose as add-on or monotherapy in a range of patients: The Gluco VIP study. *Clin Drug Investig* 2013;33:263-74.
 77. Chang CH, Chang YC, Lin JW, Chen ST, Chuang LM, Lai MS. Cardiovascular risk associated with acarbose versus metformin as the first-line treatment in patients with type 2 diabetes: A nationwide cohort study. *J Clin Endocrinol Metab* 2015;100:1121-9.
 78. Acarbose Cardiovascular Evaluation Trial (ACE). Available from: <https://www.clinicaltrials.gov/ct2/show/NCT00829660>. [Last accessed on 2016 Jun 28].

79. Gallwitz B. Safety and efficacy of linagliptin in type 2 diabetes patients with common renal and cardiovascular risk factors. *Ther Adv Endocrinol Metab* 2013;4:95-105.
80. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, *et al.* Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015;373:232-42.
81. McGuire DK, Van de Werf F, Armstrong PW, Standl E, Koglin J, Green JB, *et al.* Association between sitagliptin use and heart failure hospitalization and related outcomes in type 2 diabetes mellitus: Secondary analysis of a randomized clinical trial. *JAMA Cardiol* 2016;1:126-35.
82. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, *et al.* Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369:1327-35.
83. Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, *et al.* Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: A multicentre, randomised, double-blind trial. *Lancet* 2015;385:2067-76.
84. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, *et al.* Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;369:1317-26.
85. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, *et al.* Heart failure, saxagliptin, and diabetes mellitus: Observations from the SAVOR-TIMI 53 randomized trial. *Circulation* 2014;130:1579-88.
86. O'Riordan M. Vildagliptin in HF patients with diabetes meets echo end point, but questions remain. 2013; Lisbon, Portugal. *Sophia Antipolis: European Society of Cardiology*; 2013. p. 99.
87. Rosenstock J, Marx N, Neubacher D, Seck T, Patel S, Woerle HJ, *et al.* Cardiovascular safety of linagliptin in type 2 diabetes: A comprehensive patient-level pooled analysis of prospectively adjudicated cardiovascular events. *Cardiovasc Diabetol* 2015;14:57.
88. Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus (CARMELINA). Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01897532>. [Last accessed on 2016 Jun 28].
89. Onglyza (Saxagliptin) Tablet, Prescribing Information. Princeton, NJ: Bristol-Myers Squibb; July, 2009. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/0223501bl.pdf. [Last accessed on 2016 Jul 06].
90. Galvus (Vildagliptin) Tablet, Summary of Product Characteristics. Camberley, GU: Novartis; July, 2012. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000771/WC500020327.pdf. [Last accessed on 2016 Jul 06].
91. FDA-Approved drug Products with Therapeutic Equivalence Evaluations. Available from: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf>. [Last accessed on 2016 Jul 06].
92. Invokana (Canagliflozin) Tablet, Summary of Product Characteristics. Latina, Italy: Janssen-Cilag SpA; November, 2013. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002649/WC500156456.pdf. [Last accessed on 2016 Jul 06].
93. Forxiga (Dapagliflozin) Tablet, Summary of Product Characteristics. Wedel, Germany: AstraZeneca; December, 2012. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002322/WC500136026.pdf. [Last accessed on 2016 Jul 06].
94. Jardiance (Empagliflozin) Tablet, Summary of Product Characteristics. Ingelheim am Rhein, Germany: Boehringer Ingelheim Pharma. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002677/WC500168592.pdf. [Last accessed on 2016 Jul 06].
95. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, *et al.* Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: A systematic review and meta-analysis. *Ann Intern Med* 2013;159:262-74.
96. Sonesson C, Johansson PA, Johnsson E, Gause-Nilsson I. Cardiovascular effects of dapagliflozin in patients with type 2 diabetes and different risk categories: A meta-analysis. *Cardiovasc Diabetol* 2016;15:37.
97. Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58). Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01730534>. [Last accessed on 2016 Jun 28].
98. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, *et al.* Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117-28.
99. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, *et al.* Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: Results of the EMPA-REG OUTCOME® trial. *Eur Heart J* 2016;37:1526-34.
100. Qiu R, Capuano G, Gary M. Efficacy and safety of twice-daily treatment with canagliflozin, a sodium glucose co-transporter 2 inhibitor, added on to metformin monotherapy in patients with type 2 diabetes mellitus. *J Clin Transl Endocrinol* 2014;1:54-60.
