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Review Article

Dapagliflozin Use in Heart Failure with Ejection Fraction Accompanied by Type 2 Diabetes Mellitus: A Systematic Review

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ABSTRACT

Heart failure patients with reduced ejection fraction (HFrEF) respond well to pharmacological therapy and show a better prognosis. Heart failure patients with reduced ejection fraction and type 2 diabetes who were given SGLT-2 inhibitor therapy showed a strong and consistent reduction in the risk of death and hospitalization. The therapy that has recently been investigated for its benefits for heart failure from the SGLT-2 inhibitor class is Dapagliflozin. The systematic review aims to analyze the effect of Dapagliflozin on the prognosis of HFrEF patients with type 2 diabetes mellitus. **Material and Methods**: The references was searched from e-database PubMed, ScienceDirect, and ClinicalTrial.gov. Quality assessment was done using the Critical Appraisal Skills Program (CASP) Randomized Controlled Trial Standard Checklist. **Results:** A total of 22,167 patients from 4 RCTs eligible studies were included. The analysis results of all of the included studies indicate that Dapagliflozin affected the patient's prognosis. Two studies discuss mortality and hospitalization, and two studies discuss symptoms, functional status, and Quality of Life (QoL). **Conclusion:** Dapagliflozin can improve the prognosis of HFrEF patients with type 2 DM. The improved prognosis includes reduced mortality, reduced hospitalizations by minimizing disease worsening, reducing symptoms, improving functional status and QoL.

Introduction

Heart failure is a clinical syndrome characterized by an abnormality in the structure or function of the heart that results in the heart unable to pump blood to meet the metabolic needs of the tissue. Heart failure is classified into three subtypes according to their ejection fraction, namely Heart Failure with reduced ejection fraction (HFrEF), Heart Failure with preserved ejection fraction (HFpEF), and Heart Failure mid-range ejection fraction (HFmrEF) [1]. The prevalence of HFrEF is lower than HFpEF. However, patients with HFrEF are at a higher risk of disease progression, worsening clinical condition characterized by an increased history of repeated hospitalizations and lastly, death. So far, it has been analyzed that patients with HFrEF have good response to pharmacological therapy and showed a better prognosis than patients suffering from HFpEF [2].

Several recent reports indicate that the overall number of people suffering from heart failure is increasing due to a substantial increase in predisposing or comorbid diseases (such as diabetes, obesity, and hypertension) and aging population in general [3]. Patients suffering from diabetes mellitus have twice the risk of developing heart failure than patients without it. Heart failure patients with diabetes mellitus also have a worse clinical outcome than heart failure patients without diabetes mellitus. The risk of hospitalization in heart failure patients with diabetes mellitus is 50% higher than those without it [4].

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors are classes of drugs developed to treat type 2 diabetes, which will lower glucose concentrations by increasing the urinary glucose excretion [5]. Drugs in the SGLT-2 inhibitor class include canagliflozin, Dapagliflozin, and empagliflozin. As stated before, the therapy that has recently been researched for its benefits for heart failure from the SGLT -2 inhibitor class is Dapagliflozin. In order to understand the studies regarding the effects of Dapagliflozin, we conducted a systematic review to evaluate the evidence of the effect of Dapagliflozin pharmacological therapy on the prognosis of patients with HFrEF with type 2 diabetes mellitus.

Material and Methods

Study design

This research is secondary in the form of a systematic review that follows the PRISMA guidelines.

Search strategies

A literature search in this study was conducted through the PubMed, Science Direct, and ClinicalTrial.gov electronic databases to systematically identify relevant research. The literature search was carried out using Boolean Operators including OR/AND with search terms including (Dapagliflozin OR DAPA OR SGLT 2 inhibitor) AND (prognosis OR outcomes OR effects OR benefits) AND (heart failure OR HFrEF) AND (Type 2 DM). The keywords used are entered together into the electronic database search engine using the advanced search.

