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Dapagliflozin effects on hospitalization for heart failure reduction, and major adverse cardiovascular events

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REVIEW

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ABSTRACT

Background
Until recently, there are no available preventive measures for macrovascular complications of diabetes mellitus (DM). Sodium-glucose co-transporter inhibitors (SGLT-2i) are a relatively new class of medications with cardio-renal protection. However, it is unknown, whether this is a class effect. Also, the exact mechanisms of action are not fully understood.

Aims
The current review aimed to assess dapagliflozin effects on the major cardiovascular adverse events (MACE) and heart failure hospitalization rate (HHF) and its mechanisms of action.

Methods
The Pub Med, MEDLINE, and Google Scholar databases were systematically searched for relevant articles. Articles published in the English language from the first available article up to November 2019 were approached. The terms dapagliflozin, SGLT-2i, MACE, HHF, and mechanisms of action were used with proteans AND or OR. Out of two hundred-ten articles retrieved, only twenty-nine fulfilled the inclusion and exclusion criteria.

Results
Dapagliflozin reduced HHF, all-cause mortality, bumetanide induced hyperuricemia, and interstitial fluid volume with a lower rate of diuretic use. Possible mechanisms of action were: a reduction of oxidative stress, lowering of cardiac hexosamine biosynthetic pathway activation, reduced cytosolic sodium and calcium, and increased serum magnesium. Dapagliflozin effects on MACE are mixed. The above effects seem to be a class character across various population including normal people without diabetes with no differences across gender.

Conclusion
Dapagliflozin reduced HHF (superior to empagliflozin) and all-cause mortality. The drug acts at cellular levels and not simple diuresis and haemoconcentration.

Key Words
Dapagliflozin, heart failure hospitalization, major cardiovascular adverse effects, mechanisms of action

What this review adds:

1. What is known about this subject?
Dapagliflozin reduces HHF, while its effects on MACE and mechanisms of action are matters of controversy.

2. What new information is offered in this review?
Dapagliflozin acts on cardiac muscles and fibroblasts, induces vasodilatation in both the heart and arteries. The drug improved both systolic and diastolic dysfunction and prevent cardiac concentric remodelling. Dapagliflozin effects on electrolytes, pH, intracellular pathways, and oxidative seem to be a class effect. Furthermore, the drug exerts favourable effects on hyperuricemia (a common morbid disease among patients with diabetes mellitus) and reduced diuretic use. Dapagliflozin is superior to empagliflozin in terms of HHF.

3. What are the implications for research, policy, or practice?
Dapagliflozin can be used safely among patients with both systolic and diastolic HF even among patients with prediabetes or normal sugar profile in particular for patients with bumetanide due to its favourable effects on hyperuricemia. Dapagliflozin is superior to empagliflozin (the first SGLT-2i to show CV benefits especially mortality) for HHF reduction.

Introduction

Diabetes mellitus (DM) is a public health burden (worldwide 8 per cent are affected and nearly a third are suffering from the disease in the Kingdom of Saudi Arabia).DM co-existence with hypertension, dyslipidaemia, and a high body mass index (overweight/obesity) is well-established in the context of the metabolic syndrome. The metabolic syndrome components are major risk factors for mortality, cardiovascular disease (CVD), and end-stage renal disease.[1,2] SGLT-2i are Novel class of medications with cardio-renal protection, they are recommended as a second-line treatment with metformin for DM in patients at increased cardiovascular (CV) risk, chronic kidney disease or heart failure (HF).[1]

HF and DM independently contribute to significant CV mortality and morbidity. DM is the most common comorbidity among patients with HF, and present in up to 45 per cent of patients. Atherosclerotic CVD outcomes are thought to be the major cause of morbidity and mortality among patients with diabetes. However, HF death and hospitalization have been recognized as being just as common. HF and DM are morbid costly disorders with high hospital use and mortality.[3-5]

