

Metformin: A Novel Drug and Helper for Heart Failure with Type 2 Diabetes

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Abstract

Heart failure (HF) is a complex clinical syndrome and it is one of the common cardiovascular complication seen in diabetes mellitus (DM). The coexistence of heart failure and diabetes is not rare and affects vice versa between severity of Diabetes and Heart Failure in complex pathophysiology. The management of diabetes in heart failure patients is carefully tackled in clinical setting due to different adverse reaction of oral hypoglycemic agents that may affect and worsen the condition of heart failure. So, the selection of the use of effective oral hypoglycemic agents in heart failure especially in patients with heart failure reduced ejection fraction (HFrEF) is very important to control the cardio-endocrinological benefit. Metformin is a biguanide class of antidiabetic medications, was first described in the scientific literature in 1922, as a product in the synthesis of N,N-dimethyl guanidine. Generally, the suppressive action of metformin on liver glucose production (hepatic gluconeogenesis) decreases blood glucose level. Recent multicenter observational studies show metformin is associated with lower mortality rate and reduced the hospitalization in heart failure. This article focuses the metabolic disturbances of Type 2 DM in heart failure and the safely usefulness metformin of in Type 2 diabetes with heart failure.

Keywords: Type 2 DM; Heart Failure; Oral Hypoglycemic Agents; Metformin

Introduction

Heart failure is a complex cardio-hormonal syndrome which affects overall around 2% of global population [1]. In the Reykjavik study in the general population, the prevalence of type 2 Diabetes patients who have heart failure that has been accounted to 12% [2]. Diabetes accelerates the natural course of atherosclerosis in all groups of patients and involves a greater number of coronary artery diseases with more diffuse atherosclerosis lesions leads to heart failure. The Framingham Heart Study showed that Diabetes are twice as likely to develop congestive heart failure in male compared to non-diabetes counterparts and had five-fold increase in the rate of congestive heart failure in female. According to CHARM trial, both HFrEF and HFpEF were more likely to die of all subtypes of cardiovascular death [i.e. death due to HF, sudden cardiac death (SCD), death due to MI and death due to stroke in patients with T2DM [3]. When it comes to oral hypoglycemic agents for controlling blood glucose level in heart failure patients, there is no significant multicenter randomize control trials showed that which antidiabetic drug is significantly benefit to use in HFrEF. Even though no RCTs in that unknown benefit/risk ratio, metformin is associated with lower mortality rates than sulphonylureas or insulin in observational studies [4].

Correlation of type 2 DM and heart failure

Diabetes-related left ventricular failure characterized by both systolic and diastolic dysfunction is caused by multifactorial etiologies. The pathophysiological mechanism leads to left ventricular impaired function in DM is caused by following:

1. Hypertension
2. Left ventricular hypertrophy

3. Obesity
4. Endothelial dysfunctions
5. Coronary atherosclerotic disease
6. Coronary microvasculature diseases
7. Autonomic dysfunctions
8. Metabolic abnormalities
9. Hypercoagulability.

Heart failure in a patient with diabetes may derive from myocardial damage resulting from an ischemic, thrombotic event. In this case, oxidation, endothelial dysfunction and glycation of atherogenic lipids, and the hypercoagulability of the blood are major contributors to the patient’s resulting heart failure shown in figure 1. In many cases, however, heart failure in patients with diabetes may have a non-thrombotic etiology and other pathophysiological factors are at play, as in the case of diabetic cardiomyopathy.