Inclusion and exclusion criteria

Studies included in this review must meet the following inclusion criteria:

- Research had only been published in the last three years (2018-2021)
- English
- Access to full-text file
- The subject of the study is heart failure patients with reduced and ejection fraction (HFrEF) accompanied by type 2 diabetes mellitus
- The study included the prognosis of patients who received Dapagliflozin pharmacological treatment

There were studies that were excluded for the following reasons:

- Resources coming from non-research studies (conference papers, book chapters, reports).
- Subject of the study is not patients of heart failure with reduced ejection fraction (HFrEF)
- Subject of the study is not patients with type 2 DM
- Research with pharmacological therapy other than Dapagliflozin
- Ordinary literature review (literature review, systematic review)

Data extraction

The investigator independently screened and assessed the title and abstracts before retrieving the full-text. The data extracted from these studies included the author, year of publication, title, research method, number of research participants, given intervention, inclusion criteria, exclusion criteria, variables, and results obtained. Excel 2010 (Microsoft Corporation) software program was used to organize extracted data.

Quality Assessment

The two reviewers independently rated study quality using the Critical Appraisal Skills Program (CASP) Randomized Controlled Trial Standard Checklist. This tool consists of 4 main questions described in 11 question points to help answer the problem systematically. There are three kinds of answers provided to answer the points above, namely yes (Y), no (N), cannot tell (C). The final result is obtained from the conclusion of the whole answer whether the journal can be included (include) or not (exclude).

Data Synthesis

The study results will be analyzed in a narrative way that is described and explained to facilitate deeper understanding and provide more apparent conclusion to the reader.

Result

Study selection

A total of 1,312 studies were found on keyword searches through 3 databases PubMed, ScienceDirect, and ClinicalTrial.gov, as shown in Figure 1. Then from the 1,312 studies, 72 duplicated articles were eliminated, resulting in 1,239 articles remaining. Researchers screened based on titles and abstracts that matched the topic and excluded 1,207 less relevant studies. Then among the 32 articles reviewed by accessing the full text of the literature, four articles do not focus on pharmacological therapy of SGLT-2 inhibitors other than Dapagliflozin, 15 articles do not focus on the prognosis of HFrEF patients, 2 articles do not show precise results about the effect of Dapagliflozin, 6 articles compared the pharmacological therapy of Dapagliflozin with other therapies (not placebo), and 1 article was from a non-research study. In the final result, 4 articles meet the inclusion and exclusion criteria and are then included in this systematic review. The included studies are presented in Table 1.

Quality assessment

All studies that have met the criteria are then assessed for quality of evidence using the Critical Appraisal Skills Program (CASP) Randomized Controlled Trial Standard Checklist. The four studies fulfill the assessment points, with details of the assessment results on each component are presented in Table 2

The effects of Dapagliflozin

After reviewing the four articles, a total of 22,167 patients were involved in the study. Two studies discuss Dapagliflozin on the mortality of HFrEF patients accompanied by type 2 diabetes [6-7]. The result of this study is that Dapagliflozin can reduce cardiovascular mortality only in patients with HFrEF but not in patients without HFrEF.

From the articles reviewed, two articles discuss Dapagliflozin on the incidence of hospitalization in HFrEF patients accompanied by type 2 diabetes. It was found that Dapagliflozin reduced the incidence of hospitalization in patients with HFrEF compared to patients without HFrEF [6-7].

Two articles discuss the effect of Dapagliflozin on symptoms, functional status, and QoL of HFrEF patients with type 2 diabetes. The results of [8] and [9] studies were that patients given Dapagliflozin had more significant improvements in KCCQ-TSS, KCCQ-CSS, and KCCQ-OSS scores at 8 and 12 months than patients on placebo.

Discussion

The publication of the included studies began in 2019-2020, where research related to the effect of Dapagliflozin on heart failure was still classified as a new study that began in 2018 [10].

