ISSN 0973-3930

Volume 41 | Supplement 1 | January–March 2021

International Journal of Diabetes in Developing Countries

Official Publication of
Research Society for the Study of Diabetes in India

Diabetes Mellitus and Heart Failure: Consensus Statement by the Research Society for the Study of Diabetes in India

Springer

Abbott

For the use of a registered medical practitioner or hospital or laboratories only.

LIFE CHANGING SOLUTIONS FOR HEALTHIER LIVES

Gledepa®

Dapagliflozin Tablets 5mg/10mg

Gledepa | MET™ XR

Dapagliflozin 10mg + Metformin 500/1000mg Extended Release

Gledepa | MET™

Dapagliflozin 5mg + Metformin 1000mg Immediate Release

Abbott Healthcare Pvt. Ltd.
Floor 17, Godrej BKC, Plot No. - 68, BKC,
Near MCA Club, Bandra (E), Mumbai - 400051.

Image for representation purpose only

International Journal of Diabetes in Developing Countries
Incorporating Diabetes Bulletin

INTERNATIONAL ADVISORY BOARD

Aims and Scope

International Journal of Diabetes in Developing Countries targets a readership consisting of clinicians, research workers, paramedical personnel, nutritionists and health care personnel working in the field of diabetes. Original research work and reviews of interest to the above group of readers is considered for publication in the journal.

The journal has a goal of serving as an important resource material in diabetes for its readers, mainly in the developing world.

Copyright Information

For Authors

As soon as an article is accepted for publication, authors will be requested to assign copyright of the article (or to grant exclusive publication and dissemination rights) to the publisher (respective the owner if other than Springer Nature). This will ensure the widest possible protection and dissemination of information under copyright laws.

More information about copyright regulations for this journal is available at www.springer.com/13410

For Readers

While the advice and information in this journal is believed to be true and accurate at the date of its publication, neither the authors, the editors, nor the publisher can accept any legal responsibility for any errors or omissions that may have been made. The publisher makes no warranty, express or implied, with respect to the material contained herein.

Subscription Information

International Journal of Diabetes in Developing Countries is published 4 times a year. Volume 41 (4 issues) of will be published in 2021.

ISSN 0973-3930 print version
ISSN 1998-3832 electronic version

For information on subscription rates please contact Springer Nature Customer Service Center: customerservice@springernature.com

The Americas (North, South, Central America and the Caribbean)
Springer Journal Fulfillment, 233 Spring Street, New York, NY, 10013-1578, USA
Tel. 800-SPRINGER (777-4643); 212-460-1500 (outside North America)

Outside the Americas
Springer Nature Customer Service Center GmbH
Tiergartenstr. 15, 69121 Heidelberg, Germany
Tel.: +49-6221-345-4303

Advertisements

Disclaimer

Journal Website

www.springer.com/13410
Electronic edition: link.springer.com/journal/13410

For the actual version of record please always check the online version of the publication.

Office of Publication

Springer Science+Business Media B.V., Van Godewijckstraat 30, 3311 GX Dordrecht, The Netherlands

International Journal of Diabetes in Developing Countries

Volume 41 · Supplement 1 · January–March 2021

Further articles can be found at www.springerlink.com

Abstracted/Indexed in *CAB Abstracts, CNKI, Chemical Abstracts Service (CAS), Dimensions, EBSCO Academic Search, EBSCO CINAHL, EBSCO Discovery Service, EBSCO STM Source, EMBASE, EMCare, Google Scholar, Institute of Scientific and Technical Information of China, Japanese Science and Technology Agency (JST), Journal Citation Reports/Science Edition, Naver, OCLC WorldCat Discovery Service, ProQuest Biological Science Database, ProQuest Central, ProQuest Health & Medical Collection, ProQuest Health Research Premium Collection, ProQuest Immunology Abstracts, ProQuest India Database, ProQuest Natural Science Collection, ProQuest Nursing & Allied Health Database, ProQuest Pharma Collection, ProQuest Research Library, ProQuest SciTech Premium Collection, ProQuest-ExLibris Primo, ProQuest-ExLibris Summon, SCImago, SCOPUS, Science Citation Index Expanded (SciSearch), Semantic Scholar, TD Net Discovery Service, UGC-CARE List (India)*

Instructions for Authors for *Int J Diabetes Dev Ctries* are available at www.springer.com/13410.

Compliance with Ethical Requirements

International journal of Diabetes in Developing Countries requests that all authors comply with Springer's ethical policies. To view our ethics statements please visit the following:

· Conflict of Interest and Ethical Standards: http://www.springer.com/authors?SGWID=0-111-6-791531-0

· Informed Consent: http://www.springer.com/authors?SGWID=0-111-6-608209-0

Statement of Human and Animal Rights: http://www.springer.com/authors?SGWID=0-111-6-608309-0

Disclaimer: This Consensus Statement on Diabetes and Heart failure was prepared by Research Society for the Study of Diabetes in India (RSSDI) and is a proprietary work of RSSDI as a service to the medical profession. The views expressed and stated in this publication are the independent views of the authors and not of Abbott. Abbott has got limited license to share this guidance with relevant stakeholders within the Indian healthcare ecosystem. This statement is being disseminated purely for information and awareness of healthcare professionals and is not meant for patients. Healthcare professionals should exercise their own professional judgement while referring to these guidelines. While every effort is made to ensure the accuracy of the contents hereof, any liability for error, omission or consequence arising from the use of this information is hereby disclaimed. The contents herein do not constitute or imply an endorsement, sponsorship or recommendation of any kind by Abbott.

Diabetes Mellitus and Heart Failure: A Consensus Statement

Primary Authors:

Banshi Saboo[1], Sanjay Agarwal[2], AK Singh[3] , Brij Makkar[4], Rajeev Chawla[5], Sujoy Ghosh[6], Vijay Viswanathan ,[7]Sunil Gupta ,[8]Vasanth Kumar ,[9]Anuj Maheshwari [10]

Affiliations

1 Diabetologist and Chairman, Diabetes Care & Hormone Clinic Dia-Care. Ahmedabad-15 National President, RSSDI

2 MD, FACE, Director, Aegle Clinic-Diabetes Care Head, Dept. of Medicine and Diabetes, Ruby Hall Clinic, Sr.Consultant in Diabetes & Medicine, Jehangir Hospital National Secretary, RSSDI

3 M.D., D.M (Endo) Consultant Endocrinologist GD Hospital & Diabetes Institute, Kolkata (India)

4 MD, FIAMS, FICP, FRCP(Glasg, Edin), FACP(USA), FACE(USA), FRSSDI Diabetologist & Bariatric Physician, Dr Makkar's Diabetes & Obesity Centre A-5B/122, Paschim Vihar, New Delhi-110063

5 Director, North Delhi Diabetes Centre Hony Prof Jaipur National University, 180 Jai Apartment Sec-9 Rohini, New Delhi-110085

6 Dept of Endocrinology Institute of Post Graduate Medical Education and Research Kolkata Room 9B. 4th floor. Ronald Ross building Institute of Post Graduate Medical Education and Research Kolkata 244 A J C Bose Road Kolkata 700020

7 No.4, West Mada Church Street Royapuram, Chennai - 600 013 Tamilnadu, India

8 Managing Director, Sunil's Diabetes Care n' Research Centre Pvt.Ltd 42, Lendra Park, Ramdaspeth, Nagpur-440010 Maharashtra India

9 Senior Consultant, Apollo Hospitals. Hyderabad, India

10 Vice President Research Society for Study of Diabetes in India (RSSDI) Professor and Head, Department of Medicine, BBD University, Lucknow Governor, American College of Physicians, India Chapter

Corresponding Author:
Sanjay Agarwal[1a]Secretary, RSSDI; Pune
Address: Aegle Clinic - Diabetes Care, A-11 Narsimha Housing Society,
194 Boat Club Road, Pune - 411011
Email: agarwalclinic@gmail.com

Extended Panel of Experts:

[1]AK Das
[2]Anand Moses
[3]Anant Nigam,
[4]Bikash Bhattacharjee
[5]HB Chandalia
[6]JJ Mukherjee
[7]J. K. Sharma
[8]L.Sreenivasa Murthy
[9]Mangesh Tiwaskar
[10]Neeta Deshpande
[11]Pratap Jethwani
[12]Rakesh Sahay
[13]Rajiv Kovil
[14]Sanjay Kalra
[15]Sanjeev Phatak
[16]Sanjay Reddy
[17]Shalini Jaggi
[18]Shashank Joshi
[19]Siddarth Das
[20]Sudhir Bhandari
[21]S.V Madhu
[22]SR Aravind
[23]V. Mohan
[24]Vijay Panikar

Word count: 6995
No. of figures: 3
No. of tables: 4

Introduction:

Based on the clinical and epidemiological data, it has been documented that in addition to myocardial infarction (MI) and atherosclerosis-related cardiovascular diseases (CVD), heart failure (HF) is a potential contributor to the morbidity and mortality in patients with diabetes.(1) Type 2 diabetes mellitus (T2DM) is a distinguished predisposing factor for HF(1). The pathophysiology of these two conditions is closely associated. Timely identification and immediate suitable intervention generate to a better outcome. Majority of patients with co-existing T2DM and CVD along with other co-morbidities (e.g., atherosclerotic CVD, HF, chronic kidney disease (CKD), and obesity) augments the need of a specific approach in the selection of appropriate antidiabetic drugs.(2) The present consensus document provides an evidence-based assessment on risk factors, prognosis, and proper management to reduce the morbidity and mortality. It also discusses the management strategies for patients of HF with concomitant T2DM.

Epidemiology of diabetes mellitus and heart failure:

Numerous studies have shown that pre-diabetes is associated with a high risk of HF and suggest an age-adjusted hazard ratio (HR) between 1.2 and 1.7 in different populations of patients with impaired fasting glucose. However, the results are conflicting and hence, no agreement could be established among all studies. As a matter of fact, the risk of developing HF in subjects with pre-diabetes is lower than in subjects with diabetes.(3)

In a systematic review, consisting of 4,549,481 patients with T2DM, documented a 14.9% prevalence of HF, 14.6% of angina, and 10% of myocardial infarction (MI) in patients with T2DM (4). Additionally, in a Swedish and Spanish HF registry data, the prevalence of T2DM in patients with HF were 24% and 45.3% respectively (5). Similarly, in a study which recruited 1082 patients with HF, 490 (45.3%) constituted concomitant diabetes patient. In course of follow-up, it was observed that a total of 151 patients (30.8%) with T2DM died, and 197 patients (40.2%) with T2DM were readmitted because of HF. Increased all-cause mortality (ACM) [hazard ratio (HR) 1.49]; and readmissions [HR 1.39] in T2DM was significantly associated in that study (6). Further, a study by Parry et al., revealed that glycated hemoglobin (HbA 1c) < 6 % (HR 1. 60) as well as HbA1c > 10% (HR 1.80) were independently associated with the risk of HF(6).

A retrospective observational study was conducted in South India by Devarajan A. et al., 2020, among 397 individuals who visited two tertiary care centers. They were classified into 4 groups - DM with HF(DM-HF), DM without HF, non-DM with HF (non-DM-HF) and non-DM without HF. Authors assessed and compared the clinical profile of DM with HF vs. DM without HF and non-DM with HF groups respectively. The parameters such as age, BMI, BP, eGFR showed significant difference between the groups. People with DM-HF were older compared to DM without HF group (58.9 ± 9.2vs.49.5 ± 9.3; $p < 0.001$). An increasing trend was observed in HF prevalence with increasing duration of DM among the DM-HF group. DM-HF showed a higher prevalence of hypertension and coronary artery disease (CAD) by history than DM without HF group. DM-HF group (91.2%) had HF with preserved left ventricular ejection fraction (HFpEF) whereas a high proportion (43.5%) of non-DM-HF group had HF with reduced LV ejection fraction (HFrEF) (7).

Variability in HbA1c has also been found to be associated with HF incidence. It has been postulated that the HbA1c variability augment cell apoptosis and oxidative stress which may lead to HF in patients with diabetes(6). Additionally, CKD increases mortality and the overall progression of CVD as well as HF(5). Further, the prevalence of CKD (eGFR < 60 mL/min/1.73 m in patients with HF was observed to be 63%. This was associated with an 11% increase in hospitalization and a 17% increase in mortality. Renal function abnormality and mortality were prevalent in patients with DM when compared to the reference group (32% vs. 25%) (8). A study conducted by Indian Council of Medical Research the-INDIAB, estimated that approximately 77.2 million people in India are prediabetic. Nearly around 36 million (52%) people comprise undiagnosed DM(9). The most frequent cardiac abnormality associated with asymptomatic DM includes left ventricular (LV) diastolic dysfunction. The other modifiable risk-factors for HF, which commonly coexist in T2DM, are, the obesity, CAD, hypertension (HTN), anemia and obstructive sleep apnea (OSA) (10).

Key take home messages

1. Approximately half (50%) of patients with chronic HF have diabetes in India.
2. The rate of HF in India is expected to increase by 18% annually.
3. HF is more prevalent than MI in patients with T2DM.

