Assessment of the Utility and Impact of IV Magnesium Infusion on Patient Outcomes and Quality of Life in Acute Heart Failure

by

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Abstract

Heart failure (HF) is a complex condition which is a growing and lethal public health issue in Canada and internationally. In the last several decades, the number of treatments for HF with reduced ejection fraction, which makes up a large portion of the HF population, has grown. The recommended therapy for HF patients is a combination of medications known as guideline-directed medical therapy or GDMT. However, as HF is a condition characterized by progressive deterioration many individuals who suffer from chronic HF (CHF) experience frequent episodes of acute decompensation leading to hospitalization for worsening HF also known as acute HF (AHF) even though they are being treated with GDMT. Patients are often given intravenous (IV) magnesium during AHF episodes, but little is known about the frequency and pattern of magnesium testing and treatment, and even less is known about the impact of magnesium treatment on patient outcomes and health-related quality of life (QoL).

The main goal of this study was to determine the current patterns of IV magnesium use and its impact on patient outcomes in acute heart failure. An extension of this goal was to develop the foundational research needed for a future study to assess the impact of IV magnesium therapy on QoL. Consequently, we designed a retrospective cohort study that involved the collection and analysis of data from 42,763 patients and 78,957 episodes of emergency department (ED) visits or hospitalization over 8 years to determine the rates and outcomes of magnesium testing, replacement, and hypomagnesemia. Furthermore, we conducted a network meta-analysis and systematic

review to determine what impact, if any, from IV magnesium would justify its continued use, the sample size needed for a sufficiently powered future prospective study, and the effect of different treatment combinations on the QoL of patients with CHF.

Our first study demonstrated that serum magnesium testing occurred in 58.7% of episodes and did not occur more frequently in patients with lower or higher potassium levels. The testing established that 31.7% of all patient episodes were hypomagnesemic and we found that with every 0.02 mmol/L unit decrease in serum magnesium level from 0.7 mmol/L and every 0.02 mmol/L unit increase in serum magnesium level from 0.86 mmol/L the risk of mortality at 2 years from the event increased significantly. This experiment also found that IV magnesium was given in 13.7% of all patient episodes and in those episodes 70.2% of the patients had hypomagnesemia. After overlap weighting, IV magnesium was associated with a higher risk of mortality at 7 and 7-30 days, but not any time points afterward. Patients with normal magnesium levels had the highest risk of mortality after receiving IV magnesium. Our second study showed that a combination of ARNi + BB + MRA + SGLT2i resulted in the largest change in QoL with an effect size of 7.11 units of change, but this effect was not significant. The treatment combination that resulted in the largest improvement in QoL was ARNi + BB + SGLT2i which had an effect size of 5.33. Our study results also showed that the individual therapy that led to the greatest improvement in QoL was SGLT2i with a mean change of 3.37 while the least effective was digoxin with a mean change of -5.34.

We concluded that hypomagnesemia may be associated with worse long-term outcomes for patients with acute heart failure, but it is not clear if this is related to physiological actions of magnesium. Furthermore, our studies showed that IV magnesium is associated with an increased risk of short-term mortality, however, whether this is caused by the administration of IV magnesium is unknown. Our network meta-analysis indicated that accepted combinations of HF treatments resulted had an effect size of 3-7 units in the KCCQ overall summary score and our findings suggest that a study evaluating IV magnesium's impact on QoL should do so both through a measurement of the mean change of QoL score and through a measurement of the proportion of patients undergoing a small, medium and large clinical change both towards improvement and deterioration of QoL due to the within-group variability in QoL experience.

Preface

This work is composed of original research conducted by Robert Margaryan. The study described in Chapter 2 of this thesis received research ethics approval from the University of Alberta Research Ethics Board, (Pro00010852). No part of this thesis has been previously published. I was responsible for writing the protocols, conducting the experiments, analysis, and manuscript writing. S. Islam assisted with the analyses in Chapter 2 in SAS. Dr. Sephervand assisted with data collection and Dr. Ouwerkerk assisted with the analysis in Chapter 3. Drs. Turgeon, McAlister, Kaul, Dover, Tromp, Sepehrvand, and Ouwerkerk contributed to the editing of the manuscripts in chapters 2 and 3. Finally, Dr. Ezekowitz is the supervisory author who contributed throughout these works.

Dedication

To my land of birth, Armenia, and to the land that adopted me, Canada.