Based on the results of the analysis of 4 studies in this systematic review, Dapagliflozin gave significant results on the prognosis of heart failure patients in the form of mortality, worsening of the disease as indicated by the incidence of hospitalization, worsening of symptoms, functional status, and QoL. In type 2 DM patients, there will be a lack of energy due to impaired glucose utilization and ultimately more dependent on free fatty acids. Elevated levels of free fatty acids lead to lipid accumulation in cardiomyocytes and lipotoxicity [11]. Excessively high levels of fatty acid oxidation contribute to abnormalities of energy metabolism, which ultimately lead to cardiomyocyte apoptosis and cell damage and cause myocardial ischemia. In addition, activation and upregulation of the renin-angiotensin-aldosterone system (RAAS) will contribute to the increased of myocardial stiffness, impaired energy availability, and decreased cardiac contractility, which will impact cardiac output hypertrophy[12].

Advanced Glycation End Products (AGEs) will accumulate in the human body with age, and accumulation is accelerated in the presence of diabetes mellitus. AGEs are molecules formed during a non-enzymatic reaction between proteins and sugar residues, called the Maillard reaction. AGEs will affect the physiological properties of proteins in the ECM, cause impaired cardiac contractility, and impact cardiac fibrosis [13,14]. Hyperglycemia can induce oxidative stress. Oxidative stress will reduce NO production and will affect endothelial dysfunction [15]. The endothelium has a vital role in maintaining blood fluidity and restoring the integrity of the blood vessel walls to avoid bleeding. Thus, endothelial dysfunction will have an impact on myocardial ischemia [16].

The conditions such as cardiac fibrosis, cardiac hypertrophy, and myocardial ischemia will trigger heart failure in the form of systolic dysfunction and diastolic dysfunction. Diastolic dysfunction often occurs in patients with type 1 DM, while systolic dysfunction occurs in patients with type 2 DM [17]. There is systolic dysfunction, better known as HFrEF, accompanied by type 2 DM. There is a new class of drugs, namely SGLT 2 inhibitors, which are believed to lower blood sugar in adults and are helpful for cardiovascular therapy, one of which is Dapagliflozin. SGLT 2 inhibitors can improve the prognosis of HFrEF patients with type 2 diabetes through the mechanisms of diuresis/natriuresis, decreased blood pressure, erythropoiesis, increased cardiac energy metabolism, reduced inflammation, inhibition of the sympathetic nervous system, prevention of adverse cardiac remodeling, prevention of ischemia [18].

Among the four articles analyzed, two articles showed that Dapagliflozin significantly reduced mortality in HFrEF patients [6,7]. It is in line with research conducted by Zinman et al[19] which showed that empagliflozin, a drug from the SGLT-2 inhibitor class, also resulted in a reduction in mortality in HFrEF patients accompanied by type 2 diabetes.

Studies from Kato et al.[6] and McMurray[7] also discussed about Dapagliflozin's ability in reducing

the incidence of hospitalization in HFrEF patients with type 2 diabetes. It is supported by research conducted by Radholm[20]. This study showed that canagliflozin, a drug from the SGLT-2 inhibitor class, reduced the incidence of repeated hospitalizations in HFrEF patients with type 2 diabetes.

Studies from Kosiborod[8] and Nassif[9] in this systematic review state that Dapagliflozin can reduce symptoms, improve functional status and QoL in HFrEF patients evaluated using the KCCQ score. It is in line with a recent study by Butler[21] which stated that empagliflozin improved the functional status of HFrEF patients. Research by [22] also showed that Dapagliflozin was the only drug of the SGLT-2 class of inhibitors that showed a clinically significant and significant reduction in mortality and disease worsening, including functional status in heart failure. Some points related to the effects of using Dapagliflozin will also be discussed further.