4. Variability in HbA1c level, co-morbid CKD, and myocardial ischemia may increase the risk of HF.
5. Both pre-diabetes and undiagnosed diabetes have a high prevalence in India.
6. Early diagnosis and therapeutic interventions will improve morbidity and mortality.
7. Modifiable co-morbidities in T2DM, including CAD, HTN, obesity, anemia, OSA, need to be addressed adequately for effective management of HF in T2DM.

Pathophysiology of DM and HF:

It is evident that T2DM is associated with atherogenic dyslipidemia and endothelial dysfunction suggesting the significance of hyperlipidemia lowering drugs in minimizing HF. A link between glucose levels and HF is well documented. Pathogenic role of insulin resistance and hyperinsulinemia are interrelated to left ventricular hypertrophy (LVH) due to T2DM(11). Hyperglycemia results in cardiac muscle stiffness. Therefore, insulin resistance decreasing antidiabetic drugs that controls the hyperglycemia is the need of the hour to reduce the rate of HF in T2DM. Although, cardiomyopathy in T2DM is independent of atherosclerotic ischemia; there is evidence of cardiomegaly as well in T2DM patients. Hence, the antidiabetic therapy which target such pathology e.g., SGLT2i, have been effective in the treatment modality(12). Further, the HF diagnosis requires signs and symptoms assessment, detailed history, evaluation of differential diagnostic biomarkers such as natriuretic peptides (NPs), and an echocardiogram (ECG). Diagnostic algorithm for heart failure in T2DM is shown in figure 1. Various HF biomarkers utility and their diagnostic accuracy are summarized in table 1 and table 2. A diagrammatic representation of the pathophysiology of HF in T2DM is depicted in figure 2.

Prognosis of Patients with Diabetes Mellitus and Heart Failure:

The most significant clinical end points are CV Death and HHF (Hospitalization with heart failure) and are determined by poor glycemic control.(4)

A study assessed the influence of diabetes on the risk of death in 5491 patients hospitalized with congestive heart failure (CHF) (13). In this study, 16% of patients had diabetes at baseline, and approximately 50% had an ejection fraction <35%, suggesting that both HFrEF and HFpEF were present in the patient population. Almost half (50%) of all HF patients with diabetes died after 3 years- revealed by the mortality analysis of the above-mentioned study (14). The Survival and

Ventricular Enlargement (SAVE) trial, Valsartan in Acute Myocardial Infarction Trial (VALIANT), and the Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity (CHARM) trials together provided an additional data on the prognosis of patients with diabetes and HF (15). All of these studies demonstrated an increased risk of mortality in either gender with diabetes. Further, patients with or without diabetes and HFpEF or HFrEF showed a highest mortality or HHF among HFrEF. This was followed by the patients with diabetes and HFpEF. The collective incidence rate of cardiovascular (CV) death and HHF in patients with diabetes plus HFpEF was equivalent to that in subjects without diabetes but with HFrEF. Also, a similar trend was valid for all-cause mortality (15).

Similarly, in patients with diabetes, the risk for first hospital admission due to HF was 116.6 per 1000 patient-years for those with HFpEF. Whereas the rate was 155.4 per 1000 patient-years for those with HFrEF (16). In the Medanta registry (48.7% had co-morbid DM), it was observed that half of Indian patients had HFrEF (59.1%). Indian data,the Inter-CHF study reported HFrEF prevalence of 53% (with 26% concomitant DM), while the Trivandrum HF Registry (THFR) data reported a prevalence of HFpEF 26% (with 55% concomitant DM) (17). Additionally, a study by Matsue et al., suggested that more than 1/3rd of patients who were hospitalized for HF without a definitive diagnosis of diabetes, exhibited impaired fasting glucose or impaired glucose tolerance (18).

Therefore, among patients with HF, those with concomitant diabetes had a higher risk of mortality and HHF than those without diabetes. Hence, the prevalence of prediabetes and diabetes with heart failure proves as a remarkable predictor of prognosis.(7) Table 3 summarizes characteristics of HF classification based on left ventricular ejection fraction (LVEF), time-course, or severity of symptoms.

Key take home messages

1. Prevalence of heart failure in diabetes is relatively higher, and the prognosis for patients with heart failure is inferior in those with diabetes as compared to those without diabetes.
2. The prevalence of heart failure based on ejection fraction i.e., HFrEF and HFpEF in India is similar (~ 50%) in patients with T2DM.
3. HF phenotype and stage of HF identification can guide the management.

4. Nevertheless, in spite of having no specific therapy for HFpEF, it is clinically relevant to distinguish it from HFrEF and that may lead to the efficient management of risk factors and disease progression.

Heart Failure and Glycemic Control:

Diabetes and HF are directly associated.(4) In other words, patients with diabetes have an increased risk of developing HF and those with HF are at higher risk of developing diabetes. Individually, HF has a much inferior prognosis than DM.(7) Therefore, the HF has to be a main concern for treatment in patients presenting with concomitant DM conditions. Although, there is a paucity of randomized clinical trials conducted to test the effect of cardiovascular drugs in diabetic patients with HF, however, a plethora of evidence suggests that all interventions efficient at improving prognosis in patients with HF are equally beneficial in patients with or without diabetes.(7)

Available guidelines suggest an individualized therapy approach and glycemic goal for every individual patient.(2) In general, all guidelines recommend achieving HbA1c near to a normal glycemic level. Poor glycaemic control increases risk of HF. There is data from observational studies that have calculated the risk for every 1% increase in HbA1c. Regarding the effect of strict glycaemic control on risk of HF, data is conflicting, but in balance, there was no beneficial effect on risk of HF (19). However, achieving glycemic goal is dependent on patient demographic characteristics like age, duration of diabetes, and risk of complications including hypoglycemia and co-morbidities.(20) Therefore, choosing an anti-diabetic drug is very critical and should be individualized based on the patient need.

Even after intensive glycemic control, several studies namely, UKPDS, ADVANCE, ACCORD, and VADT have shown negligible benefit in heart failure(21–23). At the same time, many observational studies have reported that optimal glycemic control is beneficial to patients. Again, an increase in HbA1c more than 8%-10% demonstrated an increase in the risk of HF in some studies.(6)

Key take home messages

1. HF is a common, yet under recognized and under diagnosed, complication of T2DM.
2. Evidence on the burden and impact of concomitant HF and DM in India is limited.
3. HF has a much poorer prognosis than DM alone.
4. Choosing an anti-diabetic drug in co-existing HF patient is very critical and should be individualized based on the patient need.

Effect of Anti-diabetic Drugs on Heart Failure:

While several studies have demonstrated increased risk of HF with worsening glycemic control in people with T2DM, an efficient glycemic control could not be established as a tool to improve HF outcomes. The recent clinical trials conducted in patients with HF who had diabetes showed a diverse response to standard medication.(15) However, these patients are believed to be more susceptible towards the development of side-effects than patients with the same degree of HF but without DM. Therefore, considering cardiovascular safety, a careful selection of antidiabetic therapy becomes imperative in optimizing diabetes treatment modality.(1) The current section reviews the use of individual antidiabetic agents in a person with T2DM plus HF.

Few prominent features of anti-diabetic drugs before considering them for therapy are as follows:

Metformin: FDA in 2006 removed restrictions on use of metformin in patients with medically treated heart failure (24). Metformin users have better outcomes than patients treated with other antihyperglycemic agents as per observational studies. (25). Except renal impairment or another contraindication, metformin is the first line of treatment in glycemic management. Metformin is safe and generally well tolerated. Apart from the observational studies and experimental data, definitive evidence from a randomized controlled trial (RCT) to establish the clinical benefit of metformin in patients of T2DM and HF is still warranted. ESC 2016 guidelines mention that in patients' of T2DM with HF, metformin is a safe first-line therapy for glycemic control. Further, a population-based retrospective cohort study supports a reduced risk of hospitalization for HF associated with metformin use in patients with type 2 diabetes mellitus (26). However, metformin is contraindicated in individuals with severe HF (New York Heart Association, NYHA, classes III –IV), due to concerns of lactic acidosis, with an estimated mortality rate of 50% (27). Additionally, within permissive kidney function limits (eGFR> 30 mL/ min/1.73 m^2),

metformin may be used for the management of hyperglycemia in patients with stable heart failure (28).

Sulfonylurea (SU), thiazolidinediones (TZD), dipeptidyl dipeptidase-4 inhibitor (DPP4i), sodium glucose co-transporter 2 (SGLT-2) inhibitors, and GLP1 agonists constitute second line therapy in case patient fails to achieve glycemic control on first line therapy. This is followed by third line therapy, which include either adding third oral antidiabetic agent or starting insulin.(2)

Thiazolidinediones are insulin sensitizer drug known to cause fluid retention.(2) Use of TZD is contraindicated in patients with HF of class NYHA - III-IV. The safety of sulfonylureas in HF with concomitant T2DM is not fully established. Both TZD and sulfonylureas should be used with utmost care as they might increase the risk of HF worsening.(2) Interestingly, the recent Cardiovascular Outcome Trial of LINAgliptin Versus Glimepiride (CAROLINA) has shown no increase in risk of HHF with glimepiride when compared with linagliptin in T2DM patients without HF[2] (29).

Consensus recommendation

1. ESC 2016 guidelines declare that in patients of T2DM with HF, metformin is a safe first line therapy for glycemic control. Metformin is associated with better short-term and long-term prognosis in patients with HF.
2. The CAROLINA trial evaluating CV outcomes has shown no increase in the risk of HHF with glimepiride in T2DM patients without HF.
3. Reports on effect of TZD on CV safety are conflicting, however, a meta-analysis reported an increased risk of MI with rosiglitazone. Because of the associated side effects such as fluid retention and weight gain with TZD, its use in NYHA III and IV grade HF is avoided.

Glucagon-like peptide (GLP) - 1 Receptor Agonists: Evidence from Cardiovascular Outcome Trials (CVOTs)

GLP-1 receptor agonist belongs to the incretin class of drug having a number of non-glycemic effect including anorexia, hypotension, and increased pulse rate. The accomplished CVOTs with GLP-1 agonist included ‘LEADER’ and ‘SUSTAIN’ studies with liraglutalide and semaglutide

respectively. Trials demonstrated a reduction in MACE (HR 0.87 and 0.74 respectively), and liraglutide exhibited a positive inclination towards reducing the HHF predominantly in high CV risk T2DM patients.(30,31) However, other two studies, 'ELIXA' and 'EXSCEL' with lixisenatide and long acting exenatide respectively failed to establish CV safety.(32,33). A favorable risk benefit ratio for GLP 1 agonists with a reduction in 3- point MACE (HR 0.90; 95% CI: 0.82 -0.99; p = 0.033), CV mortality (HR 0·87; 95% CI: 0·79-0·96; p = 0·007), and ACM (HR 0.88; 95% CI 0.81- 0.95; p = 0·002) were demonstrated in a meta-analysis of 4 CVOTs (LEADER, SUSTAIN-6, ELIXA, and EXSCEL. Albiglutide in 'HARMONY' trial showed a significant decrease in MACE (HR0.78; 95% CI 0.68 to 0.90; p < 0.001) and MI (HR0.75; 95% CI 0.61 to 0.90; p = 0.03), however, did not reduce CV death, ACM, or stroke (34). Yet another, recently published REWIND trial with Dulaglutide also confirmed a reduction in MACE (HR 0.88; 95% CI 0.79 to 0.99; p = 0.026), however, there was no difference in mortality, and conversely, a higher incidence of gastrointestinal adverse events (47.4% vs. 34.1% in placebo) were noted (35).

Consensus recommendation

1. None of the GLP-1 agonist has demonstrated either decreased or increased risk of HHF in patients with T2DM.
2. Certain GLP-1 agonists have shown benefit when compared with placebo in decreasing the risk of composite CV outcomes inT2DM.
3. Current guidelines have changed to recommend GLP-1 agonist as the preferred therapy after metformin in patients with T2DM with established cardiovascular disease.
4. There are ongoing trials of GLP-1 agonist to further understand the cardiovascular benefits in T2DM with acute or chronic HF plus reduced ejection fraction.

Dipeptidylpeptidase-4 (DPP4) inhibitors or gliptins: Evidence from Cardiovascular Outcome Trials (CVOTs)

The class of gliptins (DPP4i) has accumulated evidences on HF with CV outcome trials. Gliptins have exhibited an inconsistent pattern on HHF in CVOTs. Ambiguous results in the

TECOS trial for the HHF end point (3.1% sitagliptin vs. 3.1% placebo) [(HR 1.00; 95% CI 0.83 to 1.20)] were observed with Sitagliptin (36).

In contrary of that, 'SAVOR-TIMI 53' trial revealed an increased risk of HHF (3.5% in saxagliptin vs. 2.8% in placebo) [(HR 1.27; 95% CI 1.07 to 1.51)] with saxagliptin.(37) However, 'EXAMINE' study results conferred an increased HHF trend (3.9% alogliptin vs. 3.3% placebo)[(HR 1.19; 95% CI 0.89 to 1.58)] with alogliptin (38).