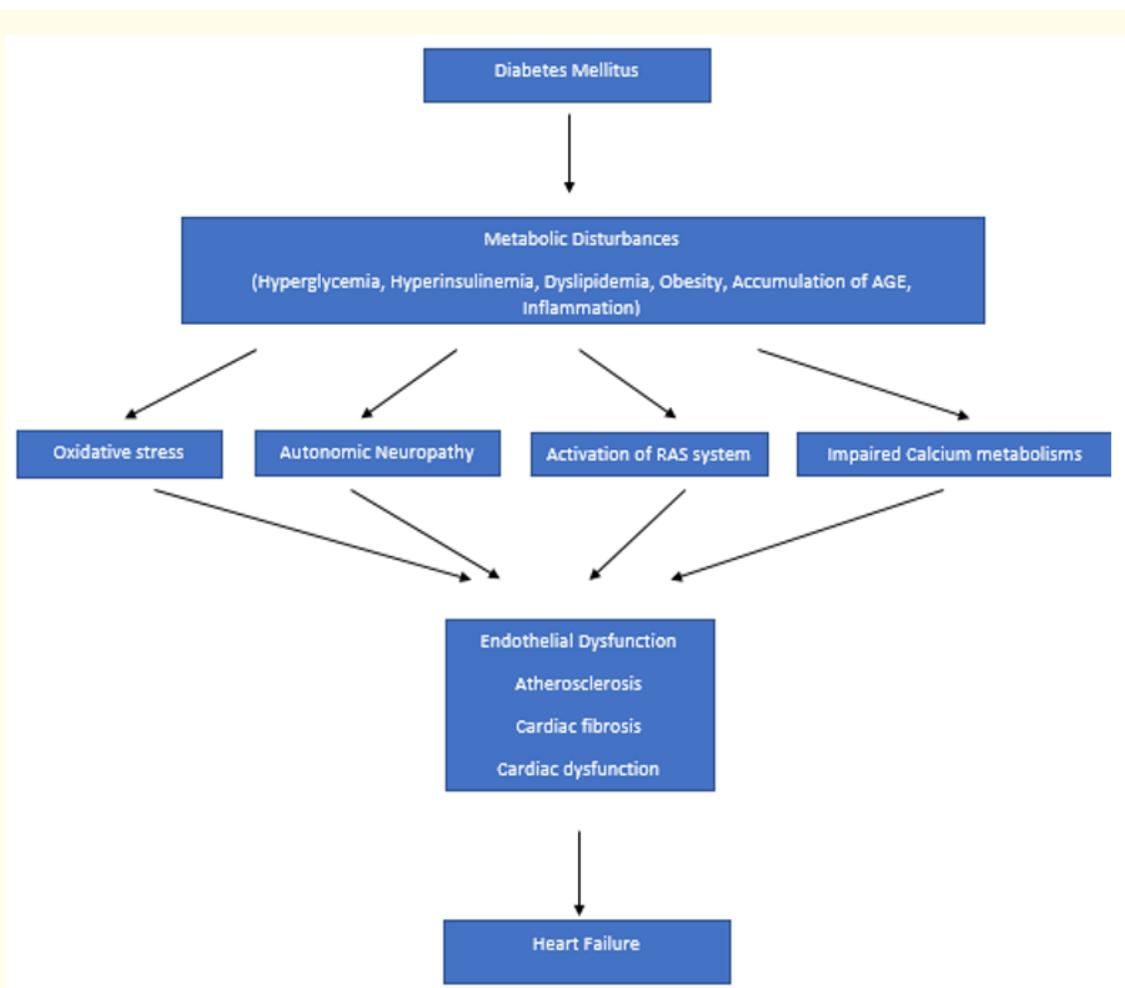


Figure 1: Mechanism of Diabetes Mellitus leading to Heart Failure

Diabetic cardiomyopathy is term used as myocardial disease in patients with diabetes that cannot be attributed to any other known CVD, such as hypertension or CAD [5]. Patients with diabetes are very vulnerable to heart failure and coronary artery diseases even early in the course of their disease because the structural and functional changes that occur in diabetic cardiomyopathy. Impaired early diastolic filling, prolonged isovolumetric relaxation, and increased atrial filling has caused eft ventricular diastolic dysfunction in young patients with type 1 diabetes. Histological studies of autopsy and biopsy specimens demonstrate that diabetic humans and animals made abnormal cardiac morphologies, including myocyte hypertrophy, perivascular fibrosis, and increased quantities of matrix collagen, myo-cellular lipid droplets, and cell membrane lipids [6,7].

In 1954, Lundbaek was the first to propose the existence of a specific diabetic heart muscle disease without involvement of CAD or hypertension. Two decades later, Rubler, *et al.* described diabetic-related post-mortem findings in four patients with T2DM, glomerulosclerosis and HFrEF with normal epicardial coronary arteries. This suggests that severity and duration of hyperglycemia are important for the development of left ventricular dysfunction.

