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REVIEW ARTICLE

Use of Antidiabetic / Hypoglycaemic Agents in Cardiovascular Disease

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Introduction

Cardiovascular (CV) complications are the most important cause of morbidity and mortality in diabetes. Diabetics are three times more prone to CV events, four times for heart failure and two times higher risk for death as compared to non-diabetics. The effect of improved glycaemic control on CV complication has been well established through clinical trials and meta-analyses. However, several studies have suggested that some antidiabetic drugs increase CV risk, despite being effective at lowering blood glucose in type 2 diabetes. When choosing the appropriate treatment strategy for patients with type 2 diabetes with CV risk, not only the glucose-lowering effects but also overall benefits and risks for CV disease should be taken into consideration.

CURRENT PLACE IN GUIDELINES/ RECOMMENDATIONS

American Diabetes Association (ADA) recommends less stringent HbA1c goals (such as <8%) for patients with advanced micro vascular or macro vascular complications. American Association of Clinical Endocrinologists (AACE) / American College of Endocrinology (ACE) 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 hypoglycaemia or adverse consequences from hypoglycaemia, patient motivation, and adherence. Further, an HbA1C ≤6.5% is considered optimal if it can be achieved in a safe and affordable manner without hypoglycaemia, but higher targets may be appropriate for certain individuals and may change for a given individual over time. Similarly, ADA-European Association for the Study of Diabetes (EASD) position statement recommends for personalization of the treatment, while balancing the benefits of glycaemic control with its potential risks, taking into account the adverse effects of glucose-lowering medications (particularly hypoglycaemia), the patient's age and health status, among other concerns.

Properties and Cardiovascular Effects of Noninsulin Glucose-Lowering Drugs for the Treatment of Type 2 Diabetes

Drug Class	CV Effects Clinical	Use in Patients with CVD
Biguanides	Few randomized, but many observational studies available. Reduces risk of MI by 39%, diabetes-relatedendpoint by 32%, diabetes-related death by 42%, mortality by 36% (UKPDS)	First choice in T2DM patients with and without atherosclerotic vascular disease Precautions should be taken in patients with ACS, HF, CKD (stages IV and V) Not indicated in the presence of acidosis or dehydration

Sulphonylureas (SUs)	Safety concerns on the association with sulphonylureas Several observational studies available Reduction of microvascular complications (UKPDS) Increased CV mortality (UGDP trial) Impairment of is chaemic preconditioning (?)	Combination therapy in T2DM patients with and without CVD (if HbA1c target not achieved after3 months of mono therapy with metformin) Precautions should be taken in patients with multiple comorbidities, ACS, HF and advanced CKD (stages IV and V)
Thiazolidinediones	Reduce risk of MI and stroke (PRO Active and IRIS trials with pioglitazone) Improve diabetic dyslipidaemia Increase HF hospitalization	Combination therapy in T2DM patients with and without CVD and/or CKD (up to stage V, eGFR <15 mL/min/1.73 m2) Precautions should be taken in patients with ACS Contraindicated in patients with or at risk of HF
Glucagon-like peptide-1 receptor agonists	Significant reduction of composite CV endpoints in LEADER and SUSTAIN-6 trials No significant effects on CV mortality, nonfatal MI, and hospitalization for HF with liraglutide and semaglutide Reduced risk of nonfatal stroke with semaglutide	Combination therapy in T2DM patients with and without CVD (including HF and ACS) Limited data in patients with advanced CKD (stages IV and V) Exenatide is eliminated by renal mechanisms and should not be given in patients with severe ESRD Liraglutide is not eliminated by renal or hepatic mechanisms, but it should be used with caution since there are only limited data in patients with renal or hepatic impairment
Dipeptidyl peptidase-4 inhibitors	Well tolerated No reduction of CV endpoints (SAVOR-TIMI 53, EXAMINE, TECOS) Increased risk of HF with saxagliptin and alogliptin (?)	Combination therapy in T2DM patients with and without CVD. Although sitagliptin seems to be safe, the use of alogliptin and saxagliptin in patients with pre-existing HF is still debated Linagliptin can be used in patients with CKD (any stage)
Sodium glucoseco-transporter 2inhibitors	In the EMPA-REG OUTCOME trial, empagliflozin reduced CV death, HF hospitalization and total mortality by 38%, 35% and 32%, respectively No direct effect on the rates of MI or stroke with empagliflozin Reduction of systolic and diastolic BP	Combination therapy in T2DM patients with and without CVD (paucity of data on SGLT2 in primary prevention) Evidence of benefit in patients with HF No evidence of benefit in ACS
Alpha-glucosidase inhibitors	ACE trial reduce the incidence of new-onset diabetes by 18%, although the CVD event rate wasn't reduced in the study, "the reduced incidence of diabetes seen with acarbose in the ACE trial might help to reduce CV risk in the longer term by delaying the onset of diabetes in the high-risk population studied"	No recommendations due to lack of evidence
Repaglinide	No RCTs	No recommendations due to lack of evidence