The only gliptin trial in HFrEF i.e. vildagliptin in the 'VIVID' study had demonstrated no major effect on ejection fraction (EF), however, caused a statistically significant increase in LV volumes (LV end-diastolic volume by 17.06 ml; 95% CI: 4.62 to 29.51; $p = 0.007$ and LV end-systolic volume by 9.44 ml; 95% CI: − 0.49 to 19.38; $p = 0.062$) (39). However, the significance of this result is yet to decipher. It is important to mention that only saxagliptin and alogliptin have shown increased risk of HHF and not vildagliptin, linagliptin, and sitagliptin. Hence, it is prudent to consider the risk benefit before using these drugs in patients with HF and DM.

Consensus recommendation

1. Certain gliptins, such as, saxagliptin, and possibly alogliptin, may increase the risk of HHF in T2DM patients with high CV risk and CKD.
2. The choice of a particular gliptin should be based on clinical judgment and an evidence-based informed decision should be made.

Sodium-glucose co-transporter-2 inhibitors (SGLT2i): Evidence from Cardiovascular Outcome Trials (CVOTs)

SGLT2i reduce glucose reuptake in the kidney by inhibiting the SGLT-2 transport protein.(40) Thus, it also causes glucosuria and volume loss. There is promising favorable evidence for SGLT2i starting from the initial stages of HF. It has a favorable HHF and mortality outcomes in various CVOTs in T2DM patients. These favorable HF results have been demonstrated both in patients with or without the HF. A recent meta-analysis confirmed statistically significant benefits with SGLT2i on HHF and CV death (HR 0.77; 95% CI 0.71 to 0.84; $p < 0.001$), particularly in patients with or without pre-existing HF, representing benefits in the initial HF stages (40).

The 'EMPA-REG OUTCOME' and 'DECLARE-TIMI 58' studies for empagliflozin and dapagliflozin respectively, revealed a significant reduction in HHF (HR=0.65; 95% CI: 0.50 to 0.85; p = 0.002 and HR=0.73; 95% CI 0.61 to 0.88, respectively) (41,42). The 'CANVAS' database also exhibited a reduction in HHF with canagliflozin vs placebo (HR 0.64; 95% CI: 0.35 to 1.15 vs. HR 0.68; 95% CI: 0.51 to 0.90; interaction p value = 0.91) in the primary and secondary outcome cohort respectively (43). Both 'EMPA-REG OUTCOME' and 'CANVAS' trial demonstrated a significantly decreased nephropathy progression and adverse renal outcomes.(41,43) Empagliflozin and canagliflozin have been approved by US FDA for lowering CV death and MACE in patients with T2DM and established CVD.

In patients with risk factors without baseline CVD or HF, the 'DECLARE-TIMI 58' study results demonstrated a lower incidence of cardiovascular death or HHF (4.9% vs. 5.8%; HR 0.83; 95% CI: 0.73 to 0.95; p = 0.005)(44). DECLARE TIMI results when segregated basis on EF, showed a HHF reduction in patients with (HR 0.64; 95% CI 0.43 to 0.95) and without (HR 0.76, 95% CI 0.62 to 0.92) HFrEF. Also, a reduced mortality (HR 0.55, 95% CI 0.34 to 0.90), and ACM (HR 0.59; 95% CI 0.40 to 0.88) in HFrEF was recorded. Very recently presented DAPA-HF results have exhibited a significant morbidity and mortality benefit with dapagliflozin in HFrEF patients with and without T2DM (with 42% concomitant T2DM) (45).

The EMPEROR-Reduced trial showed that empagliflozin is superior to placebo in improving HF outcomes among patients with symptomatic stable HFrEF (EF ≤40%) on excellent baseline guideline-directed medical therapy (GDMT), irrespective of diabetes status. The primary outcome, cardiovascular death or HF hospitalization, for empagliflozin vs. placebo, was 19.4% vs. 24.7% (hazard ratio [HR]=0.75, 95% CI: 0.65-0.86, p < 0.001). Similarly, cardiovascular death: 10% vs. 10.8% (HR 0.92, 95% CI 0.75-1.12), and HHF were 13.2% vs. 18.3% (HR=0.69, 95% CI 0.59-0.81) (46).

Subgroup analysis of DAPA-HF suggests that Dapagliflozin is effective and safe in patients with heart failure, regardless of Age.(47) Given concerns regarding the safety and efficacy of dapagliflozin in the elderly, the investigators conducted a subgroup analysis to examine the effects of this drug according to age. Patients receiving optimal medical therapy for symptomatic HF (left ventricular EF ≤40%) were included. Patients were randomly assigned to receive 10 mg of dapagliflozin daily or placebo (n = 4,744). Patient ages were as follows: 636 (13.4%) were

<55 years; 1,242 (26.2%) were 55–64 years; 1,717 (36.2%) were 65–74 years; and 1,149 (24.2%) were ≥75 years. The incidence of the primary composite outcome of first episode of worsening HF (hospitalization or an urgent care visit for HF) or CV death was lower in the dapagliflozin group than in the placebo group for each age range. Hazard ratios were as follows: 0.87 (95% CI 0.6–1.28) for <55 years; 0.71 (95% CI 0.55–0.93) for 55–64 years; 0.76 (95% CI 0.61–0.95) for 65–74 years; and 0.68 (95% CI 0.53–0.88) for ≥75 years (P value for interaction = 0.76). There were no differences in treatment discontinuation or adverse events including volume depletion, renal dysfunction, and hypoglycemia between the treatment groups for each age range (47).

In a recent compendium by Singh et al. (48), authors systematically reviewed the literature from Medline, Cochrane Library, and other relevant databases and attempted to provide evidence-based recommendations for the positioning of SGLT2i in the management of diabetes in the Indian population. Executive summary of the compendium is as follows:

- SGLT2i decrease blood glucose concentration by reducing glucose reabsorption from proximal convoluted tubules and by increasing urinary glucose excretion (Grade A, Evidence Level (EL) 1)
- SGLT2i are associated with durable glycaemic efficacy, body weight and blood pressure (BP) reduction with cardiovascular benefits and renoprotective action without a higher risk of hypoglycaemia (Grade A, EL 2)
- Treatment with SGLT2i is associated with side-effects such as genital tract infections (GTIs) and volume depletion-related adverse events; however, these can be minimized with proper education and counselling with close patient monitoring (Grade A, EL 2)
- Body weight, HbA1c and systolic BP are important parameters that can be used to identify non-responders to SGLT2i therapy (Grade B, EL2)
- Treatment with SGLT2i results in persistent calorie loss, which leads to weight loss. There is also some evidence of a reduction in β-cell stress and hyperinsulinaemia, and an increase in insulin sensitivity and the rate of insulin secretion (Grade C, EL 4).

SGLT2i: Indian Phenotype

- SGLT2i are emerging agents that can provide multiple benefits in Indian diabetes patients (Grade B, EL 3).

- The weight reduction associated with SGLT2i is due to loss of fat mass primarily from the abdomen rather than lean mass (Grade A, EL 2).
- The benefits associated with SGLT2i such as improvement of β-cell function and reduction of insulin resistance may be more useful in Indian patients with diabetes (Grade A, EL 2).

On May 5th 2020, the U.S. FDA approved dapagliflozin oral tablets for adults with heart failure with reduced ejection fraction to reduce the risk of CV death and HHF. With the approval, Dapagliflozin was the first among SGLT2 inhibitors, approved to treat adults with New York Heart Association's functional class II-IV heart failure with reduced EF.(49)

In a clinical trial, Dapagliflozin shown improvement in survival and reduced the need for hospitalization in adults with HF with reduced ejection fraction.(50) Safety and effectiveness data were evaluated in a randomized, double-blind, placebo-controlled study of 4,744 participants. The average age of participants was 66 years and more participants were male (77%) than female. After about 18 months, people who received Dapagliflozin had fewer CV deaths, HHF, and urgent HF visits than those receiving the placebo (50).

SGLT2i-Importance of weight loss:

Patients receiving SGLT2 inhibitors steadily experience weight reduction. Meta-analysis had revealed that in comparison to other antidiabetic agents, SGLT2 inhibitors reduced the body weight with a mean difference of 1.8 kg (95% CI: −3.5, −0.1) (51,52). As per European Medicines Agency assessment report, approximately 2–3 kg reduction in body weight was noted in the majority of phase III dapagliflozin studies(53). Early reduction of weight may represent fluid loss because of osmotic diuretic effect of these agents, whereas over consecutive weeks, increasing weight loss is most probably due to caloric loss. The glucose excreted in the urine as a result of SGLT2 inhibition equals to about 200–300 calories each day (54,55).

Plenty of studies have shown added metabolic benefits like improvement in body weight, blood pressure, lipid profile, insulin sensitivity, and cardiac function. SGLT2i has the advantage of efficient glycemic control with added cardiovascular benefit.(55) Needless to say, several mechanisms influence the empagliflozin and canagliflozin towards its inherent positive HF outcome.(55)

Consensus recommendation

1. SGLT2-inhibitors, namely empagliflozin, canagliflozin, and dapagliflozin have demonstrated promising results in reducing the risk of HHF.
2. These anti-diabetic agents may be considered for improving HF related to T2DM patients, who are at increased risk of HF or in those with stable HF.
3. There is clear evidence for patients of T2DM who have stable HF with mid-range ejection fraction (HFrEF); SGLT2-i may be safe to use in such patients.
4. Patient-specific and medication-related factors should be considered when selecting a particular SGLT2-i.

Insulin: Evidence from Cardiovascular Outcome Trials (CVOTs)

Insulin is recognized for sodium retention that might contribute to development of HF.(56) The Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE) study, evaluating 7637 patients of T2DM and high risk for CV events, reported to have a similar CV safety profiles of insulin degludec and insulin glargine when assessed by 3-point MACE. Incidence rate of HF events was 2.34 per 100 patient-years with insulin degludec as compared to 2.73 per 100 patient-years with insulin glargine (57).

Consensus recommendation

1. Many patients with T2DM with added co-morbidities, including HF may require addition of Insulin for good glycemic control.
2. CVOT with long-acting insulin analogs do not demonstrate increased HF.
3. However, the evidence to support the safety of insulin use in patients with T2DM with HF is not clearly established.

In a newly published consensus recommendation for clinical practice in Indian scenario for the management of glycemia in a person with T2DM with HF, Mukherjee et al.(58) summarized the OADs that (i) increase the risk for heart failure (ii) contraindicated with clinically compensated heart failure, (iii) preferred in clinically compensated heart failure, (iv) have neutral effect in

clinically compensated heart failure, and (v) are safe for use in people with type 2 diabetes mellitus with acute decompensated heart failure.

Which oral anti-diabetic agents increase the risk for heart failure in people with type 2 diabetes mellitus?

- Thiazolidinediones (TZDs) can cause, or exacerbate, heart failure in patients with type 2 diabetes mellitus. Patients receiving TZDs should be monitored for symptoms and signs of heart failure. If heart failure is suspected, TZDs should be discontinued, and heart failure should be managed as per standards of care.
- Saxagliptin and possibly alogliptin, may increase the risk of hospitalizations for heart failure in patients of type 2 diabetes mellitus with high cardiovascular risk and chronic kidney disease stage 3 & above. Patients should be observed for symptoms and signs of heart failure during therapy. If heart failure is suspected, saxagliptin or alogliptin should be discontinued, and heart failure should be managed as per standards of care.
- The choice of a particular DPP4 inhibitor should be based on clinical judgment, guided by pertinent factors related to the patient and the drug. An evidence-based informed decision should be made.
- Teneligliptin may cause QT interval prolongation in patients with or without history of arrhythmia, severe bradycardia, low serum potassium, congenital prolonged QT syndrome, history of Torsades de pointes, on antiarrhythmic medications.

Which oral anti-diabetic agents are contraindicated in people with type 2 diabetes mellitus with clinically compensated Heart Failure?

- TZDs are not recommended in patients with symptomatic heart failure, and are absolutely contraindicated in patients with established heart failure.
- Saxagliptin may increase the risk of hospitalization for heart failure, and should be avoided in patients with a history of heart failure. Alogliptin might also increase the risk of hospitalization for heart failure.

- Sitagliptin and Linagliptin do not increase the risk for hospitalization for heart failure in this group of patients but more information is required before recommending their routine use in the presence of compensated heart failure. It is prudent to avoid DPP4 inhibitors in a patient of type 2 diabetes mellitus with decompensated heart failure until further information is available, and critically reviewed by various regulatory bodies.
- Teneligliptin may cause QT interval prolongation in patients with heart failure**.**

Which Oral Antidiabetic Agents are Preferred in people with type 2 diabetes mellitus with clinically compensated Heart Failure?