Hypoglycemic agents in left ventricular failure

Trials of anti-diabetic agents are now designed to assess CV safety, but frequently HF is not included as a primary endpoint. However, HF in patients with diabetes is more frequent than other CV events and seems to be underestimated. A burning question is therefore if the most used trial design to monitor CV safety, i.e. non-inferiority, allows clinical translation of trial findings.

Sulfonylureas

Sulfonylureas is a pancreatic β -cells by binding to the sulfonylurea receptor 1, which is part of the Kir6.2 adenosine triphosphate-sensitive potassium channel. In available several observational studies show reduction of microvascular complications (UKPDS) University Group Diabetes Program shows that it increased CV mortality (UGDP trial). Preterax and Diamicon MR Controlled Evaluation (ADVANCE); and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials, in which sulfonylureas were highly represented in the intensive glucose-lowering arms, no increased CV risk was reported by the investigators [8]. Combination therapy in T2DM patients with and without CVD (if HbA1c target not achieved after 3 months of monotherapy with metformin). Precautions should be taken in patients with multiple comorbidities, ACS, HF, and advanced CKD (stages IV and V).

Thiazolidinediones

The glucose-lowering effect of thiazolidinediones is due to their ability to activate the peroxisome proliferator-activated receptor (PPAR)- γ , thus fostering insulin sensitivity in skeletal muscle, liver, and adipose tissue. Insulin Resistance Intervention After Stroke (IRIS) trial and Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROActive) trial and with pioglitazone shows reduce risk of MI and stroke. But it increases HF hospitalization and contraindicated in patients with or at risk of HF [9].

Glucagon-like peptide-1 receptor agonists

The receptor for GLP-1 is abundantly expressed in the vascular endothelium, smooth muscle cells, and cardiomyocytes, suggesting that these drugs may act on the entire CV system [10]. GLP1 antagonist shows significant reduction of composite CV endpoints in Liraglutide Effect and Action in Diabetes (LEADER) and Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) trials It shows no significant effects on CV mortality, nonfatal MI, and hospitalization for HF with liraglutide and semaglutide. There is no large RCTs about the GLP1 on heart failure. Two small RCTs reported Liraglutide has no effect on LV function, hierarchical composite of death and HF hospitalization with BNP change [11,12].

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors block the degradation of glucagon-like peptide-1 (GLP-1), gastric inhibitory peptide, and a variety of other peptides, including brain natriuretic peptide [13]. Even though it is well tolerated, no reduction of CV endpoints (SAVOR-TIMI 53, EXAMINE, TECOS). Data from both Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53) trial and Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial confirmed that DPP-4 inhibitors may increase HF hospitalization in patients with pre-existing HF and high brain natriuretic peptide (BNP) levels at baseline [14]. Although sitagliptin does not increase HF hospitalization even after adjustment for pre-existing HFA in Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) trail [15], recent large meta-analysis including SAVOR-TIMI 53 and EXAMINE trials has confirmed a 25% increase in HF hospitalizations related to DPP-4 inhibitors.

Sodium glucose cotransporter 2 inhibitors

Sodium glucose cotransporter 2 (SGLT2) inhibitors are the newest class of oral agents approved for the treatment of T2DM. Their mechanism of action is inhibition of SGLT2, sodium-glucose cotransporter located in the proximal tubule. Inhibition of SGLT2 leads to the elimination of 60 - 80g glucose per day; however, this value is highly dependent on renal function and the hyperglycemic burden [16]. In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) trial, empagliflozin reduced CV death, HF hospitalization, and total mortality by 38%, 35%, and 32%, respectively but no direct effect on the rates of MI or stroke with empagliflozin. Both EMPA-REG OUTCOME for Empagliflozin vs Placebo and (CANVAS) Canagliflozin and cardiovascular and renal events in type 2 diabetes show reduced HF hospitalization [17,18].