Type 2 diabetes mellitus (T2DM) is a major risk factor for several CV conditions, including HF. However, until recently, no therapy to treat patients with diabetes could also reduce CV risks related to HF. HF affects approximately 2 per cent of the population worldwide, remaining a major cause of hospitalization and mortality despite innovative therapeutic approaches introduced in the past few decades. SGLT-2i including dapagliflozin seem to represent a shift in healthcare due to their favourable effects on HF and mortality. The final goal in the management of patients with T2DM is a reduction in CV complications and total mortality. Despite the strong evidence that SGLT-2 inhibitors are effective in HF reduction among patients with at-risk/established CVD and represents a paradigm shift in the management of patients with T2DM and atherosclerotic CV disease or CV risk factors,[6] a striking discordance exists between evidence-based-guideline-recommended SGLT-2 inhibitors use and actual uptake in clinical practice. Paradoxically, patients with HF, hypertension, CVD, and chronic kidney disease were less likely to receive an SGLT2 inhibitor compared to their counterparts. Plausible explanations could be that doctors may be reluctant to prescribe SGLT-2i if they don't have experience using them to treat frail patients who have many comorbidities. Although it is very important to be cautious with our frail patients. However, it is unwanted to deprive them of clinically preferred treatment. In spite of being recommended for patients with CV and renal disease, SGLT-2i are currently under prescribed, and when they are prescribed they're being prescribed to the patients who are not likely to benefit the most.[7,8] The current review aimed to assess the mechanisms of action of dapagliflozin and its effects on HHF and MACE.

Methodology

Eligibility criteria according to population intervention comparison outcome study design (PICOS):
Randomized controlled trials (RCTs), experimental, and observational studies investigating the mechanisms of action and effects of dapagliflozin on HHF and MACE were included (case reports and series were excluded).

Type of participants: Studies among adults with or without T2DM and prediabetes and experimental studies were eligible. Studies conducted on type 1 DM were not included.

Outcomes measures: HHF, nonfatal myocardial infarction, non-fatal stroke, CV death, mortality, and mechanisms of action of dapagliflozin.

Information source and search methods: A systematic electronic search was conducted in Pub Med including Epub and ahead of print, MEDLINE, Scopus, ScienceDirect and Google Scholar for relevant articles. Articles published in the English language from the first published up to November

2019 were approached. The terms dapagliflozin, SGLT-2i, MACE, HHF, myocardial infarction, non-fatal stroke, CV death, all-cause mortality, and mechanisms of action were used in different combinations.

Studies selection and data extraction: The retrieved articles were manually searched for relevant articles, two authors (H.M. I.A.) screened the titles and abstracts to exclude irrelevant articles and any discrepancy was resolved by consensus. Out of two hundred-ten articles retrieved, only twenty-nine fulfilled the inclusion and exclusion criteria. The author's name, county, year of publication, type of study, number of patients included, the duration of follow-up if applicable, and the results were reported. The different stages of the review process were shown in the PRISMA chart[9] Figure 1.

Results

There were two hundred and ten articles, one hundred thirty-eight manuscripts remain after the removal of duplication and irrelevant articles, and only twenty-nine articles fulfilled the inclusion and exclusion criteria. There were ten randomized controlled trials, nine retrospective studies, five experimental studies, two analyses of pooled data, a prospective cohort, a post hoc analysis, and a real-life cohort study. Fourteen studies were from Europe, eight were published in the USA, six articles from Asia, and one from Australia, 803642 participants were included. The retrieved RCTs included 56709 patients, 40 per cent were from Europe, while 30 per cent were published in the USA and Asia each, the duration of the studies ranged from 2-219 weeks with a mean of 81.64±97.15 weeks. Tables 1 and 2 depicted dapagliflozin effects and mechanism of action. Dapagliflozin reduced HHF (improved both systolic and diastolic dysfunctions and reduced remodelling) and all-cause mortality, bumetanide induced hyperuricemia, interstitial fluid volume, and the rate of diuretic use were also lowered. Possible mechanisms were a reduction of oxidative stress, lowering of cardiac hexosamine biosynthetic pathway activation, reduced cytosolic sodium and calcium, increased serum magnesium and mitochondrial calcium, and induced vasodilatation in the heart. This novel drug by targeting sodium-proton antiporter on cells leading to the restoration of pH within cells. Dapagliflozin effects on BNP and MACE are mixed. The above effects seem to be class effect across various population including normal people without diabetes with no difference between women and men. However, dapagliflozin was more effective in terms of reduction of hospitalization for heart failure compared to empagliflozin.