ACS - acute coronary syndrome; BP - blood pressure; CKD - chronic kidney disease; CVD - cardiovascular disease; eGFR - estimated glomerular filtration rate; EMPA-REG OUTCOME - Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients Removing Excess Glucose; ESRD - end-stage renal disease; EXAMINE - Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; HF - heart failure; IRIS - Insulin Resistance Intervention After Stroke; LEADER - Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MACE - major adverse cardiovascular events; MI - myocardial infarction; PRO Active - Prospective Pioglitazone Clinical Trial in Macrovascular Events; SAVOR-TIMI 53 - Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction; SGLT2 - sodium glucose cotransporter 2; SUSTAIN-6 - Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; T2DM - type 2 diabetes mellitus; TECOS - Trial Evaluating Cardiovascular Outcomes with Sitagliptin; UGDP - University Group Diabetes Program; UKPDS - UK Prospective Diabetes Study; RCTs – Randomised Control Trials.

Antidiabetic / Hypoglycaemic Agents – Suggestion from Published Literature and Recommendations in Heart Failure Patients.		
Agents	**Suggestions from published lectures**	**Recommendations**
Biguanides Metformin	Limited data. Marginal improvement in 1 year mortality compared to SU	ADA recommends use of metformin in stable CHF patients with the absence of renal impairment and restricts its usage in unstable and hospitalized patients European Society of Cardiology (ESC) guidelines recommends metformin in patients with heart failure without other comorbidities such as liver or renal dysfunction The Australian Diabetes Society does not recommend metformin in patients with severe cardiac failure International Diabetes Federation (IDF) does not recommend metformin in elderly patients with *Congestive heart failure* (CHF) Indian Council of Medical Research (ICMR) also does not recommend metformin in patients with CHF
Sulphonylureas Glyburide/ Glibenclamide Glipizide Glimepiride Gliclazide	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 An observational study compared the long-term mortality of SUs in patients with diabetes and CHF, found HR for mortality with glimepiride (HR 1.10), glibenclamide (HR 1.12) and glipizide (HR 1.14). Gliclazide has been suggested as a better SU agent for patients with T2DM and CV risk. The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study found that rigorous glucose control with gliclazide has no significant effect on major macro vascular events. In addition, recent studies have documented lower risk of CV events and mortality with gliclazide.	No specific guidelines are available pertaining to SU
Thazolidiediones Pioglitazone	Fluid retention may aggravate heart failure and lead to increased number of hospitalizations	ADA, ESC and ICMR recommend restricting the usage of thiazolidinediones in CHF patients
α-Glucosidase inhibitors Acarbose Voglibose Miglitol	A meta-analysis demonstrated that acarbose reduced CV events in patients withT2DM. However, an intension-to-treat cohort study reported that acarbose was associated with higher risk of CV events, heart failure and ischemic stroke compared to metformin No any studies on voglibose or miglitol with CV risk	There are no guidelines specific to use of AGIs in patients with heart failure
Dipeptidyl peptidase-4 inhibitors (DPP4i) Sitagliptin Saxagliptin Vildagliptin Linagliptin Gemigliptin Teneligliptin	The Vildagliptin in Ventricular Dysfunction Diabetes trialincluded patients with NYHA Class I to III heart failure. The trial reported more CV deaths in the treatment arm than in the placebo arm. A comprehensive patient-level pooled analysis of 19 double-blinded RCTs of linagliptin versus placebo in patients with T2DM reported all-cause mortality and hospitalization for CHF. The study concluded that linagliptin is not associated with increased CV risk versus active comparators. The Cardiovascular and Renal Microvascular Outcome Study with linagliptin trial is presently ongoing	There are no specific guidelines pertaining to the use of DPP-4 inhibitors in patients with heart failure