101. Rosenthal N, Meininger G, Ways K, Polidori D, Desai M, Qiu R, *et al.* Canagliflozin: A sodium glucose co-transporter 2 inhibitor for the treatment of type 2 diabetes mellitus. *Ann N Y Acad Sci* 2015;1358:28-43.
102. Committee for Medicinal Products for Human Use. European public assessment report (EPAR) canagliflozin. *Eur Med Agency* 2013. [EMA/374133/2013].
103. Tanaka A, Inoue T, Kitakaze M, Oyama J, Sata M, Taguchi I, *et al.* Rationale and design of a randomized trial to test the safety and non-inferiority of canagliflozin in patients with diabetes with chronic heart failure: The CANDLE trial. *Cardiovasc Diabetol* 2016;15:57.
104. Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy (CREDENCE). Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02065791>. [Last accessed on 2016 Jun 28].
105. CANVAS – CANagliflozin cardioVascular Assessment Study (CANVAS). Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01032629>. [Last accessed on 2016 Jun 28].
106. A Study of the Effects of Canagliflozin (JNJ-28431754) on Renal Endpoints in Adult Participants with Type 2 Diabetes Mellitus (CANVAS-R). Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01989754>. [Last accessed on 2016 Jun 28].
107. Schnell O, Standl E, Catrinou D, Genovese S, Lalic N, Skra J, *et al.* Report from the 1st Cardiovascular Outcome Trial (CVOT) summit of the Diabetes and Cardiovascular Disease (D&CVD) EASD study group. *Cardiovasc Diabetol* 2016;15:33.
108. Canadian Diabetes Association (CDA). Pharmacologic management of type 2 diabetes: 2016 interim update. *Can J Diabetes* 2016;40:193-5.
109. Seufert J, Gallwitz B. The extra-pancreatic effects of GLP-1 receptor agonists: A focus on the cardiovascular, gastrointestinal and central nervous systems. *Diabetes Obes Metab* 2014;16:673-88.
110. Herzlinger S, Horton ES. Extraglycemic effects of glp-1-based therapeutics: Addressing metabolic and cardiovascular risks associated with type 2 diabetes. *Diabetes Res Clin Pract* 2013;100:1-10.
111. Burgmaier M, Heinrich C, Marx N. Cardiovascular effects of GLP-1 and GLP-1-based therapies: Implications for the cardiovascular continuum in diabetes? *Diabet Med* 2013;30:289-99.
112. van Genugten RE, Möller-Goede DL, van Raalte DH, Diamant M. Extra-pancreatic effects of incretin-based therapies: Potential benefit for cardiovascular-risk management in type 2 diabetes. *Diabetes Obes Metab* 2013;15:593-606.
113. Monami M, Dicembrini I, Nardini C, Fiordelli I, Mannucci E. Effects of glucagon-like peptide-1 receptor agonists on cardiovascular risk: A meta-analysis of randomized clinical trials. *Diabetes Obes Metab* 2014;16:38-47.
114. Katout M, Zhu H, Rutsky J, Shah P, Brook RD, Zhong J, *et al.* Effect of GLP-1 mimetics on blood pressure and relationship to weight loss and glycemia lowering: Results of a systematic meta-analysis and meta-regression. *Am J Hypertens* 2014;27:130-9.
115. Filion KB, Azoulay L, Platt RW, Dahl M, Dormuth CR, Clemens KK, *et al.* A multicenter observational study of incretin-based drugs and heart failure. *N Engl J Med* 2016;374:1145-54.
116. Best JH, Hoogwerf BJ, Herman WH, Pelletier EM, Smith DB, Wenten M, *et al.* Risk of cardiovascular disease events in patients with type 2 diabetes prescribed the glucagon-like peptide 1 (GLP-1) receptor

- agonist exenatide twice daily or other glucose-lowering therapies: A retrospective analysis of the LifeLink database. *Diabetes Care* 2011;34:90-5.
117. Novonordisk Press Release: Victoza Significantly Reduces the Risk of Major Adverse Cardiovascular Events in the LEADER Trial. Available from: <https://www.novonordisk.com/bin/getPDF.1991879.pdf>. [Last accessed on 2016 Mar 04].