Discussion

In the current review, a medical claims, hospital cases/records, and medical registries-based study[10] showed that SGLT-2i was associated with a lower risk of HHF and death that may be a class effects, a pooled data from five RCTs[11] concluded similar findings regarding HF among users of dapagliflozin, a retrospective study[12] observes a lower death among patients who received dapagliflozin. Regarding the mechanism of action, it is thought that dapagliflozin down-regulates MMP 2 expression in the HCFs,[13] other benefits of dapagliflozin is the reduction of bumetanide-induced hyperuricemia as shown by a RCT.[14] In the current review, a mouse model[15] showed that SGLT-2i including dapagliflozin induce vasodilatation in healthy heart and reduce Na+, while a mathematical model[16] concluded that dapagliflozin reduce interstitial fluid volume to a greater extent than blood volume, thus, SGLT2 inhibitors might provide better control of congestion without reducing arterial filling and perfusion. A multi-national real-life study[17] included 40958 and showed that dapagliflozin reduced HHF, lower risks of CV events and all-cause mortality compared with DPP-4 inhibitors in a real-world clinical setting and a broad T2D population. Another mechanism of action of dapagliflozin is the activation and improving cardiac function and left ventricular diastolic dysfunction and reduction of hexosamine biosynthetic pathway.[18,19] The current data showed conflicting evidence regarding the MACE. However, reduction of mortality and HHF were observed[20,21] the lower HHF was supported by Dawwas and colleagues,[22] and Idzerda et al.[23] The largest randomized controlled trial on dapagliflozin (DECLARE-TIMI 58, included 17 160 patients with either established atherosclerotic CVD or multiple risk factors) showed that Dapagliflozin robustly reduced MACE and CV death/HHF among patients with myocardial infarction. Furthermore, the drug reduced HHF in patients with and without reduced ejection fraction (HFrEF<45 per cent). In addition, the drug reduced CV death and all-cause mortality in patients with HFrEF.[24-26] A Markov model study of 20 years concluded the cost-effectiveness of dapagliflozin as a second-line after metformin,[27] a relatively small RCT (49 patients followed for six months) showed that dapagliflozin is superior to vildagliptin regarding extraglycaemic effects.[28] A real-world study showed that dapagliflozin was safe with regard to CV outcomes and resulted in lower event rates of HHF and CV mortality,[29] while Weeda et al.[30] observed that new loop diuretic use was less frequent among SGLT2I users; however, patterns of loop diuretic use did not differ between cohorts in those on loop diuretics at baseline. Further mechanisms of actions were increased dieresis, osmolar clearance, and serum magnesium, while sodium

clearance and GFR were not affected. However, Eickhoff and colleagues[32] concluded that Dapagliflozin exerts both osmotic and natriuretic diuretic effects in patients with type 2 diabetes and kidney damage. In the present review, Pasternak et al.[33] conducted a retrospective study in Sweden and showed that SGLT-2 use was associated with reduced risk of HF and any cause death, but not with MACE, further studies[34] concluded the reduction of HHF among patients taking dapagliflozin. An interesting result was shown by Nassif and colleagues[35] who published an RCT in the USA and showed that ≥5-point improvement in Kansas City Cardiomyopathy Questionnaire overall summary score. Radholm et al.[36] showed no difference between men and women regarding the risk ratio and safety outcomes, Zhang et al.[37] in their study on animal model found that dapagliflozin reverses LV concentric remodelling in HFpEF pigs partly by restraining sympathetic tone in the aorta, while Bonora et al.[38] conducted a RCT and concluded no change in cardiac function using impedance cardiography.