Use of Dapagliflozin Compared to Other Types of SGLT2 Inhibitors

Dapagliflozin, canagliflozin, and empagliflozin are in the same drug class as sodium-glucose co-transporter 2 (SGLT2) inhibitors. They work in a similar way to treat type 2 diabetes. Dapagliflozin has been shown to reduce the risk of hospitalization for heart failure by decreasing ejection fraction in adults with type 2 diabetes without being accompanied by type 2 DM [23]. In contrast, Empagliflozin and Canagliflozin are currently FDA-approved to reduce the risk of heart disease-related death only in people with type 2 diabetes. The effects of Dapagliflozin and empagliflozin on hemoglobin A1c (HbA1c) are similar.

Mechanism of Action of Dapagliflozin

The mechanism of action of Dapagliflozin is to inhibit the Sodium-Glucose co-transporter 2 (SGLT2), which is mainly located in the proximal tubule of the nephron. SGLT2 facilitates 90% of glucose reabsorption in the kidney so that its inhibition allows glucose to be excreted in the urine [24]. It will cause an osmotic diuresis due to excessive urinary glucose excretion. This excretion allows reasonable glycemic control in patients with type 2 diabetes mellitus and the potential for weight loss. Decreased sodium reabsorption leads to increased sodium delivery to the distal tubule. It possibly decreases cardiac preload and afterload and reduces sympathetic activity, thereby reducing symptoms of heart failure. 75.2% of the dose of Dapagliflozin was excreted in the urine, with 1.6% of the dose unchanged by metabolism. 21% of the dose of Dapagliflozin is excreted in the feces, with 15% of the dose unchanged by metabolism.

Blood Sugar and Cardiovascular Relationship

There is an estimate of a relationship between elevated blood sugar levels and cardiovascular events in patients with type 2 diabetes. An observational study by Shah[25] showed that cardiovascular events such as peripheral arterial disease, heart failure, coronary heart disease, ischemic stroke, and others were 1.5 to 3 times higher in patients with type 2 DM than patients without diabetes. However, this is refuted by the results of observational studies from Krannenburg[26], who stated that in patients with type 2 diabetes, there was a modest relationship between HbA1c levels and cardiovascular events, but no statistically significant interaction (there was no significant relationship). The effect of baseline HbA1c levels on all-cause mortality was similar in patients with and without vascular disease. In patients with vascular disease, hyperglycemia is not

the only factor that causes progressive vascular damage. Other factors such as hypertension and dyslipidemia are strongly associated with cardiovascular events in patients with type 2 diabetes.

Research by Krannenburg[26] is also in line with previous research conducted by Castagno[27], who stated that tight glycemic control in patients with type 2 diabetes did not reduc e the risk of heart failure and, when achieved with thiazolidinediones, increased the risk. The reasons why intensive glucose control did not lead to the previously predicted reduction in heart failure risk are uncertain. However, it may be the influence of several factors such as duration of treatment or inadequate follow-up, treatment intervention late in the course of the disease, toxicity of the off - targeted treatment, or because hyperglycemia itself does not directly cause heart failure in diabetic patients.

The study results by the ADVANCE group[28] also showed HbA1c levels to a relatively low level of 6.5% did not reduce the incidence of death, myocardial infarction, ischemic stroke. Thus the success of SGLT 2 inhibitors in reducing cardiovascular events in patients with type 2 diabetes cannot be said to be a direct impact on lowering blood sugar.

Effect of Dapagliflozin on Heart

Expression of SGLT2 is concrete for renal tissue, with some expression possibly occurring in pancreatic cells. However, SGLT2 expression was not found in the human heart, where the heart only found expression of SGLT1 but was very small [29]. Therefore, the potential effects of SGLT2 inhibitors on cardiac structure and function are likely to be indirect and mediated by systemic hemodynamic and metabolic effects. Thus, the relationship between type 2 diabetes and heart failure is complex and multifactorial.

Effect of Dapagliflozin on HFrEF Patients Without Type 2 DM

An exploratory analysis of randomized clinical trials that included 4744 patients by Petrie[30], administration of Dapagliflozin with the recommended therapy significantly reduced the risk of heart failure and cardiovascular death in patients with type 2 diabetes (Hazard ratio of 0.75) and patients without type 2 diabetes (Hazard ratio of 0.73). For patients without type 2 diabetes with glycated hemoglobin of at least 5.7%, the incidence of hospitalization had a hazard ratio of 0.74 and 0.67 in those with less than 5.7%.