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<tr><td></td><td>No dedicated CVOT is currently being conducted for teneligliptin, one TOPLEVEL (Teneligliptin on the Progressive Left Ventricular Diastolic Dysfunction With Type 2 Diabetes Mellitus) study is currently examining the effect of teneligliptin on diastolicechocardiographic parametersas a primary outcome. TOPLEVEL is a 2-year (mean) study and expected to recruit ~936 T2DM patients of age 20 to 85 years with the ejection fraction of >40%, with expected completion in June 2019. From cardiac safety point of view, prolongation of QTc is a unique issue with teneligliptin not observed with any other available DPP-4Is.</td><td></td></tr>
<tr><td>Sodium glucose cotranspoters 2 inhibitors
Dapagliflozin (Da)
Canagliflozin (Ca)
Empagliflozin (Em)</td><td>A recent meta-analysis compared dapagliflozin with control in T2DM patients. Dapagliflozin reported CV beneficial effect for both overall population and in patients with a history of CVD. In addition, hHF with dapagliflozin was lower compared to control. The CV effects of dapagliflozin are being tested in the ongoing DECLARE-TIMI58 study.
The EMPA-REG outcome trial evaluated empagliflozin in high-risk CVD patients for a median duration of 3.1 years. Empagliflozin compared to placebo groupreported 38% and 35% RRR for CV death and hHF, respectively. In addition, empagliflozin was also associated with 32% RRR of death from all causes than placebo. Recent reports from the trial show that empagliflozin reduced hHF and CV death in all patients irrespective of history of heart failure.
Canagliflozin proved its safety and efficacy in a wide range of patients with T2DM but CV effects still remain uncertain. Atpresent, according to the interim analysis of the CAN agliflozincardio Vascular Assessment Study (CANVAS) study, canagliflozin may not increase the overall CV risk. The ongoing CANDLE trial in patients with T2DM and CHF (NYHA I–III class) evaluates the clinical safety and efficacy of canagliflozin</td><td>Canadian guidelines recommend adding an SGLT2 inhibitor to the anti-hyperglycaemic therapy in patients with uncontrolled hyperglycaemia and a history of CVD
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<tr><th colspan="5">Prescribing Information NYHA Grade</th></tr>
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<tr><td>Da</td><td colspan="2">Limited Data</td><td colspan="2">No Data</td></tr>
<tr><td>Ca</td><td colspan="4">Interim Data only</td></tr>
<tr><td>Em</td><td colspan="2">Limited Data</td><td colspan="2">No Data</td></tr>
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<tr><td>Glucagon-like peptide 1 receptor agonist
Exenatide (Exe)
Liraglutide (Lir)
Dulagutide (Dul)
Lixisenatide (Lix)</td><td>The LEADER trial investigated effect of liraglutide in patients with T2DM and CV risk. It demonstrated a statistically significant reduction in CV risk (CV death,nonfatal myocardial infarction or nonfatal stroke).
A study evaluating dulaglutide in patients with T2DM on three or fewer-medications for hypertension-demonstrated that dulaglutide resulted in significantly lower Systolic Blood Pressure. In addition, the Researching Cardiovascular Events With a Weekly Incretin in Diabetes study is presently ongoing
The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) study was conducted to establish the CV safety of lixisenatide. The findings of ELIXA study showed no increased risk for the primary composite endpoint, lixisenatide versus placebo. There was no significant difference in the rate of hHF lixisenatide versus placebo, and rate of death between the groups.</td><td>There are no guidelines specific to use of GLP1 RAs in patients with heart failure.
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<tr><th colspan="5">Prescribing Information NYHA Grade</th></tr>
<tr><td></td><td>I</td><td>II</td><td>III</td><td>IV</td></tr>
<tr><td>Exe</td><td colspan="4">No Data Available</td></tr>
<tr><td>Lir</td><td colspan="2">Limited Data</td><td colspan="2">No Data</td></tr>
<tr><td></td><td colspan="4">No Data Available</td></tr>
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Insulin Insulin Regular (R) NPH Fiasp Aspart (Asp) Lispro (Lis) Glulisine Glargin Detemir Degludec (IDeg) Biphasic R+NPH Biphasic Aspart Biphasic Lispro IDeg+Asp	Insulin is known to contribute to arterial dilatation in skeletal muscle and is thus expected to be an attractive agent in achieving ideal glycaemic control in CV patients. Insulin is a selective skeletal muscle vasodilator that leads to increased muscle perfusion primarily through redistribution of regional blood flow. 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. The Action to Control Cardiovascular Risk in *Diabetes* (ACCORD) showed no association of insulin with the CV mortality	Indian National Consensus Group recommends use with caution and a swift clinical action is recommended if any deterioration in cardiac symptoms occur. Prescribing information of insulin glargine, insulin glulisine, insulin aspart 30/70, insulin degludec and I Deg Asp recommends dosage reduction or discontinuation of thiazolidinediones during concomitant use of insulins should be considered if signs and symptoms of heart failure occur.

CONCLUSION

Diabetics are prone for CV comorbidities, it is a challenge for the clinicians to maintain euglycaemia in diabetics and even become more difficult with heart failure. Most of the agents discussed in the present article do lack CV safety data. This article was aimed at providing simple and practical recommendations on the use of anti diabetic agents in patients with T2DM and CV disease. However, this article is also is lacking of published and robust evidence from studies among local people. I believe that this article will be a beneficial tool for physicians in daily practice.

Agent	NYHA I	NYHA II	NYHA III	NYHA IV
Metformin				
Glibenclamide				
Glipizide				
Glimepiride				
Gliclazide				
Pioglitazone				
Acarbose				
Voglibose				
Miglitol				
Sitagliptin				
Saxagliptin				
Vildagliptin				
Linagliptin				
Gemigliptin				
Teneligliptin				
Dapagliflozin				
Canagliflozin				
Empagliflozin				
Exenatide				
Liraglutide				

Dulaglutide				
Lixisenatide				
Insulin regular				
NPH				
Fiasp				
Aspart				
Lispro				
Glulisine				
Glargin				
Detemir				
Degludec				
Biphasic R+NPH				
Biphagic Aspart				
Biphasic Lispro				
IDeg+Asp				
	Use Safely	Use with Caution	Don't Use	