Conclusion

Dapagliflozin reduced HHF and all-cause mortality, oxidative stress, bumetanide induced hyperuricemia, and interstitial fluid volume to a greater extent than blood volume allowing for better control of congestion without reducing arterial filling and perfusion, and a lower rate of diuretic use. Also, the drug lowered cardiac hexosamine biosynthetic pathway activation. Thus, improving cardiac function and cardiomyopathy, besides, dapagliflozin improved diastolic dysfunction, reversed concentric cardiac remodelling, reduced cytosolic sodium, and calcium, increased serum magnesium and mitochondrial calcium. This novel drug by targeting sodium-proton antiporter on cells leading to the restoration of pH within cells (beneficial effects including HHF) or inability to rapidly recover pH (unwanted side effects including ketoacidosis). No effects on MPP expression were observed. Dapagliflozin effects on BNP and MACE are mixed. The above effects seem to be a class effect across various population including normal people without diabetes with no difference between women and men. However, dapagliflozin was more effective in terms of reduction of HHF.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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ETHICS COMMITTEE APPROVAL

N/A

Figure 1: Flow diagram through the different phases of the systematic review (PRISMA flowchart)

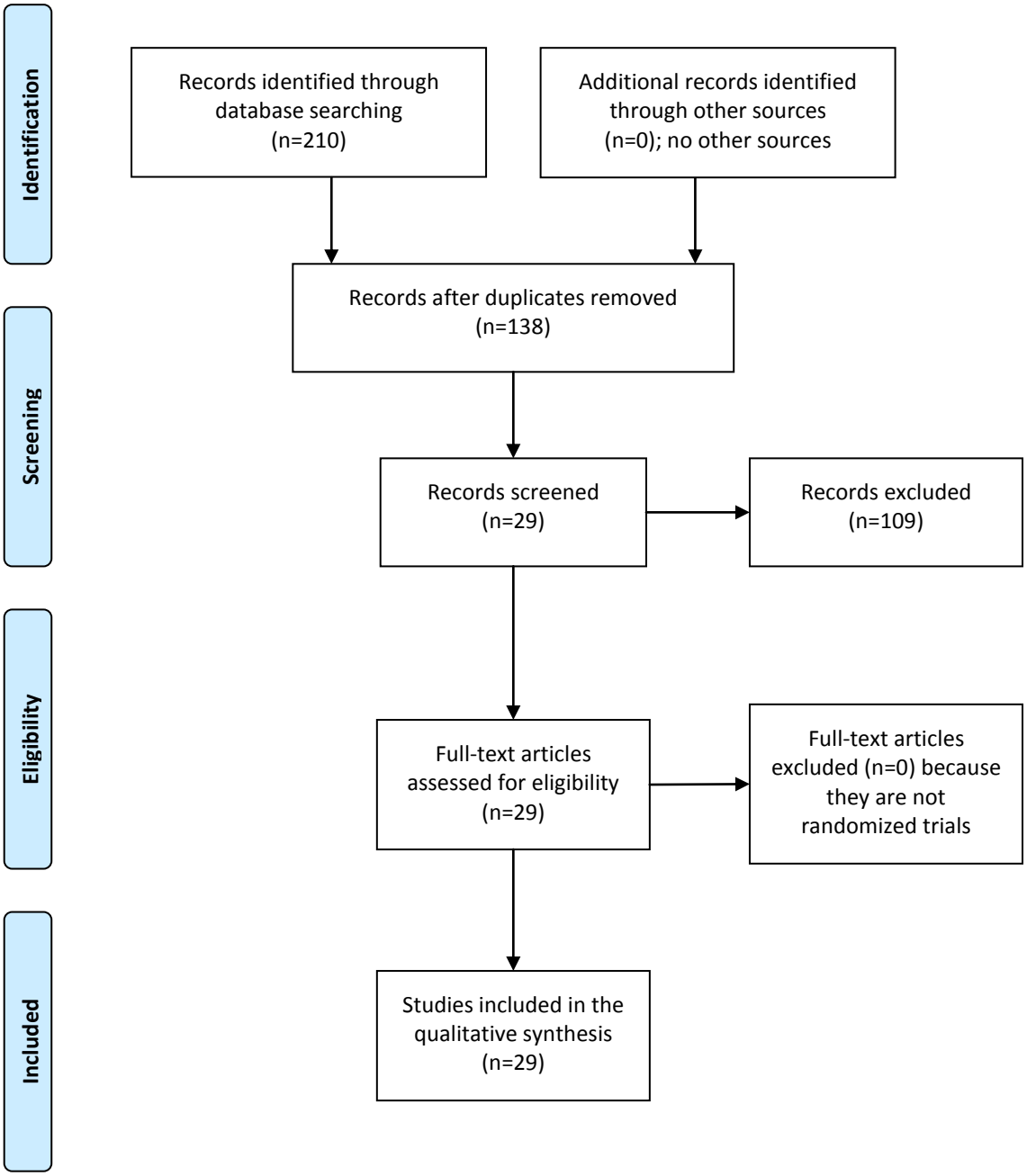

Table 1: Dapagliflozin effects on heart failure and major adverse cardiovascular events (observational and experimental studies)

Author	Year	Country	No of patients	Duration	Results
Kosiborod et al.	2017	USA	Retrospective (4,63,584 patients)		SGLT-2i was associated with a lower risk of HHF and death that may be a class effects
Kosiborod et al.	2017	USA	Pooled data from five RCTs		Dapagliflozin reduced HbA_{1c}, weight, and SBP in patients with T2DM and HF, and was well tolerated.
Toulis et al.	2017	UK	Retrospective (22,124 patients)		Lower death observed among patients received dapagliflozin
Meng et al.	2018	Japan	Experimental study		SGLT1, but not dapagliflozin (SGLT-2 mainly) inhibition (through MPP regulation in HCF) may be a novel strategy for the treatment of DCM.
Uthman et al.	2018	Netherlands	Mouse model		SGLT-2i induce vasodilatation in a healthy heart and reduce Na^+
Hallow et al.	2018	Georgia	Mathematical model		By reducing I interstitial fluid volume to a greater extent than blood volume, SGLT2 inhibitors might provide better control of congestion without reducing arterial filling and perfusion