երազ իմ երկիր հայրենի,	My Dream Armenia,
Հոգսերդ շատ, հույսդ մեծ,	Your worries are many, your hope is great
Քարքարոտ երկիր:	Rocky country.
Ես մի բուռն եմ ֆո հողի,	I am a fist of your soil
Ես մի ծիլն եմ ֆո արտի,	I am a sprout of your field,
Ես մի թերթն եմ ֆո ծաղկի,	I am a leaf in your flower,
Հայրենի երկիր,	Fatherland,
Հայաստան:	Armenia.
Երազի իմ երկիր հայրենի,	My Dream Armenia,
Հոգսերդ շատ, հույսդ մեծ,	Your worries are many, your hope is great
Արծվաբուն երկիր:	Eagles nest country.
Իմ պապերն են ֆեզ շահել,	My grandfathers won you,
Իմ եղբայրքն են ֆեզ պահել,	My brothers kept you,
Քոնն են որդիքն իմ ջահել,	Yours are my children, young
Հայրենի երկիր,	Fatherland,
Հայաստան:	Armenia.

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Finally, to my friends and family who have supported me: the greatest thank you.

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List of Abbreviations and Symbols

HF: heart failure

HFpEF: heart failure with preserved ejection fraction

HFrEF: heart failure with reduced ejection fraction

HFmrEF: heart failure with mildly reduced ejection fraction

EF: ejection fraction

RCT: randomized controlled trial

CHF: chronic heart failure

AHF: acute heart failure

CAD: coronary artery disease

COPD: chronic obstructive pulmonary disease

ARNi: angiotensin receptor blocker/neprilysin inhibitors

ACEi: angiotensin-converting enzyme inhibitors

ARB: angiotensin receptor blockers

BB: beta blockers

MRA: mineralocorticoid receptor antagonists

SGLT2i: sodium-glucose cotransporter 2 inhibitors

H-ISDN: hydralazine and isosorbide dinitrate

GDMT: guideline-directed medical therapy

IV: intravenous

HRQoL: health-related quality of life

$MgSO_4$: magnesium sulfate

Chapter 1 - Introduction and Review

1.1 THE SYNDROME OF HEART FAILURE:

1.1.1 The Condition

Heart failure (HF) is a complex condition occurring when the heart fails to pump sufficient amounts of blood due to structural or functional changes in the heart that prevent the heart muscle, or myocardium, from relaxing or contracting appropriately. Declared an emerging epidemic in 1997, heart failure is a growing and lethal public health issue in Canada and internationally.[1] It is estimated that more than 750,000 Canadians currently have a form of HF and while the incidence of heart failure has been falling, an aging Canadian population has resulted in a continued high burden of heart failure.[2-3] HF is expected to cost the Canadian healthcare system billions of dollars by 2030, several hundred million of which is due solely to the growing number of hospitalizations with a primary complaint of HF.[4] The severe nature of heart failure yields frequent emergency room visits and hospitalizations and a 5-year mortality rate of roughly 50%.[4] The severe impact of HF on public health is a result of the gradual or sudden onset of symptoms and continuous degeneration of health that eventually impairs daily living.

1.1.2 HF types

What happens in HF pathophysiology when the myocardium fails to contract and relax appropriately is analogous to a traffic jam, the location and result of which depends on whether heart failure occurs in the left, right, or both ventricles. Left-sided HF is more common and it leads to reduced perfusion of the organs, increased blood volume, and pressure in the pulmonary system. Right-sided HF is generally a result of the pressure and volume overload of the right ventricle and congestion of the pulmonary system which occurs during the failure of the left ventricle to effectively pump blood in left-sided HF, among other causes.[5] The result of right-sided HF is generally the development of swelling throughout the body and breathlessness as the right ventricle

struggles to pump blood into the pulmonary system. Left-sided HF can be further subdivided into HF with reduced ejection fraction (HFrEF), HF with mildly reduced ejection fraction (HFmrEF), and HF with preserved ejection fraction (HFpEF) - ejection fraction (EF) being the ratio of the amount of blood that is pumped out of the heart compared to the amount pumped in.

1.1.3 HFrEF/HFmrEF/HFpEF

The proportion of people who develop HFrEF compared to HFpEF/HFmrEF is roughly equal but varies from country to country.[6] The remodeling which results in reduced cardiac output leading to heart failure has different causes in HFrEF and HFpEF. HFrEF generally occurs under conditions of ischemia, which leads to loss of cardiomyocytes, such as myocardial infarction - colloquially known as a heart attack.[7-10] Under these conditions eccentric remodeling occurs along with fibrosis and cardiomyocyte autophagy, which essentially results in a thinning of the heart muscle and a loss of contractile capacity in the left ventricle.[7-10] Patients with HFpEF generally have several comorbidities like hypertension, obesity, and chronic obstructive pulmonary disease (COPD) before HF which lead to a continuous low-grade inflammatory response.[7-10] The persistent inflammation eventually leads to concentric remodeling, fibrosis, and further inflammation which essentially thickens the heart muscle, which weakens it and reduces the ability of the left ventricle to relax.[11] Compared to individuals with HFpEF patients with HFrEF are younger, more likely to be male, more likely to have higher biomarker levels, more likely to have severe symptoms, more likely to have an ischemic etiology, more likely to have coronary artery disease (CAD) and kidney disease.[7-10] There is also some evidence to suggest that patients with HFmrEF are closer clinically to HFrEF than to HFpEF as they are generally younger, have a higher likelihood of having ischemic etiologies, are more likely to have coronary artery disease than patients with HFpEF, but have less severe symptoms, lower biomarker levels, and higher blood pressure than patients with HFrEF.[7-10] Consequently, it is suggested that HFmrEF may be a milder form of HFrEF. It is also uncertain as to whether there is a difference in outcomes between individuals across the EF spectrum as some evidence suggests that patients with HFrEF