Insulin

Insulin is a peptide hormone produced by beta cells of the pancreatic islets, and it is considered to be the main anabolic hormone of the body. It regulates the metabolism of carbohydrates, fats and protein by promoting the absorption of, especially, glucose from the blood into liver, fat and skeletal muscle cell [19]. The development of HF in several clinical studies has been shown that there is a strong association between insulin resistance and HF. Glucose, obesity, metabolic syndrome, and diabetes relevance to incidence of heart failure [20]. Background biochemical signaling pathways of insulin is to growth and remodeling responses and this in turn causes myocardial hypertrophy, cardiac fibrosis, impaired myocardial-endothelial signaling and death of myocardial and endothelial cells [21].

Since the action of insulin induces significant sodium retention and hypoglycemia precipitating worsening of heart failure that is usually to be vigilant in clinical care, its use might be associated with worse outcomes. In observational studies in HF, insulin was associated with higher mortality rates than metformin [3]. Real world 4 million subjects of administrative Registry was done in Puglia Region, Italy shows Insulin treatment was associated with a significantly higher risk of all cause death and hospitalization for heart failure.

Metformin

Metformin Hydrochloride (HCl) Tablets, USP is an oral antihyperglycemic drug mostly used in the management of type 2 diabetes, was first described in the scientific literature in 1922, by Emil Werner and James Bell [22]. Metformin HCl, USP (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents.

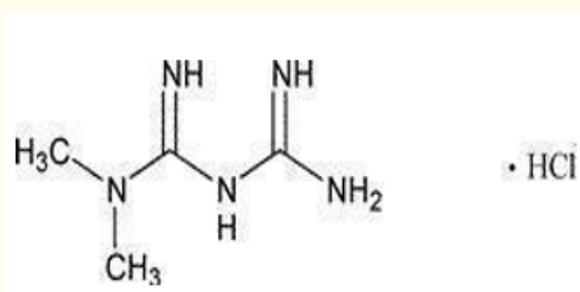


Figure 2: Molecular Structure of Metformin

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Metformin action on cardiovascular system

Metformin produces AMP-activated kinase (AMPK) dependent and independent effects at the cellular level [23]. This drug improves endothelial function, protects from oxidative stress and inflammation, and from the negative effects of angiotensin II at the systemic level.

	Type	Population	Intervention	Comparison	Outcomes
Aguilar (2011) [27]	5	National cohort of 6185 patients with HF + DM	Metformin	Not receiving metformin	Mortality HR 0.76; 95% CI 0.63 - 0.92
Eurich (2005) [28]	5	1833 HF patients with diabetes and new OAD	Metformin monotherapy	SU mono- or combination therapy	A reduction in deaths or hospitalizations was also observed: 658 (85%) for SU monotherapy vs. 160 (77%) for metformin monotherapy (0.83; 0.70 - 0.99) and 681 (80%) for combination therapy (0.86; 0.77 - 0.96)
Masoudi (2005) [29]	5	16 417 DM + HF	Metformin or glitazones	Non-insulin-ensitizing drugs	Reduced 1-year mortality with either drug compared with controls (P, 0.0001) Higher risk of readmission for HF with glitazones (HR 1.06, 95% CI 1.00 - 1.09) and a lower risk with metformin (HR 0.92, 95% CI 0.92 - 0.99).
McAlister (2008) [30]	5	5631 patients with new OAD; Saskatchewan database, Canada, retrospective cohort study	Metformin monotherapy	SU monotherapy	Users of high-dose SUs were more likely to develop incident HF than users of high-dose metformin (adjusted HR 1.24, 95% CI 1.01-1.54). There was no differential effect of high dose vs. low dose metformin (HR 1.06, 95% CI 0.81 - 1.41).
Home (2009) [31]	2	4447 diabetic patients on metformin or SUs	Addition of RSG	Combination of metformin with SUs	HF causing admission to hospital or death higher with RSG: HR 2.10, 1.35-3.27
Tzoulaki (2009) [32]	5	91 521 patients with diabetes, retrospective cohort	Metformin	Other oral antidiabetic drugs	Total mortality reduced vs. SU (P < 0.001). Incident HF reduced vs. SU (P < 0.05).
Romero (2011) [33]	5	1519 patients with new-onset HF/DM, 9-year FU	Metformin	Non-metformin treatment	Metformin was associated with a decreased mortality (HR 0.85, 95% CI 0.82-0.88), mainly due to a reduced CV mortality (HR 0.78, 95% CI 0.74-0.82), and with a lower hospitalization rate (HR 0.81, 95% CI 0.79-0.84). Metformin was not associated with an improved prognosis of HF patients with a mean HbA1c ≤7.0%.
Andersson (2010) [34]	5	10 920 DM patients hospitalized for incident HF	Multiple comparisons		All-cause mortality vs. SU: Metformin: adjusted HR 0.85, 95% CI 0.75-0.98 Metformin + SU: adjusted HR 0.89, 95% CI 0.82-0.96 Metformin + insulin: adjusted HR 0.96, 95% CI 0.82 - 1.13 Metformin + insulin +SU: adjusted HR 0.94, 95% CI 0.77 - 1.15
MacDonald (2010) [4]		1633 new-onset DM + HF out of UK General Practice Research Database	No antidiabetic drug	Any antidiabetic drug	Compared with patients who were not exposed to antidiabetic drugs, metformin monotherapy (adjusted OR 0.65, 95% CI 0.48 - 0.87 or metformin with or without other agents OR 0.72, 95% CI 0.59 - 0.90 was associated with lower mortality