Persson et al.	2018	Sweden, Denmark, Norway, UK	Real-world 40,958		Dapagliflozin reduced hospitalization for heart failure, lower risks of CV events and all-cause mortality compared with DPP-4 inhibitors in a real-world clinical setting and a broad T2D population
Lugat et al.	2018	France	Mouse-model		Dapagliflozin improved cardiomyopathy by hexosamine biosynthetic pathway reduction
Kosiborod et al.	2018	USA	Retrospective study(2,35,064 patients)		SGLT-2i were associated with a lower risk of CV events across a broad range of outcomes and patient characteristics (with and without cardiovascular disease).
Dawwas et al.	2019	USA	A retrospective study		Lower hospitalization compared to other antidiabetic, and a lower amputation risk compared to sulphonylureas
Idzerda et al.	2019	Netherlands	Pooled data from seven RCTs, 482 patients included		Dapagliflozin reduced heart and kidney failure events among patients with diabetic kidney disease
Chin et al.	2019	Australia	Markov model	20 years model period	Compared to first-line metformin monotherapy followed by the gradual addition of dapagliflozin, first-line use of combination dapagliflozin and metformin is likely to be a cost-effective
Norhammar et al.	2019	Sweden	Observational study. 28 408 participants		Dapagliflozin was safe about CV outcomes and resulted in lower event rates of HHF and CV mortality in real-world
Weeda et al.	2019	USA	Prospective cohort including 1,500 heart failure patients	12 months	New loop diuretic use was less frequent among SGLT2I users; however, patterns of loop diuretic use did not differ between cohorts in those on loop diuretics at baseline.
Eickhoff et	2019	Denmark	Post-hoc analysis of two	12 weeks	Dapagliflozin exerts both osmotic and

al.			RCTs=69 with albuminuria		natriuretic diuretic effects in patients with type 2 diabetes and kidney damage
Pasternak et al.	2018	Sweden	Retrospective, 20,983 patients	42 months	SGLT-2 use was associated with reduced risk of heart failure and any cause of death, but not with major cardiovascular events
Shao et al,	2019	Taiwan	Comparative study, 12,681patients on dapagliflozin *vs.* empagliflozin		Lower risk of heart failure observed with dapagliflozin compared to empagliflozin
Rådholm et al.	2019	Sweden	An analysis of 4 RCTs		No difference between men and women regarding the risk ratio and safety outcomes
Zhang et al.	2019	China	An animal study on pigs	9 weeks	Dapagliflozin reverses LV concentric remodelling in HFpEF pigs partly by restraining sympathetic tone in the aorta