have a higher mortality and hospitalization rate than patients with HFpEF/HFmrEF, while others have found little difference in outcomes across ejection fractions.[9,12-14] This is further confused due to the differences in available treatments across ejection fractions as there are not any mortality or morbidity-reducing treatment options for patients with HFpEF, and while there is some evidence to suggest that therapies effective in HFrEF may also be effective in HFmrEF, these therapies have not yet been sufficiently assessed in standalone randomized controlled trials (RCT) in patients with HFmrEF.[3]

1.1.4 Chronic and Acute HF

Finally, it's important to consider the differences between chronic and acute HF clinical presentations. Generally, patients who have HF with an established diagnosis or a gradual onset of symptoms are described as having chronic HF (CHF). A sudden development of HF symptoms or the sudden deterioration of a person with chronic HF leading to hospitalization is referred to as acute HF (AHF). When a person presents to the hospital without an HF diagnosis acute HF is referred to as new onset or de novo HF as opposed to decompensated chronic HF when the patient has a diagnosis of HF and their symptoms deteriorate suddenly. Decompensated chronic HF is more common than de novo acute HF and tends to pose a higher long-term mortality risk than de novo acute HF as a decompensation event signals a worsening prognosis and an advancing deterioration for patients with CHF.[15-16] While AHF is a transient episode and in some cases is amenable to complete recovery, such as in viral myocarditis or alcohol-induced cardiomyopathy, CHF is a persistently deteriorating condition. Even when well managed, the mechanisms of compensation, including neurohormonal activation, overtime paradoxically lead to further damage which can eventually reach a stage of advanced HF.[17] This stage is characterized by the presence of persistent severe symptoms, accompanied by exercise intolerance and frequent episodes of acute decompensation and AHF. A patient with CHF may have several CHF decompensation episodes, that is episodes of AHF, before eventually experiencing sudden cardiac death or death due to progressive heart failure.[3]

1.2 DIAGNOSIS, HF BURDEN, AND TREATMENT

1.2.1 Diagnosis

The diagnosis of HF involves assessing the signs and symptoms of a patient, their medical history, their electrocardiogram, blood biomarker and electrolyte values, and echocardiography results.[3] In the non-acute setting clinicians may first look for signs of congestion and symptoms of difficulty breathing and swelling in areas like the ankles.[3,15] If these signs and symptoms are present, if there are abnormalities on the electrocardiogram or past conditions that are risk factors for HF (hypertension, myocardial infarction, CAD) the physicians may then order blood biomarker and electrolyte analyses.[3] These tests will determine the levels of natriuretic peptides BNP and NT-ProBNP, primarily. In healthy hearts, these hormones are present at low levels, and they form part of the compensatory mechanism for when the heart experiences volume or pressure overload; As normal heart function becomes heart failure however, BNP and NT-ProBNP levels are elevated and as a result, they can be used along with the other critical information listed previously to help rule in or rule out HF.[3,17] Finally an echocardiogram will be developed that will give information about the ejection fraction of the ventricles, whether they display eccentric or concentric hypertrophy, and whether there are regional wall motion abnormalities that may present an alternative diagnosis.[3,15] Together all of this information is used to determine whether HF is present, what type of HF it is, and thus, the most effective treatment for it. In acute settings, the diagnostic process may be reversed with echocardiography being completed before blood biomarker tests to rule out the potential for other more immediately harmful conditions before the diagnosis of HF is made for certain.[3]

1.2.2 HF Burden and Quality of Life

Beyond the risk of shortening a person's life, HF also presents the risk of decreasing the quality of a person's life.[18,19] HF symptoms include difficulty breathing and swelling in the lower extremities, but they also include exercise intolerance and fatigue, and while less common, other symptoms can include nausea, loss of appetite, confusion, and

wheezing.[3] As heart failure progresses, without effective treatment, these symptoms can become more severe and the condition as a whole can take a severe psychological toll to the point of preventing normal life activities.[15,20] Even when HF symptoms can be relatively well managed by recommended therapies and devices, patients have to suffer the side effects of these therapies which can be just as debilitating.[21-24] These side effects can include hyperkalemia -elevated potassium levels which can be dangerous-, hypotension, renal insufficiency, and a low heart rate which may lead to the intolerance of the medications required to reduce the risk of mortality and morbidity.[25] Intolerance of these medications is further complicated as patients with HF generally have a number of comorbidities such as atrial fibrillation, chronic kidney disease, COPD, depression, and diabetes mellitus some of which may also increase the likelihood of intolerability of critical therapies.[26,27] Beyond having to deal with the burden of HF symptoms and the side effects of their treatments, HF accounts for a large, and oftentimes the largest, proportion of hospitalizations in developed countries during which patients may experience decompensation which is a difficult experience.[28] Patients also have to rely on caregivers, many of whom are not prepared to support a person with HF.[29] While living with HF is not impossible, the burden that HF presents can prevent patients from fully enjoying their lives and results in a generally low quality of life for patients with HF which decreases with time. As quality of life can be as critical, if not more critical than the length of life for patients with HF across HF types, quality of life must be at the front of mind when assessing the value of current and future HF treatments.[30-32]