- Metformin is a safe anti-diabetic agent for use in eligible patients of type 2 diabetes mellitus with stable heart failure for control of blood glucose.
- SGLT2-inhibitors like empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin have demonstrated promising results in reducing the risk of hospitalizations for heart failure beyond glycemia control. These agents may be considered for improving heart failure related outcomes beyond glycemic control in patients with type 2 diabetes mellitus who are at an increased risk of heart failure. Till date, dapagliflozin and empagliflozin have data supporting their use in people with type 2 diabetes mellitus with heart failure with reduced ejection fraction (HFrEF).
- In patients with type 2 diabetes mellitus who are at increased risk of heart failure and who had achieved target glycemic goal without an SGLT2-inhibitor, the inclusion of an SGLT2-inhibitor should be considered in light of the promising results seen with SGLT-2 inhibitors in reducing the risk of hospitalizations for heart failure beyond glycemia control in this group of patients; if necessary, down-titration of or a change in other antidiabetic agents should be considered based on appropriate clinical judgment for each individual patient.
- Patient-specific and medication-related factors should be considered when selecting a particular SGLT2-inhibitor. The SGLT2-inhibitors should not be used in acute/unstable/dehydrated states. Hydration and volume-status should be monitored during SGLT2-inhibitor therapy. Concomitant use of loop diuretics may result in volume-depletion and based on the clinical situation; the dose of loop diuretic might need to be reduced.

- There is no clear evidence favoring the use of any particular oral anti-diabetic agent in people with type 2 diabetes mellitus who have compensated heart failure with mid-range ejection fraction (HFmrEF) or preserved ejection fraction (HFpEF).

Which Antidiabetic Agents are Neutral in people with type 2 diabetes mellitus with clinically compensated Heart Failure?

GLP-1 receptor agonists have NOT demonstrated to either worsen or improve the risk of hospitalization for heart failure in patients with type 2 diabetes mellitus.

- Further careful research is warranted regarding the use of GLP-1 receptor agonists in type 2 diabetic patients with acute or chronic heart failure with reduced ejection fraction.

Which antidiabetic agents are safe for use in people with type 2 diabetes mellitus with acute decompensated heart failure?

- In people with type 2 diabetes mellitus with acute decompensated heart failure, recent evidence suggests that metformin or SGLT2-inhibitors could be considered depending upon the severity of acute heart failure, the prevailing estimated glomerular filtration rate, and absence of specific contraindications for use of these medications. Under most circumstances, insulin is preferred in people with type 2 diabetes mellitus with acute decompensated heart failure, despite the fact that there is limited supportive evidence for use of insulin in this scenario.

Effect of Heart Failure Drugs on Diabetes Mellitus:

The recommended non-glycemic treatment for HF with reduced ejection fraction in patients with T2DM (symptomatic or to prevent HHF and/or death) is similar to the treatment of HF in general and includes angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), angiotensin II receptor blocker neprilysin inhibitor (ARNI), beta-blocker (BB), and Ivabradine.(59–61) Needless to mention, sodium restriction has long been the cornerstone of self-care for patients with heart failure (HF), given the relevance of fluid balance in HF and the potential contribution of dietary sodium to fluid overload.(26) This recommendation persists even though the effects of sodium restriction on quality of life and prognosis of patients with HF

have been consistently questioned over the past decade, owing to the lack of quality evidence to support this practice. In the 2016 ESC guidelines, the salt and fluid restrictions have been modified to 'avoid excessive fluid intake', 'weight-based fluid restriction may cause less thirst', and salt restriction is listed in 'Gaps in evidence' (26,62). ESC guidelines do not provide a specific maximum daily intake of sodium for patients with HF, but advise against excessive intake (defined as > 6000 mg/d of salt, equivalent to 2400 mg/d of sodium). The daily sodium intake recommendations for each stage of heart failure remains similar i.e., no specific maximum daily intake; advise restricting sodium intake to < 6000 mg/d of salt; (2400 mg/d of sodium). Emphasis is currently on the use of diuretics to reduce congestion with intensive management of comorbidities.(26,62)

The Ivabradine or ARNI should be considered in the selected cases with persistent symptoms and EF < 35%.(63) An algorithm for management of heart failure in type 2 diabetes mellitus is depicted in Figure 2.

Renin-angiotensin-aldosterone system (RAAS) inhibitors:

Six studies differentiated by data related to diagnosis of diabetes constituting a meta-analysis (n= 2398 diabetic patients and 10,188 non-diabetic patients) included CONSENSUS, SAVE, 2 SOLVD studies, SMILE, and TRACE studies (64). Meta-analysis demonstrated no difference in mortality among the patients of two different groups. The relative risk (RR) of mortality in patient population with diabetes was 0.84 (95% CI 0.70 to 1.00), while the estimate of the RR in patients without diabetes was 0.85 (95% CI 0.78 to 0.92).(64) However, yet another, large meta-analysis evaluating 47,662 patients demonstrated that, it is the ACEI and not ARBs which contribute to the statistically significant reduction in all-cause mortality (ACM) (RR 0.89; 95% CI 0.83 to 0.96; p = 0.001) and death due to CVD (RR 0.86; 95% CI 0.78 to 0.94; p = 0.001) in HF patients (59). Needless to say, no separate analysis for T2DM in this study was carried out. A subgroup analysis of 'PARADIGM-HF' study in patients of HFrEF was carried out to understand the effect of sacubitril/valsartan combination (ARNI) among diabetic and non-diabetic patients (60). The study revealed a significant reduction in HHF or mortality which was also consistent irrespective of the diabetes [RR 0.87 95% CI: 0.77-0.98] vs non-diabetes status [RR 0.68 95% CI: 0.56-0.83].(60) These results changed the guidelines for the management of HF only 2 months after presented study. Similarly, in a study named CHARM, an equivalent

effect regardless the diabetic status was observed with respect to HHF and mortality when an alternative of ACEI (candesartan) was given(65).

Consensus recommendation

1. The use of RAAS inhibitors exhibits similar efficacy profile in HF patients irrespective of diabetes status.
2. ACEi contributes to the reduction in all-cause mortality (ACM) and CV death

Beta-blockers (BB):

Data classified by diagnosis of diabetes in a meta-analysis evaluated the differential effect of beta-blockers on mortality from HF.(64) Meta-analysis included CIBIS, CPERNICUS, and MERIT-HF studies consisting of 1883 patients with diabetes and 7042 non-diabetic patients. It was observed that patients with diabetes had reduced mortality [0.77 (0.61–0.96)) when given beta-blockers. Further, the RR reduction when compared to non-diabetics was comparatively less [0.65 (0.57–0.74)] (64). Although, the RR comparison yield was not statistically significant, however, the absolute risk reduction in mortality of concomitant diabetes was comparable with non-diabetes.

As a matter of fact, beta blocker led to sharpen the hypoglycemia effect in T2DM patients with HF. In this regard, a study demonstrated that patients with CVD/HF had a higher CV events (HR 1.27; 95% CI, 1.02 to 1.60; p = 0.03), and severe hypoglycemia in patients on BB (HR 1.30; 95% CI, 1.03 to 1.64; p = 0.02).(66)

Consensus recommendation

1. The use of BB demonstrates equivocal safety profile in HF patients irrespective of diabetes status; however, it aggravates the hypoglycemia events in T2DM.

Ivabradine:

Ivabradine, is an inhibitor of the cardiac pacemaker current I_f, which reduces heart rate thereby reducing the cardiac work burden. A reduction in CV death, HHF, and death due to HF was demonstrated by 'SHIFT' study. The results revealed reduction in CV death or HHF (HR 0.82;

95% CI 0.75 to 0.90; p < 0·0001), HHF (HR 0.74; 95% CI 0.66 to 0.83; p < 0·0001) and deaths due to HF (HR 0.74; 95% CI 0.58 to 0.94; p = 0.014). The results of the study were favorable for HFrEF patients with T2DM. Thus, SHIFT results were positive irrespective of the diabetes status (61). The ESC 2016 HF guideline recommends, Ivabradine in HF patients in sinus rhythm with EF ≤ 35% and a resting heart rate (RHR) ≥ 75 bpm), else in those patients who are unable to tolerate BB with RHR ≥ 70 bpm even with maximum tolerated BB dose.(26)

Consensus recommendation
1. Ivabradine is recommended if HF symptoms persist despite treatment with BB, ACEi, and MRA (in patients with sinus rhythm > 70 bpm).

Treatment of HFpEF in T2DM:

The recent published real-world data provides evidence towards increasing prevalence of HFpEF with increased mortality. A meta-analysis revealed that ACM was decreased with BB when compared to placebo (RR 0.78; 95%CI 0.65 to 0.94, p = 0.008), however, there was no effect on HHF (RR 0.67; 95% CI 0.42 to 1.07; p = 0.10) (67).

Again, the ACE inhibitors/ARBs, or other drugs failed to exhibit improvement in HHF or ACM. Even the ARNI could not lower the rate of HHF and ACM among patients with HFpEF as evident by 'PARAGON-HF' study. The percentage death from CV causes was 8.5% in the ARNI group and 8.9% in the valsartan group (HR 0.95; 95% CI 0.79 to 1.16) (68). Table 4 enlists HF outcomes in the various HFpEF/HFrEF trials. Therefore, the current management emphasize on the use of diuretics for aggressive management of associated co-morbidities. Algorithm for management of heart failure in type 2 diabetes mellitus is depicted in Figure 3.

Consensus recommendation for HFpEF
1. For associated co-morbidities, target lipid and blood pressure levels should be achieved. 2. In patients with CAD, coronary revascularization could be a suitable option to adopt.

Therapeutic Targets for Heart Failure in Diabetes:

Apart from SGLT2-i, some novel therapeutic targets for heart failure in diabetes ongoing trials on pharmacological management of HFrEF and HFpEF are as follows:

Ularitide: A synthetic analog of the endogenous urodilatin which is investigated in several phase I and II trials. It is a renal peptide hormone secreted in response to increased pressure. Ularitide causes diuresis, vasodilatation, and inhibition of RAAS by binding to natriuretic peptide receptor (NPR-A) (69).

Levosimendan: It is an inotrope with an added action of vasodilatation and protection against ischemia and reperfusion injury. It increases the cardiac contractility in acute HF (70).

Phosphodiesterase type 5 (PDE-5) inhibitors: They are principally used in the management of pulmonary arterial hypertension and have demonstrated more benefits in HFrEF compared with HFpEF (71).

Omecamtiv: It is a specific cardiac myosin activator to improve cardiac contractility. This has exhibited promising results in phase 2 COSMIC-HF study (72).

Tafamidis: It is primarily used for the management of transthyretin amyloid cardiomyopathy. It binds with the thyroxine-binding sites of transthyretin and has demonstrated a reduction in ACM, CV-related hospitalization (73).

Canakinumab: It is an anti-inflammatory monoclonal antibody targeting IL-1β. Canakinumab has demonstrated a dose dependent reduction in HHF in patients with previous MI and increased hs-CRP (74).

Conclusion:

India registers 14% of deaths due to HF in patients with T2DM. The management of HF is based on its classification. A mixed report on the prognosis of HFrEF and HFpEF in patients with T2DM is available. Research suggests that both HFrEF and HFpEF increase the risk of hospitalization and mortality in patients with T2DM. Furthermore, in patients with newly diagnosed T2DM, the risk of MACE, HF and death increase with a higher number of comorbidities including CKD as the main contributor of mortality. Needless to say, HF diagnosis requires a detailed history, assessment of clinical signs and symptoms, assessment of

diagnostic biomarkers, an ECG, and 2D-Echo. Diabetes can be associated with other endocrine disorders which automatically qualify to classify as HF Stage A. Clinical screening should be done for all patients and TSH, testosterone where clinically indicated. This consensus document was intended to make better patient care, optimize the prognosis by executing the most efficient treatment strategies for the management of HF in T2DM. Additionally, SGLT2i play a major role in the prevention of HF in T2DM patients by its inherent ability to offer protection from CV complications along with best glycemic control. Results with dapagliflozin in DECLARE-TIMI 58 trial generated immense hope by demonstrating a significant reduction in HF in patients with T2DM. Besides the SGLT2i, new innovations may embrace the answer to transform the management of HF, in patients with T2DM.

Appendix-1

Table1: Role of biomarkers in the diagnosis of heart failure

Categories	Specific biomarkers	Recommendations for Diagnostic/Prognostic Value
Myocardial stress/injury	BNP, NT-proBNP	The upper limit of normal BNP value is 35 pg/mL, and for a NT-proBNP value is 125 pg/mL (non- acute settings). BNP >100 pg/mL and NT-pro BNP >300 pg/ml (acute setting) strongly suggests the possibility of HF.
	Troponin	Diagnostic of myocardial infarction, Elevated levels predict HF deaths, suggest ongoing myocyte injury or necrosis in affected patients. Associated with impaired hemodynamics, progressive LV dysfunction.
Remodeling	ST-2	Elevated levels of ST2 have prognostic value in the management of HF. It predicts mortality, and HF events.
	Galectin-3	Predict rehospitalization and death in HFpEF Predict HF events.

ST2: suppressor of tumorigenicity 2; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal- proBNP.