Research by Nassif[7] stated that 55% of the patients included were patients without diabetes mellitus. The conclusion was that heart failure patients with reduced ejection fraction who received the SGLT2 inhibitor dapagliflozin had a lower risk of worsening heart failure or cardiovascular death than those who received placebo, regardless of the presence or absence of diabetes mellitus. It suggests that Dapagliflozin effectively reduces cardiovascular morbidity and mortality in patients with heart failure with reduced ejection fraction regardless of diabetes status.

Effect of Dapagliflozin on the Kidney

In the study of Zelniker[31], after 12 weeks of observation, it was found that dapagliflozin induced moderate glucosuria (52-85 g urine glucose/day) and showed significant glycemic improvement. There are no changes that lead to kidney function. Serum uric acid levels decrease, serum magnesium levels increase, serum phosphate levels increase at high doses. Administration of Dapagliflozin did not show clinically significant persistent and clinically significant changes in osmolarity, volume, or renal status.

It is also in line with the study by Docherty[32], who conducted a study of 1265 patients (7.4%) with eGFR below 60 mL/min/1.73m2, and 5199 patients (30.9%) had albuminuria. The effect of Dapagliflozin on patients at relative risk for cardiovascular events was consistent across the eGFR and UACR groups, with the most significant absolute benefit occurring in patients with reduced eGFR and albuminuria.

Drugs Other Than Dapagliflozin Also Given During The Study

The first study in this systematic review was the study of Nassif[7]. Patients with heart failure were asked to receive therapy in the form of an implantable cardioverter-defibrillator, cardiac resynchronization therapy, or both and standard drug therapy, including angiotensin-converting–enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARB), or sacubitril-valsartan plus a beta-blocker. These drugs are discontinued if their use is contraindicated or results in unacceptable side effects. In addition, the use of mineralocorticoid receptor antagonists is also recommended. Patients with type 2 diabetes are also given other glucose-lowering therapies such as insulin and sulfonylureas. Most of the patients in this study were treated with diuretics and mineralocorticoid receptor antagonists from the start.

The following study was from Kato[6], of 17,160 patients, 671 had an ejection fraction of <45% and were classified as having HFrEF. Patients with a history of heart failure, especially those with HFrEF, were generally well treated according to standard HF therapy, including 86.0% given angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and 80.7% given -blockers. Two-thirds received diuretics, and 30.3% used mineralocorticoid receptor antagonists.

In a subsequent study by Nassif[9], 97% of patients took beta-blockers, 61% took mineralocorticoid antagonists, 59% of patients took angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 33% took ARNIs, 62% had implanted cardiac defibrillators, including 35% with cardiac resynchronization therapy. The majority of 86% also used diuretics. Meanwhile, in type 2 diabetes patients, the risk of hypoglycemia was reduced by giving a sulfonylurea and metiglinide to patients with an initial hemoglobin A1c (HbA1c) of 7%.

The success of Dapagliflozin in reducing morbidity and mortality in heart failure patients with or without type 2 diabetes occurs when Dapagliflozin is combined with all other types of antidiabetics such as metformin, sulfonylureas, DPP-4 inhibitors, insulin, and others [33].

Limitations

Three of the four articles reviewed in this systematic review were research funded by AstraZeneca.

Conclusion

This systematic review concludes that pharmacological therapy of Dapagliflozin can improve the prognosis in patients with HFrEF who are accompanied by type 2 DM. The improved prognosis is in the form of decreased mortality, reduced incidence of hospitalization by minimizing disease worsening, reducing symptoms, improving functional status and quality of life (QOL).

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There is no conflict of interest.