1.2.3 HF Treatments

The treatments available for HF can be divided into treatments that reduce mortality and morbidity and treatments that reduce symptoms of HF and other comorbidities. To date, there is only evidence of mortality and morbidity-reducing treatments for HFrEF and within this group, there are several classes of drugs that are recommended by the American College of Cardiology, American Heart Association, and the European Society of Cardiology.[3,15] The recommendations include angiotensin receptor blocker/neprilysin inhibitors (ARNi) or in cases of intolerance

angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) on their own. They also include beta blockers (BB), mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter 2 inhibitors (SGLT2i). Together these 4 classes of drugs form guideline-directed medical therapy or GDMT. In certain scenarios, drugs including ivabradine, soluble guanylate cyclase receptor stimulators like vericiguat, and nitrates like hydralazine and isosorbide dinitrate (H-ISDN) can be added to GDMT to further support the health of patients with HFrEF.[3,15] While some of these drugs are prescribed for patients with HFpEF and HFmrEF to treat comorbidities like hypertension there is limited evidence that they reduce mortality and morbidity in these patients. Devices like cardioverter-defibrillators or defibrillators for cardiac resynchronization therapy may also be indicated depending on the clinical characteristics of a patient.[3,15] Patients experiencing de novo HF may have GDMT initiated if this aligns with the etiology and type of their HF and patients experiencing decompensation of chronic HFrEF may have their current treatments adjusted, but in an acute setting, the primary goal is to manage symptoms and reduce damage to the heart in the short term which is why GDMT, which is titrated over a period of time for maximal efficacy, is not the primary treatment for a patient with an acute presentation. The treatments which are available to reduce symptoms of HF in the acute setting are used for all HF types including HFpEF, HFmrEF, and HFrEF. These treatments are mainly focused on controlling blood volume and fluid balance using diuretics, managing the other conditions experienced by patients through beta blockers or ACEi, and particularly in acute settings, managing blood pressure through vasodilators and vasopressors as needed.[3,15]

While not recommended by leading cardiovascular associations, other treatments may be used in acute settings. However, unlike GDMTs whose efficacy in improving patient outcomes is supported by countless high-quality studies, there has been little research into how treatments in the acute setting impact patient outcomes including mortality and morbidity as well as patient quality of life during and following AHF. As acute episodes of HF are a critical time for patients with new onset HF to define the

trajectory of their condition and a persistent feature of the experience of patients with CHF, it is important to better understand the efficacy of treatments in AHF.

1.3 ACUTE HF TREATMENT AND THE ROLE OF MAGNESIUM

1.3.1 Acute HF presentations and treatments

Acute HF can present clinically in 4 major ways and its management relies on three main therapies which may or may not be used depending on the presentation. AHF may present in the form of acute decompensated HF which is the most common presentation and mostly occurs in patients with CHF. This presentation is mainly characterized by a generally gradual development of congestion due to fluid retention. Cardiogenic shock is another presentation that is generally much more severe as it involves a life-threatening lack of blood flow throughout the body. This presentation occurs in advanced HF or in cases of severe ischemia, where a lack of blood flow to the heart leads to myocardial death. The last two presentations include acute pulmonary oedema and isolated right ventricular failure. Patients who are diagnosed with AHF are treated first for the underlying cause of the episode (myocardial infarction, acute coronary syndrome, hypertensive emergencies, etc.) then management is largely based on the clinical presentation.

Acute decompensated HF, pulmonary oedema, and right ventricular failure presentations can all be treated with diuretics to resolve fluid retention. Cardiogenic shock, acute decompensated HF, and right ventricular failure if there is evidence of hypoperfusion of the tissues can be treated with inotropes and/or pressors to increase blood flow to the body. Finally, pulmonary oedema may be treated with vasodilators to help alleviate congestion in the pulmonary system. While in theory patients with AHF would fall neatly into the categories listed above, this may not be the case and often the 3 therapies listed will be mixed and matched to achieve the desired outcome. If these 3 treatments -diuretics, vasopressors/vasodilators, and inotropic agents- don't relieve the symptoms of the patient renal replacement therapy or mechanical circulatory support may

be indicated, but this is largely the entire toolkit available for the treatment of AHF. Unfortunately, these treatments may reduce congestion and prevent immediate organ failure from hypoperfusion, but there is limited evidence that they provide a morbidity or mortality benefit.