Table: Trials and studies on metformin in heart failure.

CI: Confidence Interval; CRT: Cardiac Resynchronization Therapy; CV: Cardiovascular; DM: Diabetes Mellitus; DPP-4: Dipeptidyl Peptidase-4; EF: Ejection Fraction; ER: Emergency Room; FU: Follow-Up; GLP-1: Glucagon-Like Peptide-1; HbA1c: Glycated Hemoglobin; HF: Heart Failure; HR: Hazard Ratio; LVEF: Left Ventricular Ejection Fraction; MI: Myocardial Infarction; NYHA: New York Heart Association; OAD: Oral Antidiabetic; OR: Odds Ratio; RCT: Randomized Controlled Trial; RR: Relative Risk; RSG: Rosiglitazone; SU: Sulfonylurea; T2D: Type 2 Diabetes; TZD: Thiazide Diuretic.

Type: 1: RCT outcomes data in patients with diabetes and heart failure; 2: RCT data on incident heart failure in type 2 diabetes; 3: RCT subgroup analyses; 4: Other clinical studies and meta-analyses; 5: Observational studies/registries.

On the myocardium metformin attenuates ischemia-reperfusion injury and prevents adverse remodeling induced by humoral and hemodynamic factors [24]. During an acute increase in workload and in the early stages of diabetic/hypertensive cardiomyopathy as confirmed by few small clinical trials and some observational studies, abnormal myocardial cell metabolism and contractile dysfunction could be relevant during transient ischemia. The favorable protective effect of metformin with respect to both vascular events and progression to heart failure are seen by the overall evidence emerging from both clinical trials and real-world registry. Metformin also improves cardiac efficiency through reducing ER stress, and, presumably, rates of myocardial protein turnover [25]. Then, according to comprehensive search of "Cochrane Review" in 2010 acclaimed that there was no evidence that metformin was associated with increased risk of lactic acidosis [26].

Conclusion

The causes of HF in T2DM are complex and caused by multifactorial background pathophysiology, and coexistence of Type2 DM with HF has impacted to higher mortality rate by evidence from recent large-scale clinical trials and registries. Metformin is one of the Essential Medicines list of World Health Organization and it is also one of the most effective and safe medicines needed in a health system.

Since numbers of research and clinical data show metformin has several benefits to protect heart and coronary vessels, it is safe to use in Type 2 DM with HF. It is also associated with decreased mortality and reduces the hospitalization of heart failure than sulfonylureas or insulin that has been shown in numbers of observational studies. Insulin is associated with an increased risk of death or hospitalization due to worsening heart failure. Although SGLT2 inhibitors has benefits to control Type 2 DM with HF by several clinical trials and studies, it is still expensive and not easily to use in resource limited clinical setting of developing countries. There are numbers of ongoing clinical trials and studies have done for the cost effectiveness of SGLT1 inhibitors. Metformin has been available for treating diabetes since the 1950s along with strong real-world clinical benefits evidence in Cardiovascular safely. Metformin is an old drug but a good friend in Type 2 DM with Heart Failure.

Declaration of Interest

I declare there is no any conflict of interest.

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