Table 2: Natriuretic peptide cutoff points and diagnostic accuracy

Acute Dyspnea	**To exclude acute HF**	**Cut-off Value**	**Sensitivity**	**Specificity**
	BNP	<30-50 pg/mL	97%	62%
	NT-proBNP	<300 pg/mL	99%	68%
	To identify acute HF			
	BNP	<100 pg/mL	90%	76%
	NT-proBNP	<900 pg/mL	90%	85%
	NT-proBNP, age-stratified approach		90%	84%
		<450 pg/ml for <50y <900 pg/ml for 50–75y <1800 pg/ml for >85y		

Table 3: Characteristics of heart failure classification:

Based on Left Ventricular Ejection Fraction:	Based on Time-course	NHYA classification	
1. HFrEF: EF < 40%	1. Chronic HF: Present for ≥3 months	Class I	No limitation in physical activity
2. HFmrEF: EF = 40% to 49%	2. Acute HF: Sudden onset HF or worsening of HF symptoms/signs	Class II	Slight limitation in physical activity. (Ordinary activity results in symptoms. Patient is comfortable at rest).
3. HFpEF: EF ≥ 50%		Class III	Marked limitation in physical activity. (Daily routine activity results in symptoms. Patient is comfortable at rest).
		Class IV	Marked limitation in physical activity. (Daily routine activity results in symptoms. Patient is comfortable at rest).

AHA: Stages of heart failure	
Stage A:	High risk, without symptoms (diabetes, hypertension, CAD)
Stage B:	Structural heart disease, without symptoms (previous MI, LV remodeling including LVH and low EF)
Stage C:	Structural heart disease with previous or current symptoms (known structural heart disease and shortness of breath and fatigue)
Stage D:	Structural heart disease with refractory symptoms (patients who have symptoms at rest)

EF: Ejection fraction; HF: Heart failure; HFmrEF: Heart failure with mid-range ejection fraction; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; NYHA: New-York Heart Association; AHA: American Heart Association;

Table 4: HF outcomes in the various HFpEF/HFrEF trials.

4a. Clinical trials in heart failure with preserved ejection fraction			
Drug	**Study**	**Drug/Intervention, Dosage, Median Follow-up**	**HF Outcomes**
ARB	CHARM-Preserve (65)	Candesartan 32 mg vs. placebo FU: 36.6 months	CV death or hospitalization for CHF: 0.86 (0.74-1.0) p = 0.051 CV death: 0·95 (0·76–1·18) p = 0·635 Hospitalization for CHF: 0·84 (0·70–1·00) p = 0·047 CV death, hospitalization for CHF, MI: 0·87 (0·75–1·00) p = 0·051 CV death, hospitalization for CHF, MI, stroke: 0·86 (0·75–0·99) p = 0·037
ACEI	PEP-CHF (75)	Perindopril 4 mg FU- 2.1 year	Death or hospitalization: 0.919 (0.700–1.208) p = 0.545 Hospitalization for HF: 0.86 (0.61–1.20) p = 0.375 Death: 1.09(0.75–1.58) p = 0.665 CV death: 0.98 (0.63–1.53) p = 0.928
	Aldo-DHF (76)	Spironolactone25 mg or placebo FU-12 months	Diastolic function: -1.5 (-2.0 to-0.9) p < 0.001 Maximal exercise capacity: 0.1 (-0.6 to 0.8) p = 0.81 LV ejection fraction: 1.6(0.1–3.1) p = 0.04
BB	SENIORS (77)	Nebivolol up to10 mg vs. placebo FU: 21 months	All-cause mortality or CV hospitalization: 0.86 (0.74–0.99) p = 0.039 All-causemortality:0.88(0.71–1.08) p = 0.21 CV mortality: 0.84 (0.66–1.07) p = 0.17 CV hospitalization:0.90 (0.76–1.06) p = 0.20(
4b. Clinical trials in heart failure with reduced ejection fraction			
Drug	**Study**	**Drug/Intervention, Dosage, Median Follow-up**	**HF Outcomes**
ACEI	SOVLD (78)	Enalapril at doses of 2.5 to 20 mg per day vs placebo	Mortality39.7% vs35.2%, (RRR= 16%, CI: 5 to 26%) p=0.0036)
ARNI	PARADIGM-HF Trial (79)	Enalapril 10 mg twice daily or LCZ696 200 mg	CV death or HHF: HR: 0.80; 95% CI: 0.73 - 0.87; p < 0.001) Death (HR: 0.84; 95% CI: 0.76-0.93; p < 0.001), First HHF (HR: 0.79; 95% CI:0.71-0.89; p < 0.001
Beta blocker	CIBIS II (80)	Bisoprolol 1·25 mg (n=1327) or placebo FU: 1.3 years	All-cause mortality: 11·8% vs 17·3%, HR: 0·66 (95% CI0·54–0·81, p<0·0001) Hospital admission for worsening HF: 18% vs 12%, HR: 0·64 (95% CI: 0·53–0·79), p = 0·0001
	MERIT-HF (81)	Metoprolol 12.5/25 mg or placebo	All-cause mortality: 7.2% vs 11%, HR: 0.66; 95% CI: 0.53-0.81; p = 0.00009

Figure 1: Diagnostic algorithm for heart failure in T2DM.

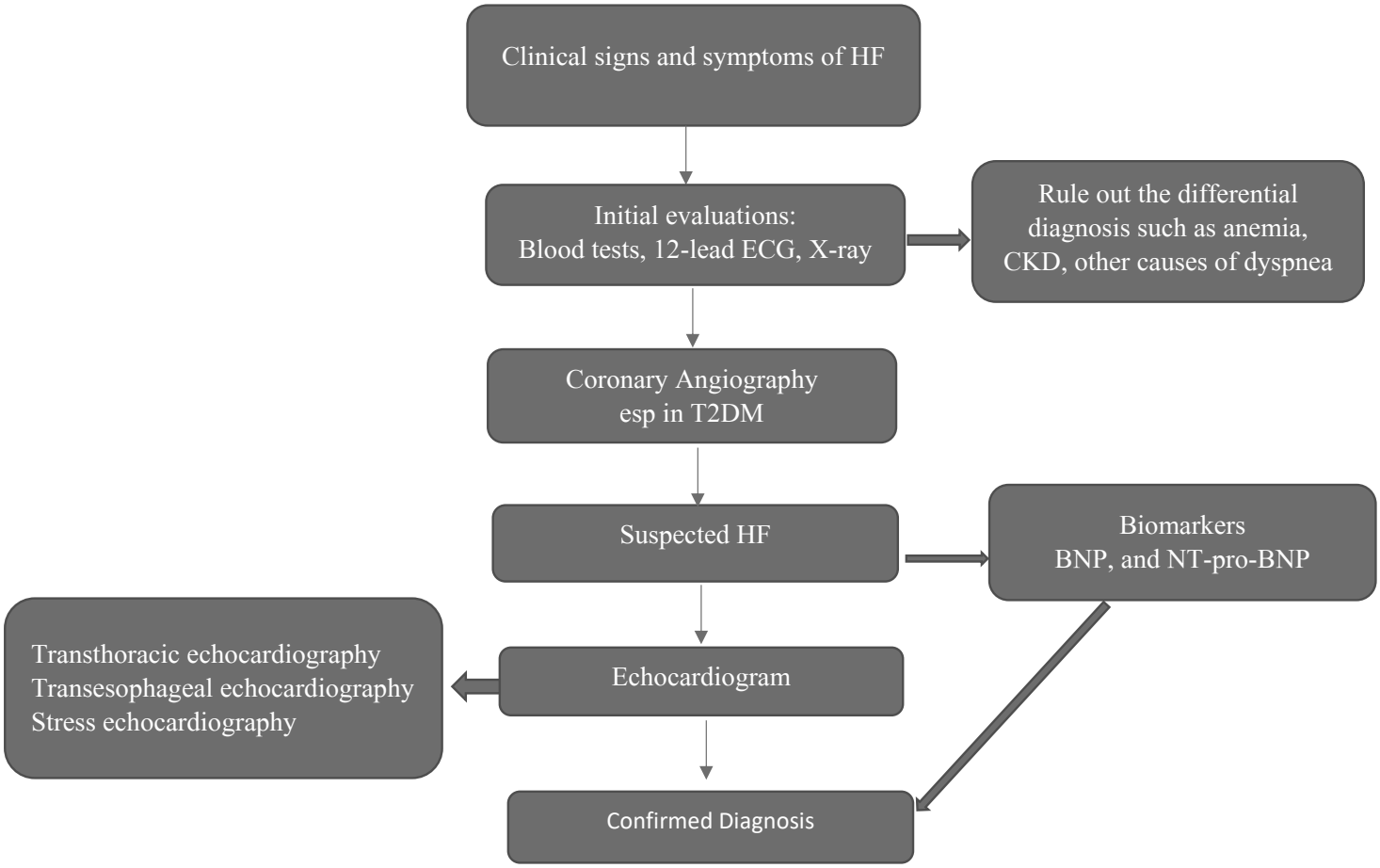
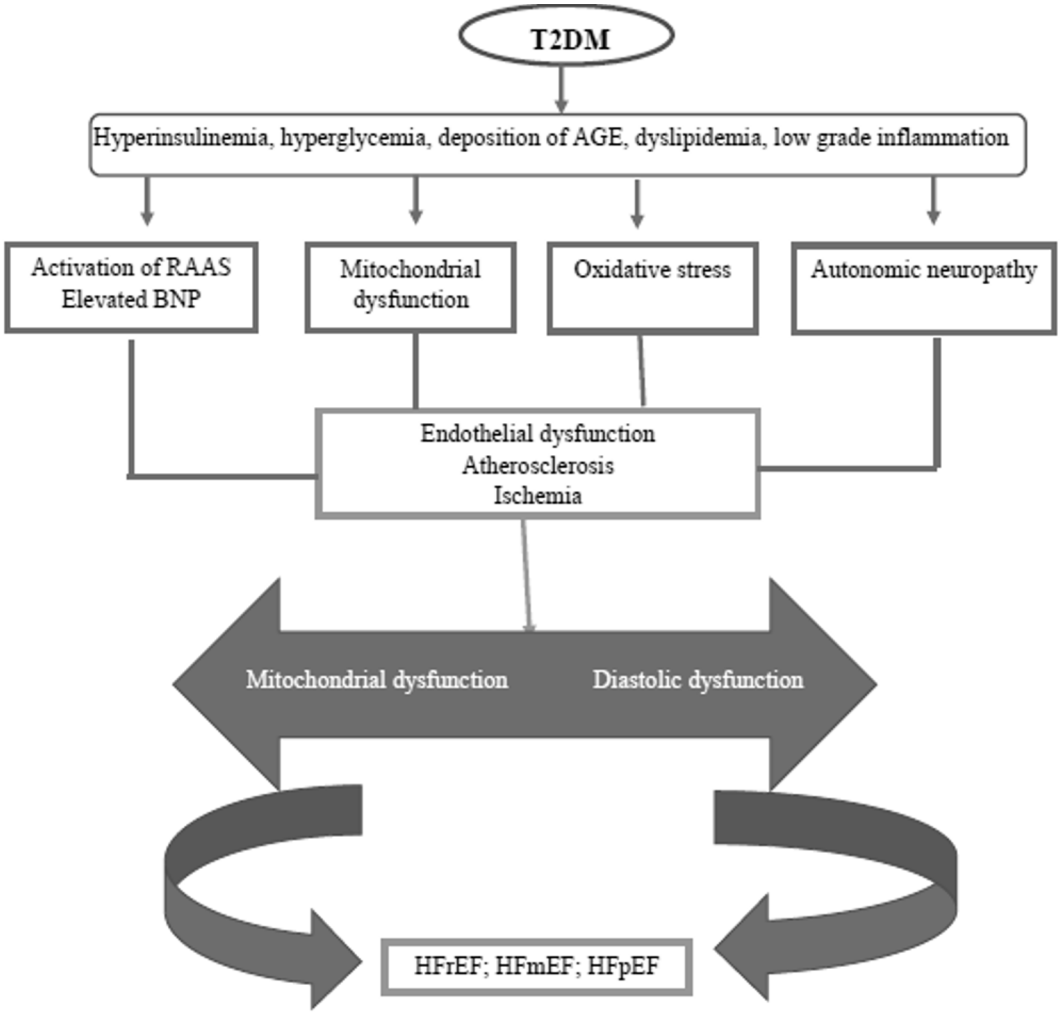
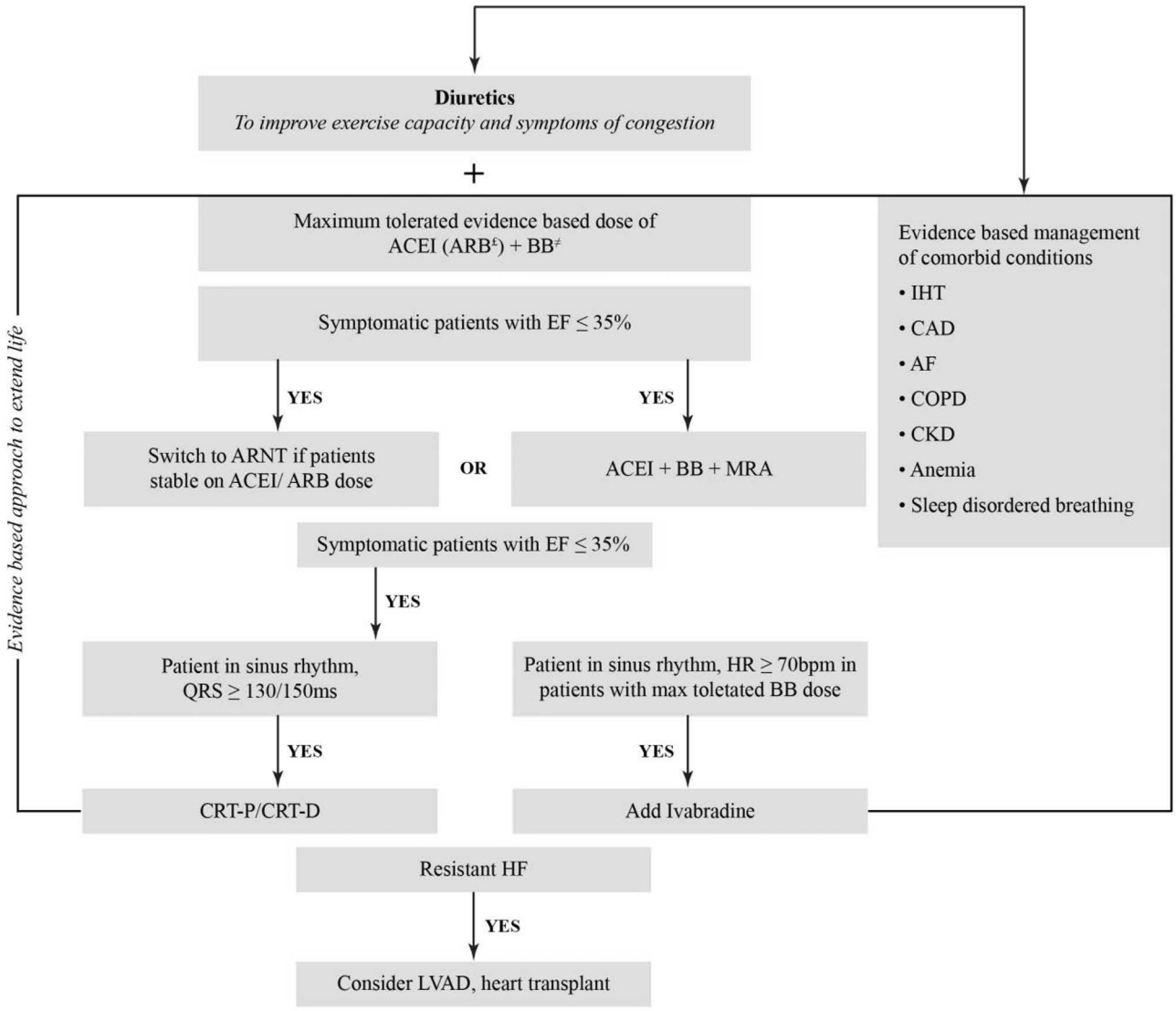