It has been proposed that relieving congestion and reducing blood volumes through vasodilators and diuretics would reduce the risk of mortality because it would result in a reduction of the burden on an already weak heart, but there is no evidence to support this.[21,33-36] While there is also no evidence for a reduction in the risk of mortality with the use of diuretics, there is a consensus that they are indicated for all patients who present to the emergency room with signs of congestion and fluid retention.[3,15,37-38] The role and use of vasodilators are much more controversial, however. The AHA/ACC guidelines suggest that vasodilators may be considered for patients who present without hypotension or hypoperfusion and ESC guidelines suggest that if the patient's systolic blood pressure is higher than 100 mmHg vasodilators may provide an added decongestive benefit.[3,15,39] However both guidelines and other studies recognize the significant lack of evidence supporting an association between vasodilator use both with and instead of diuretics with reductions in mortality and the toxicity of current vasodilator options like sodium nitroprusside and nitroglycerine.[3,15,40-41] New vasodilators like ularitide and serelaxin in TRUE-AHF and RELAX-AHF respectively have also failed to show significant reductions in risk of mortality and morbidity following AHF and so have combinations of vasodilators including nitrates, RAAS blockers, and hydralazine.[36,42-43] It seems that the focus on new treatments for AHF has shifted towards revisiting diuretics and therapies for HFrEF like SGLT2is.[3,44] Regardless of the controversy surrounding the use of vasodilators as a treatment for AHF, intravenous magnesium sulfate infusions are still used within the treatment of AHF.

1.3.2 The role of magnesium in the cardiovascular system

Magnesium ions play a critical role in the body and specifically within the cardiovascular system. Magnesium is a metabolic cofactor in hundreds of enzymatic reactions,

particularly ones concerning energy utilization.[45] It is required in the sodium potassium ATPase pump and calcium ATPase pump and as such may exert a level of control on intracellular potassium and calcium concentrations.[45] Magnesium is required for nucleic acid and protein synthesis and it is involved in a number of mitochondrial processes.[45] The biochemical relationships of the magnesium ion mean it is directly involved in the regulation of the contraction and conduction of the heart and the vascular tone. As a result, administration of magnesium has been reported to result in vasodilation of both coronary arteries and the peripheral vasculature through modulation of vascular smooth muscle and endothelium dependent relaxation resulting in a reduction in mean arterial and pulmonary arterial pressures which could aid in decongestion.[46-49] By reducing pulmonary and mean arterial pressures and congestion, as has been postulated before for other vasodilators, magnesium infusions would be expected to result in a decrease in the force required by a failing heart to pump blood, potentially preventing further damage to the myocardium.[50] Additionally, magnesium administration may result in a reduction in the frequency and severity of arrhythmias and improvement in heart rhythm as hypomagnesemia - magnesium deficiency in the blood - has been associated with an increase in ventricular arrhythmias.[51-52] This action of magnesium could be due partly to the association between hypomagnesemia and hypokalemia - potassium deficiency in the blood -, which has been reported to be rectified by potassium administration only after magnesium supplementation, hypokalemia being a critical factor in the development of arrhythmias.[51, 53-54] Indeed the administration of magnesium both intravenously and orally has been shown time and again to promote better heart rhythm and reduce arrhythmias.[55-57] Additionally, oral magnesium administration for 5 weeks was found to result in a reduction of C-reactive protein in patients with chronic heart failure, potentially resulting in reduced inflammatory cascade signaling.[58] However, even with all of the evidence surrounding magnesium's key role in the cardiovascular system and in heart failure, it is still unclear whether in acute heart failure hypomagnesemia is associated with an increased mortality rate and whether magnesium treatment is associated with decreased mortality.

1.3.3 Hypomagnesemia

Due to the significant evidence supporting the importance of magnesium within the cardiovascular system it would be expected that hypomagnesemia would have a clearly defined association with patient outcomes in HF, but this isn't the case. The earliest studies already set the stage for controversy as Gottlieb et al. found that in patients with HFrEF hypomagnesemia was significantly associated with higher 1 year and 2 year mortality rates while the PROMISE study a few years later found no association between hypomagnesemia and poorer outcomes in the patients with HFrEF after adjusting for key variables.[59-60] Cohen et al would later present evidence that hypomagnesemia is associated with increased mortality in hospitalized patients with HF.[61] Further, investigators presented evidence using a propensity-matched population of patients with CHF across the EF spectrum from the DIG trial participant datasets that supported the results of Cohen et al suggesting that low magnesium was associated with cardiovascular mortality, but not hospitalizations or all cause mortality.[62] A few other studies agree with the conclusion that there is an association between low magnesium and worse outcomes in patients with HF including the trial by Nishihara et al which found an association between lower magnesium levels and higher mortality in patients with HFpEF.[63] However, these results are tempered by another set of studies such as the EVEREST and EPHESUS trials which also found no relationship between hypomagnesemia and increased mortality and hospitalization.[64-66]