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Supplementary Data

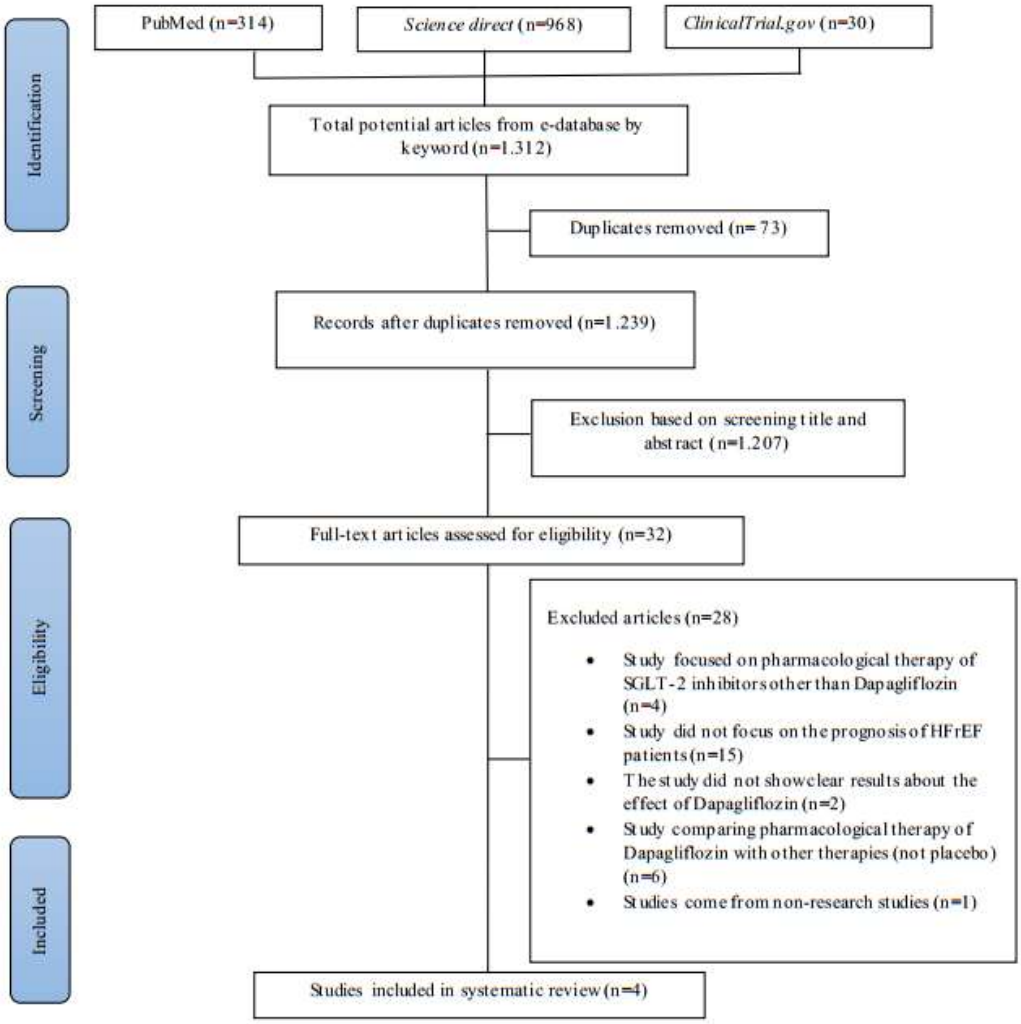

Figure 1. Study selection flow chart for systematic review

Table 1. Characteristics and results included studies in our systematic review

No.	Author, year	Article Title	Research Methods	Research Participants	Type of Intervention	Criteria Inclusion	Criteria Exclusion	Independent Variable	Dependent Variable	Results
1.	Kato et al., 2019	Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus	Randomized Controlled Trial	17160 participants	- Dapagliflo-zin 10mg - Placebo	Male/female age 40 years old - DM type 2 - High risk of cardiovascular	- DM type 1 - History of bladder cancer - Chronic cystitis Pregnant/bre astfeeding	Type of intervention given (dapagliflozin and placebo)	Heart failure prognosis (mortality and hospitalization)	- Dapagliflozin reduced the incidence of hospitalization more in patients with HFrEF (hazard ratio [HR], 0.62 [95% CI, 0.45– 0.86]), compared with patients without HFrEF (HR, 0.88 [95% CI, 0.76–1.02]; P for interaction=0.046) - - Dapagliflozin reduced cardiovascular mortality only in HFrEF patients (HR, 0.55 [95% CI, 0.34–0.90]), but not in patients without HFrEF (HR, 1.08 [95% CI, 0.89–1.31]; P for interaction=0.012)
2.	McMurray et al., 2019	Dapagliflozin in Patients Heart and Reduced Ejection Fraction	Randomized Controlled Trial	4744 participants	- Dapagliflo-zin 10mg - Placebo	- Male/female age 18 years old - HFrEF with NYHA II-IV - LVEF 40% - Increased levels of NT-	- DM type 1 - eGFR <30 mL/min/1.73 m2 - systolic BP <95 mmHg	Type of intervention given (dapagliflozin and placebo)	Heart failure prognosis (mortality and hospitalization)	- Disease worsening as indicated by hospitalization occurred in 237 participants (10%) in the dapagliflozin group, and 326 participants (13.7%) in the placebo group

						proBNP - eGFR 30 mL/min/1.73 m2				(hazard ratio, 0.70; 95% CI, 0.59 to 0.83). - Cardiovascular deaths occurred in 227 participants (9.6%) in the dapagliflozin group, and 273 (11.5%) in the placebo group (hazard ratio, 0.82; 95% CI, 0.69 to 0.98).