Figure 2: Pathophysiology of heart failure in type 2 diabetes mellitus



AGE: advanced glycation end products; ATP: adenosine triphosphate; BNP: B-type natriuretic peptide; FFA: free fatty acids; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; RAAS: renin-angiotensin-aldosterone system; T2DM: type 2 diabetes mellitus.

Figure 3. Algorithm for management of heart failure in type 2 diabetes mellitus



£If intolerant to ACEI. ≠Select from carvedilol, bisoprolol, metoprolol or nevivolol. *GLP-1 agonist with strongest CVD benifit: liraglutide>semaglutide>exenatide extended release, †SU with no CV risk: gliclazide, glimepiride. ‡Vildagliptin
ACEI: Angiotensin converting enzyme inhibitor; AF: Atrial fibrillation; ARB: Angiotensin II recevtor blocker; ARNI: angiotensin II receptor blocker neprilysin inhibitor; BB: Beta-blocker CAD: Coronary drtery disease; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease, CRT-P: Cardiac synchronization therapy-pace maker CRT-D: Cardiac synchronizapion therapy-defibnllator; EF: Ejection fraction; HF: heart failure; LVAD: ventricular assist device; MRA: Mineralocorticoid receptor antagonist

Adapted from: Kaul, U., Ray, S., Prabhakar, D. et al. Consensus document: management of heart failure in type 2 diabetes mellitus. Heart Fail Rev (2020).

References:

1. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol. 2018 Jun 8;17(1):83.

2. Chawla R, Madhu SV, Makkar BM, Ghosh S, Saboo B, Kalra S. RSSDI-ESI Clinical Practice Recommendations for the Management of Type 2 Diabetes Mellitus 2020. Indian J Endocrinol Metab. 2020;24(1):1–122.

3. Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. Lancet Lond Engl. 2012 Jun 16;379(9833):2279–90.

4. Kodama S, Fujihara K, Horikawa C, Sato T, Iwanaga M, Yamada T, et al. Diabetes mellitus and risk of new-onset and recurrent heart failure: a systematic review and meta-analysis. ESC Heart Fail. 2020 Oct;7(5):2146–74.

5. Lawson CA, Solis-Trapala I, Dahlstrom U, Mamas M, Jaarsma T, Kadam UT, et al. Comorbidity health pathways in heart failure patients: A sequences-of-regressions analysis using cross-sectional data from 10,575 patients in the Swedish Heart Failure Registry. PLoS Med. 2018 Mar;15(3):e1002540.

6. Parry HM, Deshmukh H, Levin D, Van Zuydam N, Elder DHJ, Morris AD, et al. Both high and low HbA1c predict incident heart failure in type 2 diabetes mellitus. Circ Heart Fail. 2015 Mar;8(2):236–42.

7. Devarajan A, Karuppiah K, Venkatasalam R, Avasarala S, Subramanian S, Immaneni S, et al. Heart failure in people with type 2 diabetes vs. those without diabetes: A retrospective observational study from South India. Diabetes Metab Syndr. 2021 Feb;15(1):39–43.

8. Lawson CA, Testani JM, Mamas M, Damman K, Jones PW, Teece L, et al. Chronic kidney disease, worsening renal function and outcomes in a heart failure community setting: A UK national study. Int J Cardiol. 2018 Sep 15;267:120–7.

9. Patel S, Nanda R, Abraham J, Sahoo S, Ganguly A, Mohapatra E (2017) Prediabetes and undiagnosed diabetes mellitus: the hidden danger. Indian J Med Biochem 21:91–95.

10. Tietjens JR, Claman D, Kezirian EJ, De Marco T, Mirzayan A, Sadroonri B, et al. Obstructive Sleep Apnea in Cardiovascular Disease: A Review of the Literature and Proposed Multidisciplinary Clinical Management Strategy. J Am Heart Assoc. 2019 Jan 8;8(1):e010440.

11. Levelt E, Mahmod M, Piechnik SK, Ariga R, Francis JM, Rodgers CT, et al. Relationship Between Left Ventricular Structural and Metabolic Remodeling in Type 2 Diabetes. Diabetes. 2016 Jan;65(1):44–52.

12. Brown AJM, Gandy S, McCrimmon R, Houston JG, Struthers AD, Lang CC. A randomized controlled trial of dapagliflozin on left ventricular hypertrophy in people with type two diabetes: the DAPA-LVH trial. Eur Heart J. 2020 Sep 21;41(36):3421–32.

13. Dofetilide in patients with left ventricular dysfunction and either heart failure or acute myocardial infarction: rationale, design, and patient characteristics of the DIAMOND studies. Danish Investigations of Arrhythmia and Mortality ON Dofetilide. Clin Cardiol. 1997 Aug;20(8):704–10.

14. Gustafsson I, Brendorp B, Seibaek M, Burchardt H, Hildebrandt P, Køber L, et al. Influence of diabetes and diabetes-gender interaction on the risk of death in patients hospitalized with congestive heart failure. J Am Coll Cardiol. 2004 Mar 3;43(5):771–7.

15. Lehrke M, Marx N. Diabetes Mellitus and Heart Failure. Am J Med. 2017 Jun 1;130(6, Supplement):S40–50.

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 Jun;29(11):1377–85.

17. Dewan P, Jhund PS, Shen L, Petrie MC, Abraham WT, Atif Ali M, et al. Heart failure with reduced ejection fraction: comparison of patient characteristics and clinical outcomes within Asia and between Asia, Europe and the Americas. Eur J Heart Fail. 2019 May;21(5):577–87.

18. Matsue Y, Suzuki M, Nakamura R, Abe M, Ono M, Yoshida S, et al. Prevalence and prognostic implications of pre-diabetic state in patients with heart failure. Circ J Off J Jpn Circ Soc. 2011;75(12):2833–9.

19. Dunlay Shannon M., Givertz Michael M., Aguilar David, Allen Larry A., Chan Michael, Desai Akshay S., et al. Type 2 Diabetes Mellitus and Heart Failure: A Scientific Statement From the American Heart Association and the Heart Failure Society of America: This statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. Circulation. 2019 Aug 13;140(7):e294–324.

20. Mohan V, Venkatraman JV, Pradeepa R. Epidemiology of cardiovascular disease in type 2 diabetes: the Indian scenario. J Diabetes Sci Technol. 2010 Jan 1;4(1):158–70.

21. King P, Peacock I, Donnelly R. The UK Prospective Diabetes Study (UKPDS): clinical and therapeutic implications for type 2 diabetes. Br J Clin Pharmacol. 1999 Nov;48(5):643–8.

22. 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 Jun 12;358(24):2560–72.

23. Hayward RA, Reaven PD, Wiitala WL, Bahn GD, Reda DJ, Ge L, et al. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015 Jun 4;372(23):2197–206.

24. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. JAMA. 2014 Dec 24;312(24):2668–75.

25. Abdelgadir E, Ali R, Rashid F, Bashier A. Effect of Metformin on Different Non-Diabetes Related Conditions, a Special Focus on Malignant Conditions: Review of Literature. J Clin Med Res. 2017 May;9(5):388–95.

26. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016 Jul 14;37(27):2129–200.

27. Tahrani AA, Varughese GI, Scarpello JH, Hanna FWF. Metformin, heart failure, and lactic acidosis: is metformin absolutely contraindicated? BMJ. 2007 Sep 8;335(7618):508–12.

28. Imam TH. Changes in metformin use in chronic kidney disease. Clin Kidney J. 2017 Jun;10(3):301–4.

29. Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, et al. Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes: The CAROLINA Randomized Clinical Trial. JAMA. 2019 Sep 19;

30. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016 Jul 28;375(4):311–22.

31. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016 Nov 10;375(19):1834–44.

32. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2017 Sep 28;377(13):1228–39.

33. 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 Dec 3;373(23):2247–57.

34. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB, Granger CB, Jones NP, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular

disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet Lond Engl. 2018 Oct 27;392(10157):1519–29.

35. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet Lond Engl. 2019 Jul 13;394(10193):121–30.

36. 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 Jul 16;373(3):232–42.

37. 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 Oct 28;130(18):1579–88.

38. 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 Oct 3;369(14):1327–35.

39. McMurray JJV, Ponikowski P, Bolli GB, Lukashevich V, Kozlovski P, Kothny W, et al. Effects of Vildagliptin on Ventricular Function in Patients With Type 2 Diabetes Mellitus and Heart Failure: A Randomized Placebo-Controlled Trial. JACC Heart Fail. 2018 Jan;6(1):8–17.

40. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Lond Engl. 2019 Jan 5;393(10166):31–9.

41. 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 Nov 26;373(22):2117–28.

42. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380(4):347–57.

43. Mahaffey KW, Neal B, Perkovic V, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Circulation. 2018 Jan 23;137(4):323–34.

44. Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RHM, et al. Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus. Circulation. 2019 May 28;139(22):2528–36.

45. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381(21):1995–2008.

46. Anker SD, Butler J, Filippatos G, Khan MS, Marx N, Lam CSP, et al. Effect of Empagliflozin on Cardiovascular and Renal Outcomes in Patients With Heart Failure by Baseline Diabetes Status: Results From the EMPEROR-Reduced Trial. Circulation. 2021 Jan 26;143(4):337–49.

47. Kaplinsky E. DAPA-HF trial: dapagliflozin evolves from a glucose-lowering agent to a therapy for heart failure. Drugs Context [Internet]. 2020 Feb 28 [cited 2021 Mar 30];9.

48. Singh AK, Unnikrishnan AG, Zargar AH, Kumar A, Das AK, Saboo B, et al. Evidence-Based Consensus on Positioning of SGLT2i in Type 2 Diabetes Mellitus in Indians. Diabetes Ther Res Treat Educ Diabetes Relat Disord. 2019 Apr;10(2):393–428.