There is no consensus or high quality evidence concerning whether or not magnesium levels have a prognostic significance in HF. Two factors that may contribute to this lack of consensus are the difference in study populations and the absence of a standard serum concentration of magnesium which defines hypomagnesemia. Some of the mentioned studies analyzed the relationship between serum magnesium concentration and poor outcomes in patients with HFrEF, some in patients with HFpEF, and some with all patients with HF. One study looked specifically at patients with acute HF presentations, while others were focused on patients with chronic HF. Further, some studies like Gottlieb et al considered hypomagnesemia to be serum magnesium levels

lower than 0.8 mmol/L while other studies like the EVEREST Trial considered it to be lower than 0.74 mmol/L.[59,64] Magnesium is unequivocally important to the normal functioning of the cardiovascular system, but clearly, the prognostic significance of magnesium is more complex than known previously.

1.3.4 IV magnesium

Even more unclear than the prognostic significance of magnesium in HF is the potential that intravenous (IV) magnesium infusion may have in acute HF since after a comprehensive search no study was found that endeavored to examine this. Experimental data that suggested that magnesium may be protective against ischemia inspired several studies to investigate IV magnesium infusion as a treatment for suspected acute myocardial infarction. Initial studies reported very significant, groundbreaking, protective effects in patients hospitalized with acute myocardial infarction: Shechter et al reported a 75% reduction in mortality compared to placebo in patients who didn't receive thrombolytic therapy, Raghu et al reported a 65% reduction in mortality compared to placebo in patients who received thrombolytic therapy, and a meta analysis by Horner et al reported a pooled hazard ratio of 0.46 for IV magnesium therapy in acute myocardial infarction - which is a reduction in mortality by 58% - across 8 studies.[66-70] This was enough evidence for 2 large scale randomized controlled trials, ISIS-4 and MAGIC, to be undertaken. However, neither trial was able to replicate the results that were seen in the smaller scale trials, with both reporting nearly identical mortality rates in IV magnesium treated and placebo controlled groups of patients suspected of experiencing acute myocardial infarction.[71-72] While acute myocardial infarction and acute heart failure are related and myocardial infarction can often lead to HF, more research is needed to rule out the possible efficacy of IV magnesium in AHF.

IV magnesium infusions are administered in both patients with acute HF who have a serum magnesium deficiency and those who do not and upon reviewing the currently available evidence concerning IV magnesium's potential as a treatment in acute HF this is likely based on clinical experience and anecdotal evidence. The continued use of IV

magnesium against a background of a known lack of benefit in acute myocardial infarction suggests that direct evidence evaluating the effectiveness of magnesium therapy is needed and that there may be a hidden benefit to patient outcomes justifying its use even without clear evidence of a mortality benefit. Specifically, a quality of life benefit may be imparted by IV magnesium therapy as it may potentially reduce congestion and rhythmic abnormalities during AHF which may improve patients' experience during AHF and afterward. Beyond the symptoms of HF mentioned previously such as dyspnea, fatigue, and depression which lead to a deteriorating quality of life, the experience of the acute care environment and of AHF can lead to further declines in quality of life.[73-74] Indeed the perceived severity and experience of arrhythmias and congestion seem to have a significant impact on the quality of life of patients with HF and other cardiac conditions, the impact of health conditions on the quality of one's life can be so great that patients prefer quality of life improving therapies over survival improving therapies, thus improving quality of life and care experiences is critically important.[73,75-76] This suggests that if magnesium therapy provides a quality of life benefit its use may be justified even if it does not impact mortality-related outcomes. More research is needed to understand how quality of life is influenced and if therapies like IV magnesium can improve patient outcomes or the quality of life of patients with acute heart failure. However, quality of life is not regularly assessed in clinical practice and as a result, prospective or RCT-based studies must be used to assess the impact of IV magnesium therapy on quality of life.

1.4 THESIS STRUCTURE

1.4.1 Research objective

The main goal of this study is to determine the current patterns of use of IV magnesium and its impact on outcomes such as mortality and hospitalization in patients who have experienced an acute heart failure episode. Additionally, an evaluation of the change in quality of life experienced by patients with AHF after IV magnesium therapy is necessary. Therefore, an extension of the main goal of this study is to develop the

foundational research needed to permit the future development of a study to assess the impact of IV magnesium therapy on quality of life. Consequently, we conducted a retrospective cohort study using population-based data to determine what the frequency and factors associated with serum magnesium testing and IV magnesium administration are, whether serum magnesium levels are associated with negative outcomes, whether administration of IV magnesium results in corrections of these outcomes and whether administration of IV magnesium results in improvement of outcomes regardless of magnesium level. We also used a network meta-analysis methodology in a second experiment to determine and compare the impact of various combinations of accepted treatments on changes in quality of life in patients with chronic HF to facilitate a future study that could evaluate IV magnesium.