Table 2: Dapagliflozin effects on HHF and MACE (randomized controlled trials)

Author	Year	Country	Methods	Follow-up	Results
Wilcox et al.	2018	USA	Forty-two healthy participants on fixed diet of 110mmol/day Na^+ were randomized to dapagliflozin 10mg/day and bumetanide 1mg/day or both for one week	7 days	The first dose combination was not additive regarding Na^+ excretion. However, synergistic effects were observed after one week. Also, dapaglilozin reversed bumetanide-induced hyperuricemia
Soga et al.	2018	Japan	Patients on antidiabetic medications and stable HF were prescribed dapagliflozin 5mg/day and followed for changes in mitral inflow E and mitral e' annular velocities, as primary end points, and left ventricle, atrial volumes, and brain natriuretic peptide (BNP) as secondary end points.	6 months	Dapagliflozin 5mg improved left ventricular diastolic dysfunction, no significant effects on BNP was observed
Wiviott et al.	2019	England	17,160 patients with/at risk of CVD assigned to dapagliflozin or placebo, the primary outcomes were MACE, HHF, CV death, the secondary end points were reduction in GFR, new end stage renal disease, and death from CV or renal disease, and all cause mortality.	4.2 years	MACE not affected by dapagliflozin, while HHF and CV death were reduced
Furtado et al.	2019	USA	17,160 patients with either established atherosclerotic CVD or multiple risk factors were assigned to either dapagliflozin or placebo, The primary end points were composite of MACE CV death, MI, or ischemic stroke) and the composite of CV death or HHF.	4.2 years	Dapagliflozin robustly reduced MACE and cardiovascular death/hospitalization for heart failure among patients with/at risk of CVD
Kato et al.	2019	Japan	DECLARE-TIMI 58 trial 17,160 patients with HF, ejection fraction (EF) was collected, the	4.2 years	Dapagliflozin reduced HHF in patients with and without HFrEF and reduced cardiovascular death

			patients were categorized and reduced (<45%) or normal EF.		and all-cause mortality in patients with HFrEF.
Phrommintikul et al.	2019	Thailand	Forty-nine T2D patients with coronary artery disease were randomly assigned to dapagliflozin or vildagliptin	6 months	More favourable effects of dapagliflozin compared to vildagliptin regarding blood pressure and weight reduction
Solini et al.	2019	Italy	Forty hypertensive patients were assigned to dapagliflozin 10mg or hydrochlorothiazide 12.5mg	4 weeks	Diuresis and osmolar clearance increased with dapagliflozin, and serum magnesium increased, while sodium clearance and GFR not affected.
McMurray et al.	2019	UK	4744 patients with HF (EF<40%) with and without DM were assigned to dapagliflozin 10mg or placebo	18.2 months	Dapagliflozin reduced hospitalization or an urgent visit resulting in intravenous therapy for heart failure and CV
Nassif et al.	2019	USA	RCT including 263 participants with and without DM and HF with reduced EF were assigned to dapagliflozin or placebo.	12 weeks	≥A 5-point improvement in Kansas City Cardiomyopathy Questionnaire overall summary score and HF was observed among dapagliflozin users, no effects on BNP
Bonora et al.	2019	Italy	Thirty-three patients with T2DM were given dapagliflozin or placebo	12 weeks	No change in cardiac function using impedance cardiography

DAPA-TIMI 58: Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58
HHF: hospitalization for heart failure
DCM: dilated cardiomyopathy
HFr EF: heart failure with a reduced ejection fraction
CV: cardiovascular
LV: left ventricle
BNP: brainnatriureticpeptide
MMPs: matrix metalloproteinases