49. Commissioner O of the. FDA approves new treatment for a type of heart failure [Internet]. FDA. FDA; 2020 [cited 2021 Apr 20]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-type-heart-failure

50. Berg DD, Jhund PS, Docherty KF, Murphy SA, Verma S, Inzucchi SE, et al. Time to Clinical Benefit of Dapagliflozin and Significance of Prior Heart Failure Hospitalization in Patients With Heart Failure With Reduced Ejection Fraction. JAMA Cardiol. 2021 Feb 17;

51. Pereira MJ, Eriksson JW. Emerging Role of SGLT-2 Inhibitors for the Treatment of Obesity. Drugs. 2019;79(3):219–30.

52. Smyth S, Heron A. Diabetes and obesity: the twin epidemics. Nat Med. 2006 Jan;12(1):75–80.

53. 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 Aug 20;159(4):262–74.

54. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care. 2009 Apr;32(4):650–7.

55. Baruah MP, Makkar BM, Ghatnatti VB, Mandal K. Sodium Glucose Co-transporter-2 Inhibitor: Benefits beyond Glycemic Control. Indian J Endocrinol Metab. 2019;23(1):140–9.

56. Rosano GM, Vitale C, Seferovic P. Heart Failure in Patients with Diabetes Mellitus. Card Fail Rev. 2017 Apr;3(1):52–5.

57. Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, et al. Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes. N Engl J Med. 2017 Aug 24;377(8):723–32.

58. Mukherjee JJ, Ray S, Singh AK, Ghosh D, Hazra PK, Gangopadhyay KK, Majumdar S et al. Consensus Recommendations for Clinical Practice: Management of Glycemia in a Person with Type 2 Diabetes Mellitus with Heart Failure: An Indian Perspective. J Assoc Physicians India. 2019;Aug 67.

59. Tai C, Gan T, Zou L, Sun Y, Zhang Y, Chen W, et al. Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular events in patients with heart failure: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord. 2017 Oct 5;17(1):257.

60. Kristensen SL, Preiss D, Jhund PS, Squire I, Cardoso JS, Merkely B, et al. Risk Related to Pre-Diabetes Mellitus and Diabetes Mellitus in Heart Failure With Reduced Ejection Fraction: Insights From Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial. Circ Heart Fail. 2016 Jan;9(1).

61. Komajda M, Tavazzi L, Francq BG, Böhm M, Borer JS, Ford I, et al. Efficacy and safety of ivabradine in patients with chronic systolic heart failure and diabetes: an analysis from the SHIFT trial. Eur J Heart Fail. 2015 Dec;17(12):1294–301.

62. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2016 Aug 1;37(29):2315–81.

63. Shah A, Gandhi D, Srivastava S, Shah KJ, Mansukhani R. Heart Failure: A Class Review of Pharmacotherapy. Pharm Ther. 2017 Jul;42(7):464–72.

64. Shekelle PG, Rich MW, Morton SC, Atkinson CSW, Tu W, Maglione M, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials. J Am Coll Cardiol. 2003 May 7;41(9):1529–38.

65. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet Lond Engl. 2003 Sep 6;362(9386):777–81.

66. Tsujimoto T, Sugiyama T, Shapiro MF, Noda M, Kajio H. Risk of Cardiovascular Events in Patients With Diabetes Mellitus on β-Blockers. Hypertens Dallas Tex 1979. 2017 Jul;70(1):103–10.

67. Zheng SL, Chan FT, Nabeebaccus AA, Shah AM, McDonagh T, Okonko DO, et al. Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Heart Br Card Soc. 2018 Mar;104(5):407–15.

68. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2019 Oct 24;381(17):1609–20.

69. Choi H-M, Park M-S, Youn J-C. Update on heart failure management and future directions. Korean J Intern Med. 2019 Jan;34(1):11–43.

70. Gustafsson F, Guarracino F, Schwinger RHG. The inodilator levosimendan as a treatment for acute heart failure in various settings. Eur Heart J Suppl J Eur Soc Cardiol. 2017 Mar;19(Suppl C):C2–7.

71. Hutchings DC, Anderson SG, Caldwell JL, Trafford AW. Phosphodiesterase-5 inhibitors and the heart: compound cardioprotection? Heart Br Card Soc. 2018 Aug;104(15):1244–50.

72. Teerlink JR, Felker GM, McMurray JJV, Solomon SD, Adams KF, Cleland JGF, et al. Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): a phase 2, pharmacokinetic, randomised, placebo-controlled trial. Lancet Lond Engl. 2016 Dec 10;388(10062):2895–903.

73. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018 Sep 13;379(11):1007–16.

74. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017 Sep 21;377(12):1119–31.

75. Cleland JGF, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J. 2006 Oct;27(19):2338–45.

76. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. JAMA. 2013 Feb 27;309(8):781–91.

77. Flather MD, Shibata MC, Coats AJS, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005 Feb;26(3):215–25.

78. Bangdiwala SI, Weiner DH, Bourassa MG, Friesinger GC, Ghali JK, Yusuf S. Studies of Left Ventricular Dysfunction (SOLVD) Registry: rationale, design, methods and description of baseline characteristics. Am J Cardiol. 1992 Aug 1;70(3):347–53.

79. Okumura N, Jhund PS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, et al. Effects of Sacubitril/Valsartan in the PARADIGM-HF Trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) According to Background Therapy. Circ Heart Fail. 2016 Sep;9(9).

80. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet Lond Engl. 1999 Jan 2;353(9146):9–13.

81. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet Lond Engl. 1999 Jun 12;353(9169):2001–7.

VISION STATEMENT

To be recognized as a global leader for clinical care, education, training, research, advocacy and capacity building in the field of diabetes.

MISSION STATEMENT

1. Promotion of excellence in diabetes care to make India the Diabetes Care Capital
2. Empowerment of persons living with diabetes
3. Support for diabetes research
4. Dissemination of information and knowledge in diabetes care
5. Advocacy for the cause of diabetology

NEW EXECUTIVE COMMITTEE AND OFFICE BEARERS 2021

Patrons of RSSDI

Dr. H.B. Chandalia, Mumbai
Dr. C. Munichhoodappa, Bengaluru
Dr. Ashok K. Das, Puducherry
Dr. Binode K. Sahay, Hyderabad
Dr. V. Seshiah, Chennai
Dr. P.V Rao, Hyderabad
Dr. Jitendra Singh, New Delhi
Dr. V Mohan, Chennai
Dr. Vinod Kumar, New Delhi

President

Dr. Banshi Saboo, Ahmedabad

President Elect

Dr. Ch.Vasanth Kumar, Hyderabad

Immediate Past President

Dr. Rajeev Chawla, New Delhi

Secretary

Dr. Sanjay Agarwal, Pune

Vice-President

Dr. Anuj Maheshwari, Lucknow

Vice-President

Dr. Vijay Viswanathan, Chennai

Joint Secretary

Dr. Sujoy Ghosh, Kolkata

Treasurer

Dr. Sunil Gupta, Nagpur

Executive Committee

Dr. C R Anand Moses, Chennai
Dr. Sudhir Bhandari, Jaipur
Dr. J K Sharma, New Delhi
Dr. Bikash Bhattacharjee, Guwahati
Dr. Pratap Jethwani, Rajkot
Dr. L. Sreenivasa Murthy, Bengaluru
Dr. Sanjay Reddy, Bengaluru
Dr. Shalini Jaggi, New Delhi

Co-opted

Dr. Vijay Panikar, Mumbai
Dr. Brij Makkar, New Delhi
Dr. Rakesh Sahay, Hyderabad

TRAINEE GRANTS (Up to 10 grants)

Research Grants upto INR 200000 to support outstanding thesis/ research work by first year MD/DNB/ PHD students/Research fellows from India.

Eligibility Criteria
All Postgraduates in First year MD, DM /DNB from any of the institutions in the country are eligible to apply

How to apply?
Send in your Research proposals by email to the RSSDI Secy/ Chairman research committee by email/ apply directly on web site.

Research proposal should have following proofs-

1. A supporting letter from your guide/ head of department stating that this is a bonafide project for your thesis and also mentioning the dates of you joining the program and expected date of graduation. The guide must also state that he/she will stand guarantee for the work done
2. A detailed budget
3. Thesis proposal approved by the department/appropriate institutional authority
4. Approval by the ethics committee

Selection Process
Proposals will be reviewed by the research committee of the RSSDI.

Disbursement of Grant
A minimum of 50% of the grant amount will be disbursed initially. Further disbursement will be done annually based on submission of progress reports on the work done and utilisation of sanctioned amount. These reports must be filed to the secretary of the RSSDI

Responsibility:
All grant awardees are expected to present their work at RSSDI Annual Conference during research presentation's session. Failure to file progress reports annually and when requested by the RSSDI and failure to present progress at RSSDI Annual conf may result in the forfeiture of the grant.

All awardees are expected to follow the tenets of responsible and ethical conduct of research. Unethical or fraudulent use of RSSDI research funds will warrant adverse action from the society including

forfeiture of grant, black listing in the society's databases and other legal recourses that are available to the society.

Publication
The RSSDI expects that the grant source be acknowledged in all publications and submissions made with regards to the research done with the grant.

All awardees are encouraged to submit their work to the RSDDI Journal IJDDC

CALL for RESEARCH PROPOSALS for GRANTS (up to 5 lacs)

Research proposals are invited from Indian scientists, who are members of RSSDI interested in conducting research in the field of Diabetes, Endocrinology& Metabolism, for funding by RSSDI

The proposals may of clinical or translational research importance. A maximum grant amount of INR 5 Lakhs will be sanctioned. All grants will be reviewed by the research committee.

The detailed proposals should include the following:
Title, names of principal and co investigators, summary, introduction/ background, review of literature, aims, methodology, study design and detailed plan of work & bibliography.

Brief biodata of principal investigator and other co-investigators.

Importance of work
Detailed Budget sought along with full justification/ proposed utilization, of funding sought from RSSDI

Whether the project is being partly funded from any other source? If yes, please mention the source and the amount received.

Ethics Committee clearance of the Institution or other bonafide body.

How to apply
All applications should be addressed to:
1. The Secretary , RSSDI
2. Soft copy of the research proposal should be sent to Secretary, RSSDI

When to apply
Proposals will be accepted Twice a year. Once between 1st Jan - 31st April & then July 1st to 30th Nov.

All research proposals will be reviewed by Research committee over a period of 4-6 weeks & approved proposals will be provided Research Grant after fulfilling all documentation by 30th June & then 31st December of each year.

MAJOR RESEARCH GRANT PROPOSALS- usually not more than one at a given time.

Above 10 Lacs upto a total amount of 50 Lacs will be Granted to RSSDI initiated, owned, multi-centric, clinical or translational research, having long term application of scientific and clinical findings, which can translate into strategies for improving health-care delivery, patient outcomes, and community health in India.

Such research proposals will be carried out in only centres with research capabilities across India.

TRAVEL GRANTS FOR YOUNG DIABETES RESEARCHERS TO ATTEND INTERNATIONAL CONFERENCES

Criteria for the travel grant are as follows:

- Applicant should apply 2 months in advance.
- Travel Grant is open only to the RSSDI members.
- Applicant should submit Oral paper / Poster acceptance document to RSSDI Secretariat.
- Applicant should submit Declaration that he/she has not receiving grant from any other agency / Organization – In case of receiving grant from any other Organization, RSSDI shall pay only the exceeding amount not covered by that agency.

ADVANCED CERTIFICATE COURSE IN DIABETOLOGY

(IN ASSOCIATION WITH JAIPUR NATIONAL UNIVERSITY)

Research Society for the Study of Diabetes in India (RSSDI) was founded by Prof. M.M.S. Ahuja in 1972. RSSDI is the largest body of professional doctors and researchers in Asia, working in the area of Diabetes & is the National Body recognized by IDF (International Diabetes Federation). One of the key areas of focus is to train doctors at all levels to better manage Diabetes and its complications. RSSDI recognizes this problem and runs a well-structured, full time, residential "Advanced Certificate Course in Diabetology". This two-year course is like any other post graduate course and has immensely helped doctors to practice better diabetes care. RSSDI has

List of RSSDI Accredited Centres

Sl. No	Institute Name	Institute Location
1.	Diacon Hospital	Bangalore, Karnataka
2.	North Delhi Diabetes Centre	New Delhi, Delhi
3.	Prithvi Hospital	Tumkur, Karnataka
4.	Total Diabetes Hormone Institute	Indore, Madhya Pradesh
5.	Dia Care - A Complete Diabetes Care Centre	Ahemdabad, Gujarat
6.	Sonal Diabetes Hospital	Surat, Gujarat
7.	Jothydev's Diabetes and Research Center	Trivandrum, Kerala
8.	Advanced Endocrine & Diabetes Hospital	Hyderabad, Telangana
9.	Sunil's Diabetes Care N' Research Centre	Nagpur, Maharashtra
10.	Marwari Hospital and Research Centre	Guwahati, Assam
11.	Down Town Hospital	Guwahati, Assam
12.	St.Theresa's Hospital	Hyderabad, Telangana
13.	Aegle Clinic	Pune, Maharashtra
14.	Lilavati Hospital & Research Centre	Bandra West, Mumbai
15.	Srajan Hospital	Udaipur, Rajasthan
16.	Endeavour Clinics & Dr. Sambit's Centre of Diabetes and Endocrinology	Bhubaneswar, Odisha
17.	ILS Hospital, Salt Lake	Salt Lake City, Kolkata
18.	Belle Vue Clinic	Dr. U N Brahmacahri Sreet, Kolkata
19.	Arthur Asirvatham Hospital	Mdurai, Tamil Nadu
20.	M V Hospital for Diabetes	Chennai, Tamilnadu
21.	Sarvodaya Hospital and Research Centre	Faridabad, Uttar Pradesh
22.	Galaxy Speciality Centre	Sodala, Jaipur

carefully looked into all aspects of this course & has accredited & recognized 22 centres across India at present and more centers are being inspected for accreditation. National Faculties and experts of RSSDI chosen from Academia visit these centers from time to time to ensure high standards. Now this Advanced Certificate Course has Dual Accreditation from RSSDI and Jaipur National University.