1.4.2 Research methodology

The decision to separate the experiments and use the named methodologies was based on our ability to access a set of comprehensive databases with clinical and follow-up information for 48,000 patients with acute heart failure which made a retrospective study design appropriate. However, as this database did not include quality of life scores and it was not possible to evaluate the effect of IV magnesium infusions on the quality of life of patients with acute heart failure at this time, we decided instead to build the foundation for a future study using a network meta-analysis design to answer several important questions. By determining the effect of accepted treatment combinations on quality of life in a similar patient population the network meta-analysis would allow us to determine what impact, if any, from IV magnesium would justify its continued use and what number of patients would be necessary to ensure that there was a large enough sample size for a sufficiently powered prospective study. Additionally, this study would allow us to compare the effect of different treatment combinations on the quality of life of patients with chronic HF to better understand how quality of life is influenced in this patient group which will help inform the design of a quality of life study for patients in acute HF episodes.

The thesis is divided into four chapters. Chapter one provides background information of the study and chapter four is a summary of the results, conclusions, and further recommendations. Chapters 2 and 3 are versions of manuscripts being prepared for publication under the same title.

Chapter 2 - Factors related to the testing and replacement of magnesium and its association with clinical outcomes in patients with acute heart failure: a population-based study

2.1 INTRODUCTION:

2.1.1 Choosing wisely

Discussions surrounding unnecessary tests and treatments in cardiovascular medicine have become more prevalent since 2014 when the Choosing Wisely Canada campaign was launched, but have been ongoing for several decades.[77] Decisions about whether to administer a test or provide a treatment/procedure are even more involved in complex conditions like heart failure which is a major public health problem, with frequent emergency department visits, hospital admissions, and a 5-year survival rate of roughly 50%.[3] While many tests, treatments, and procedures are being evaluated closely to determine their necessity, to our knowledge the frequency and patterns of serum magnesium level testing and intravenous (IV) magnesium treatments are unknown.

2.1.2 Hypomagnesemia and IV magnesium

Electrolyte imbalances such as hypomagnesemia, are frequently observed in HF patients with 19-53% having hypomagnesemia.[59-60,62,78-79] However, there is a limited understanding of the involvement of magnesium in the pathophysiology of HF particularly in the acute setting. Several studies have shown treatment with magnesium to be associated with greater conductive and vascular stability, with reports of decreased mean arterial pressure, systemic resistance, ventricular ectopy, tachycardia, and QT interval variability in addition to increases in heart rate variability and arterial compliance in both patients with acute or chronic HF.[55,57,59-60,62,78-79] Earlier studies in this area also indicated that there may be an association between hypomagnesemia and increased mortality risk in patients with HF. However, results have varied, consequently, there is no consensus on whether hypomagnesemia is associated with adverse outcomes in patients with acute or chronic HF.[61,62,64] Further, while large clinical trials have shown that IV Mg

does not improve survival in acute myocardial infarction, the efficacy of IV magnesium as a treatment in heart failure is still unknown.[71-72]

Thus, to address these knowledge gaps, we designed this study to explore the frequency and factors related to magnesium testing and treatment, as well as any associations between hypomagnesemia and IV magnesium treatments with patient outcomes in patients with acute HF.

2.2 METHODS:

2.2.1 Study design

This is a retrospective cohort study that used patient data collected from April 1, 2012 to March 31, 2020 in the province of Alberta through the Alberta Health Services Discharge Abstract Database (DAD) and the National Ambulatory Care Reporting System (NACRS). This period of time was chosen to avoid overlap with the abnormal care conditions stemming from the COVID-19 pandemic. Through these databases, we were able to identify all primary heart failure hospitalizations or emergency department visits (ED) during the mentioned time period. The Pharmaceutical Information Network (PIN) database provided the information (including Drug Identification Number (DIN), Anatomical Therapeutic Chemical Classification (ATC), dispensing date, amount, and days of supply) on prescribed medications dispensed to outpatients in Alberta from January 1, 2008 onwards. Hospital-based pharmaceutical datasets including DOSE and SCM were used to obtain information on IV magnesium supplementation. The laboratory testing details were collected from a province-wide laboratory repository that included inpatient, ED, and outpatient lab tests and was available from April 2012 onwards. The Population Registry database contained patients' demographic information (i.e. year of birth, sex, first three digits of patients' residential postal code) and the Vital Statistics database provided information on deaths including date of death. All of the diagnoses complied with International Classification of Diseases-10th Revision (ICD-10) codes and this study is reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

2.2.2 Patient Population

Patients included in the cohort were adults > 18 years old who visited the emergency department or were hospitalized with a primary diagnosis of HF (ICD-10: I50.x) between April 01, 2012 and March 31, 2020. We considered ED visits and hospitalizations with HF within 48 hours as a single episode of care. Recognizing the discontinuous nature of intravenous magnesium replacement in patients with HF, we analyzed each hospitalization or ED visit (except those within 48 hours) as discrete episodes of care and consequently analyses were done at the episode level rather than the patient level. Patient comorbidities were identified using ICD codes (9th and 10th revision) from any hospitalizations, ambulatory encounters, or from physician's claims in the outpatient setting (≥2 claims at least 30 days apart within one year) for all healthcare encounters up to six years prior to the index episode.