3.	Kosiborod et al., 2020	Effects of Dapagliflozin on Symptoms, Function and Quality of Life in Patirnts With Heart Failure and Reduced Ejection Fraction	Randomized Controlled Trial	4443 participants	- Dapagliflo-zin 10mg - Placebo	- Male/female age 18 years old - HFrEF with NYHA II-IV - LVEF 40% - Increased levels of NT - proBNP - eGFR 30 mL/min/1.73 m2	- DM type 1 - eGFR <30 mL/min/1.73 m2 - systolic BP <95 mmHg	Type of intervention given (dapagliflozin and placebo)	Heart failure prognosis (symptoms, functional status, and QoL)	Participants given dapagliflozin had significantly greater improvements in KCCQ-TSS, KCCQ-CSS, and KCCQ-OSS scores at 8 months than participants on placebo (2.8, 2.5, 2.3 points higher than placebo; P<0.0001)
4.	Nassif et al., 2019	Dapagliflozin Effects on Biomarker Symptoms, and Functional	Randomized Controlled Trial	263 participants	- Dapagliflo-zin 10mg - Placebo	- HFrEF with NYHA II-III - LVEF 40% - eGFR 30 mL/min/1.73 m2	- DM type 1 - eGFR <30 mL/min/1.73 m2	Type of intervention given (dapagliflozin and placebo)	Heart failure prognosis (symptoms, functional status)	- Patients given the dapagliflozin intervention had a significant improvement on the Kansas City Cardiomyopathy

Status in Patient With Heart Failure With Reduced Ejection Fraction	- BNP 100 pg/mL and/or - NT proBNP - 400 pg/ml	Questionnaire than patients given placebo at 12 months. - KCCQ-OSS dapagliflozin 3.7 points higher than placebo with P=0.037 - KCCQ-CSS dapagliflozin 4.6 points higher than placebo with P=0.007 - KCCQ-T SS dapagliflozin 4.8 points higher than placebo with P=0.012

Table 2. Study quality assessment criteria using the CASP's tool

Critical Appraisal Checklist													
No	**Author, year**	**Section A**				**Section B**			**Section C**			**Section D**	**Overal results**
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
1.	Kato et al., 2019	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Included
2	McMurray et al., 2019	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Included
3.	Kosiborod et al., 2020	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Included
4.	Nassif et al., 2019	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Included