COURSE DETAILS

Name of the Course: Advanced Certificate Course in Diabetology

Duration: 2 Years – Post MBBS & 1 Year - Post MD / DNB (Gen - Medicine)* (Full Time) Educational.

Qualification: A candidate must possess MBBS degree from ANY of the recognized university approved by Medical Council of India (*The duration of the course is 1 Year for those with MD/ DNB in Internal Medicine. Candidates having MD degree in other specialties will have to do the course over 2 Years).

Number of seats: 2 seats per year for every eligible teacher as per rules of Medical Council of India (MCI).

Selection of Candidates: Selection for the Certificate course is through a performance evaluation by Theory test for 90 marks (90 minutes duration) which is conducted at all accredited centres. The result is displayed WITHIN 3 days on the Web site of JNU and RSSDI. Post MD (Internal Medicine) will be given !

COURSE FEES:

- Rs 30000/- (for post MD/DNB (internal medicine), 1 year program)
- Rs. 50000/- (for post MBBS, MD in other branches, 2 years program)

Session: Two sessions are run annually, in January and in July. Prospectus details are available on the RSSDI website. All applications must be sent to Jaipur National University.

Dates for Admission in ACCD 2021

1) Last date of submission of Application Form – 30th June 2021
2) Screening Interview - 7th July 2021
3) Declaration of Interview Result – 10th July 2021
4) Last date of payment of course fee - 15th July 2021
5) Commencement of course - 16th July 2021

ANNOUNCEMENTS

Dear Member,

Please update your Membership details like Complete Postal Address, Email Id, Pan No. & Mobile no. after log in your membership area on our website www.rssdi.in under sub heading Membership corner, so that we can send you RSSDI Newsletter & Journals.

49th Annual Conference of RSSDI-RSSDI 2021

Date: 11th - 14th November 2021

Adis included

Springer for Hospitals & Health

Results Matter. Choose Springer.

- 12 Medical Specialty Collections
- Immediate Access to Quality Medical & Biomedical Content
- Custom Business Models

Content Solutions

- Biomedicine
- Internal Medicine & Dermatology
- Neurology
- Nuclear Medicine
- Oncology & Hematology
- Orthopedics
- Pathology
- Pharmacology & Toxicology
- Public Health
- Radiology
- Surgery & Anesthesiology
- Urology & Gynecology

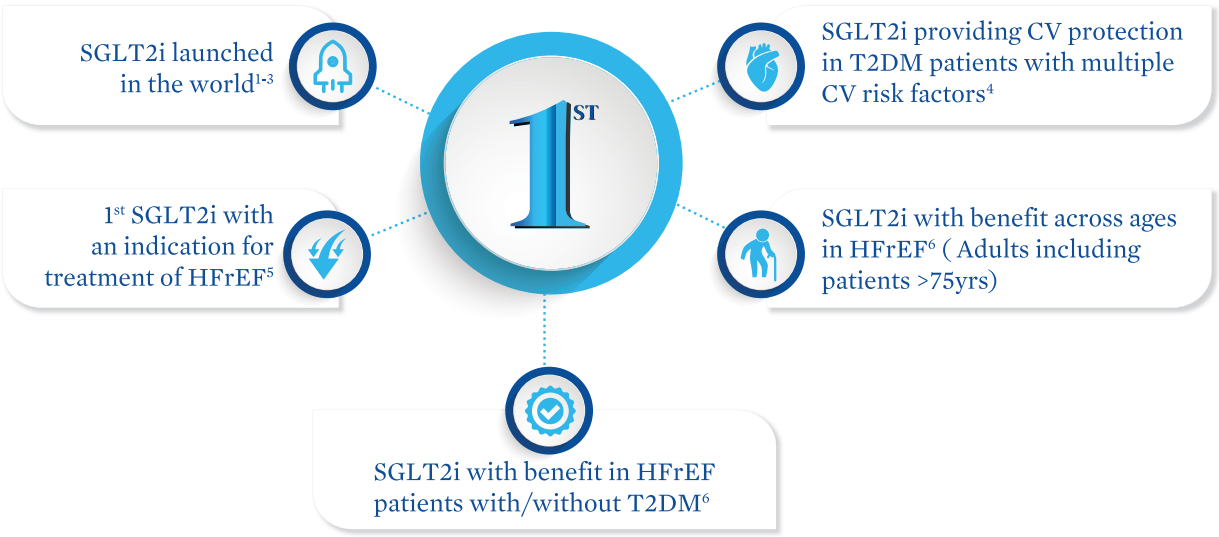
health.springer.com

For HFrEF patients with or without diabetes,

Gledepa®

Dapagliflozin Tablets 10mg

PRESCRIBE 1ST PROTECT THROUGHOUT



SGLT2i: Sodium-glucose cotransporter 2 inhibitor; hHF: Hospitalisation due to heart failure; HFrEF: Heart failure with reduced ejection fraction; T2DM: Type 2 diabetes mellitus; CV: Cardio-vascular

References:
1. https://www.ema.europa.eu/en/medicines/human/EPAR/forxiga. Accessed on 20-Aug-20
2. https://www.ema.europa.eu/en/medicines/human/EPAR/invokana. Accessed on 20-Aug-20>
3 https://www.ema.europa.eu/en/medicines/human/EPAR/jardiance#:~:text=The%20European%20Commission%20granted%20a,contact%20your%20doctor%20or%20pharmacist. Accessed on 20-Aug-20
4. Supplementary appendix to: Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347-357.
5. https://cdsco.gov.in/opencms/opencms/system/modules/CDSCOWEB/elements/common_download.jsp?num_id_pk=MTA4NQ==
6. McMurray JJ et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. New England Journal of Medicine. 2019 Nov 21;381(21):1995-2008.

For the use of a Registered Medical Practitioner (For T2DM, Heart Failure) / Nephrologist (For CKD) or a hospital or a laboratory only.
Abbreviated Prescribing Information

Gledepa®

Rx
Dapagliflozin Tablets
Gledepa® 5mg & 10 mg
GLEDEPA® is available as a film-coated tablet for oral administration.
Composition: Each film coated tablet contains: Dapagliflozin propanediol monohydrate equivalent to Dapagliflozin 5 mg or 10 mg, Titanium Dioxide IP & Iron oxide yellow Ph.Eur. **Mechanism of action:** Dapagliflozin is a highly potent, selective, and reversible inhibitor of sodium-glucose cotransporter 2 (SGLT2) that improves glycemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption leading to urinary excretion of excess glucose (glucuresis). GLEDEPA® is orally available and requires once-daily dosing. **INDICATIONS AND USAGE: Type II Diabetes Mellitus :** In adults aged 18 years and older with type II diabetic mellitus to improve glycemic control. As mono-therapy when diet and exercise alone do not provide adequate glycemic control in patients for whom use of metformin is considered in appropriate due to intolerance. As add on combination therapy in combination with other glucose–lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycemic control. For study results with respect to combination of therapies, effects on glycemic control and cardiovascular events and the population studied, see sections 4.4,4.5 and 5.1 (for Gledepa 10mg). **Heart Failure :** GLEDEPA is indicated in adults for the treatment of heart failure with reduced ejection fraction (see section 5.1; for 10mg) **Chronic kidney disease** (For 10mg) : Gledepa is indicated in adults for the treatment of patients of Chronic Kidney Disease (CKD) up to Stage III (eGFR of greater than or equal to 30ml/min/1.73m2). GLEDEPA® is not indicated for use in patients with type 1 diabetes. GLEDEPA® should not be used for the treatment of diabetic ketoacidosis For Heart failure patients GLEDEPA® can be used in patients with eGFR ≥ 30 mL/min/1.73 m2. Patients with eGFR ≤ 30 ml/min/1.73m2 were excluded from clinical study. **DOSAGE AND ADMINISTRATION:** The recommended dose of GLEDEPA® is 10 mg taken once daily at any time of the day regardless of meals. **Monotherapy and Add-On Combination Therapy** The recommended dose of GLEDEPA® is 10 mg once daily as monotherapy or as add-on to combination therapy with metformin (with or without SU), a thiazolidinedione, a sulfonylurea, a DPP4-inhibitor (with or without metformin), or insulin (with or without oral antidiabetic therapy, either metformin plus insulin dual therapy or metformin plus sulfonylurea plus insulin triple therapy). **Cardiovascular and renal outcomes (DECLARE)** *Heart failure or cardiovascular death* Dapagliflozin 10 mg demonstrated superiority versus placebo in preventing the composite of hospitalization for heart failure or cardiovascular death .The difference in treatment effect was driven by hospitalization for heart failure , with no difference in cardiovascular death. *Major adverse cardiovascular events (MACE)* Dapagliflozin 10mg demonstrated non-inferiority versus placebo for the composite of cardiovascular death, myocardial infarction or ischemic stroke (one-sided p <0.001). *Nephropathy* Dapagliflozin reduced the incidence of events of the composite of confirmed sustained eGFR decrease, end-stage renal disease, renal or cardiovascular death. *Heart Failure* Gledepa 10 mg was superior to placebo in preventing CV death and worsening heart failure, with consistent treatment effect on primary and secondary endpoints. Gledepa also reduced the total number of events of hospitalizations for heart failure (first and recurrent) and cardiovascular death. Chronic Kidney Disease Gledepa 10mg was superior to placebo in reducing the incidence of the primary composite endpoint of ≥50% sustained decline in eGFR, reaching ESKD, CV or renal death (HR 0.61 [95% CI 0.51, 0.72]; p<0.0001). **Special warnings and special precautions for use Renal Impairment** There is a limited experience with initiating treatment with Gledepa in patients with eGFR<25mL/min/1.732. The glucose lowering efficacy of Dapagliflozin is dependent on renal function and is reduced in patients where eGFR is <45mL/min/1.73m2. **Ketoacidosis in patients with diabetes mellitus** Patients treated with GLEDEPA® who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/l (250 mg/dl). If ketoacidosis is suspected, discontinuation or temporary interruption of GLEDEPA should be considered and the patient should be promptly evaluated. **Use with medications known to cause hypoglycemia** Insulin and insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with GLEDEPA in patients with type 2 diabetes mellitus **CONTRAINDICATIONS:** GLEDEPA® is contraindicated in patients with a history of any serious hypersensitivity reaction to the active substance or to any of the excipients. **PREGNANCY and LACTATION:** GLEDEPA must not be used in the second and third trimesters of pregnancy. When pregnancy is detected, GLEDEPA should be discontinued. GLEDEPA must not be used by a nursing woman **ADVERSE REACTIONS:** The common adverse reactions in patients treated with GLEDEPA 10 mg in clinical trials and postmarketing are Genital infection, Urinary tract infection, Diabetic ketoacidosis , Back pain, Pollakiuria and polyuria. **Incompatibilities:** Not applicable. Shelf life: **refer outer pack.** Storage: **Do not store above 30°C.** Pack size: **refer to outer carton. GLEDEPA® is a Registered Trademark of the AstraZeneca group of companies. For Further Information Contact: Abbott Healthcare Pvt. Ltd.** Angel Space, Bldg. D-4, Gala No. 1 to 6 & 11 to 16 Ground Floor, 101 to 106 & 111 to 116 First Floor, 201 to 206 & 211 to 216 2nd Floor, Pimplas, Dist. Thane, Bhiwandi - 421 302, India. **For more information refer full prescribing information Version 19 dated 4th February 2021**

Abbott Healthcare Pvt Ltd,
Floor 17th, Godrej BKC, Plot C-68, G-Block, Bandra Kurla Complex,
Near MCA Club, Bandra (East), Mumbai 400051. India

Abbott

Registered with Registrar of News Papers, India vide no. RNI-43019/85

International Journal of Diabetes in Developing Countries

Volume 41 | Supplement 1 | January–March 2021

Springer

IND2193443 11 JUN 2021