 118. Ferdinand KC, White WB, Calhoun DA, Lonn EM, Sager PT, Brunelle R, *et al.* Effects of the once-weekly glucagon-like peptide-1 receptor agonist dulaglutide on ambulatory blood pressure and heart rate in patients with type 2 diabetes mellitus. *Hypertension* 2014;64:731-7.
 119. Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND). Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01394952>. [Last accessed on 2016 Jun 28].
 120. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, *et al.* Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015;373:2247-57.
 121. Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL): A Trial to Evaluate Cardiovascular Outcomes after Treatment with Exenatide Once Weekly in Patients with Type 2 Diabetes Mellitus. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01144338>. [Last accessed on 2016 Jun 28].
 122. Effects of Liraglutide in Young Adults with Type 2 Diabetes (LYDIA) (LYDIA). Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02043054>. [Last accessed on 2016 Jun 28].
 123. Chaudhuri A, Kanjwal Y, Mohanty P, Rao S, Sung BH, Wilson MF, *et al.* Insulin-induced vasodilatation of internal carotid artery. *Metabolism* 1999;48:1470-3.
 124. Malmberg K, Rydén L, Efendic S, Herlitz J, Nicol P, Waldenström A, *et al.* Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): Effects on mortality at 1 year. *J Am Coll Cardiol* 1995;26:57-65.
 125. Parsonage WA, Hetmanski D, Cowley AJ. Beneficial haemodynamic effects of insulin in chronic heart failure. *Heart* 2001;85:508-13.
 126. Malmberg K, Rydén L, Wedel H, Birkeland K, Bootsma A, Dickstein K, *et al.* Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): Effects on mortality and morbidity. *Eur Heart J* 2005;26:650-61.
 127. ORIGIN Trial Investigators, Gerstein HC, Bosch J, Dagenais GR, Diaz R, Jung H, *et al.* Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012;367:319-28.
 128. ORIGIN Trial Investigators. Cardiovascular and other outcomes postintervention with insulin glargine and omega-3 fatty acids (ORIGINALE). *Diabetes Care* 2016;39:709-16.
 129. Siraj ES, Rubin DJ, Riddle MC, Miller ME, Hsu FC, Ismail-Beigi F, *et al.* Insulin dose and cardiovascular mortality in the ACCORD Trial. *Diabetes Care* 2015;38:2000-8.
 130. von Bibra H, Siegmund T, Kingreen I, Riemer M, Schuster T, Schumm-Draeger PM. Effects of analogue insulin in multiple daily injection therapy of type 2 diabetes on postprandial glucose control and cardiac function compared to human insulin: A randomized controlled long-term study. *Cardiovasc Diabetol* 2016;15:7.
 131. A Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Subjects with Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE). Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01959529>. [Last accessed on 2016 Jun 28].
 132. LANTUS (Insulin glargine [rDNA origin]) Injection, Prescribing Information. Bridgewater, NJ: Sanofi; June, 2009. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021081s0341bl.pdf. [Last accessed on 2016 Jul 06].
 133. NovoLog (insulin aspart [rDNA origin]) Injection, Prescribing Information. Princeton, NJ: Novo Nordisk; December, 2012. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020986s0821bl.pdf. [Last accessed on 2016 Jul 06].
 134. Ryzodeg 70/30 (Insulin degludec and insulin aspart) Injection, Prescribing Information. Bagsvaerd, Denmark: Novo Nordisk; September, 2015. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/2033131bl.pdf. [Last accessed on 2016 Jul 06].
 135. Tresiba (Insulin degludec) Injection, Prescribing Information. Bagsvaerd, Denmark: Novo Nordisk; September, 2015. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/2033141bl.pdf. [Last accessed on 2016 Jul 06].
 136. Apidra (Insulin glulisine) Injection, Prescribing Information. Bridgewater, NJ: Sanofi; February, 2009. Available from: <http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/pediatricadvisorycommittee/ucm214647.pdf>. [Last accessed on 2016 Jul 06].
 137. Pradeepa R, Anjana RM, Joshi SR, Bhansali A, Deepa M, Joshi PP, *et al.* Prevalence of generalized and abdominal obesity in urban & rural India – the ICMR-INDIAB Study (Phase-I) [ICMR- NDIAB-3]. *Indian J Med Res* 2015;142:139-50.