2.2.3 Serum Magnesium Definition

Serum magnesium tests and other laboratory tests were captured from the laboratory database if the test was done within ± 1 day of HF episodes. The lowest values of serum magnesium concentration were chosen when multiple tests were done during a single episode. For other laboratory tests, the tests closest to the episode start date were selected for the analysis. The main analysis evaluated serum magnesium as a continuous variable. In addition, serum magnesium levels were considered to be indicative of hypomagnesemia if they were lower than 0.75 mmol/L. A range of cutoff values were explored including 0.65 mmol/L, however, 0.75 mmol/L was chosen for the main analysis considering values in the literature.[58,61,63]

2.2.4 Intravenous Magnesium Therapy Classification

Treatment of patients in the cohort with magnesium was considered in the analysis when the magnesium compound was formulated as magnesium sulfate ($MgSO_4$) as this is the only available intravenous magnesium formulation in Canada. Administration of magnesium sulfate was only considered if it occurred within ± 1 day of HF episodes.

2.2.5 Outcomes

The primary clinical outcomes of interest included all-cause death and hospitalization (all-cause, CV related, and HF-related). Secondary outcomes of interest included ED visits (all-cause, CV related, and HF-related) and Physician claims (all-cause, CV related, and HF-related). Other outcomes included factors and rates of serum magnesium testing and hypomagnesemia. Patients in the cohort were followed from the index episode for two years until they had another episode of HF hospitalization or ED visits, moved out of the province, died or the study ended (March 31, 2020), whichever occurred first. However, the next episode of HF hospitalization or ED visit, that occurred in two years, might be considered as the outcome of the earlier episode. The time to event was measured as the time from the first episode to the first outcome event that occurred during the follow-up.

2.2.6 Statistical Analysis

Categorical variables were summarized as counts with proportions, and compared between/across groups using Chi-square tests. Continuous variables were summarized as medians with interquartile range (IQR). Mann-Whitney U test was used to compare them between two groups, and the Kruskal-Wallis test was applied when comparing more than two groups.

We used multivariable binary logistic regression models with generalized estimating equation (GEE) to determine (i) the factors associated with magnesium testing and (ii) the factors associated with hypomagnesemia. We included a number of variables such as patient demographics, comorbidities, and medications. The variables included were chosen due to their availability within databases and their clinical relevance in the context of magnesium balance within the cardiovascular system and AHF. Linearity assumption for the relationship of continuous variables such as age with magnesium testing and hypomagnesemia was assessed and included as the natural cubic spline including percentiles with 3 knots.

We determined the association between IV magnesium replacement and clinical outcomes of interest including death, hospitalization (all-cause, CV related, and HF-related), and ED visits (all-cause, CV related, and HF-related). The crude rate of outcomes in groups receiving versus not receiving magnesium therapy was presented as the rate per 100 person-months.

Time-varying cause-specific Cox regression models with weighting to balance the treatment groups were used to determine the change in risk of mortality and other clinical outcomes with IV magnesium sulfate administration. The period of measurement for outcomes in the previously mentioned subjects included the length of time from one HF hospitalization where the magnesium test was done to the next. Additionally, a second analysis explored the association between magnesium therapy and short-term hospital mortality. We limited this analysis to patients aged 60 to 90 years old, with a maximum of three HF episodes, due to the lower number of IV magnesium administration events among patients who did not meet the above criteria preventing the efficient propensity score based balancing of the treatment groups. Outcomes were reported as weighted hazard ratios (HR) with 95% confidence intervals (CI) for periods of conditional mortality. In this analysis, mortality was considered a competing risk for other outcomes. To get the propensity of receiving magnesium supplementation at each episode, we constructed a multivariable binary logistic regression model including a number of variables that were clinically relevant and accessible in the database such as patient demographics (age and sex), residence, hospital type, clinical setting (ED and admission), fiscal year, diabetes, hypertension, hyperlipidemia, CAD, PVD, Afib, thromboembolism, liver disease, renal disease, asthma, COPD, cancer, depression, dementia, medications, comorbidities and laboratory test results (sodium, potassium, magnesium, serum creatinine and hemoglobin, and BNP). The variables included were chosen due to their availability within databases and their clinical relevance in the context of magnesium balance within the cardiovascular system and AHF. Continuous variables were included in the model as natural cubic splines including percentiles method. Around 99% of patients had hemoglobin and serum creatinine tests available, while 67.5% had sodium

and potassium tests available. Missing sodium, potassium, hemoglobin and creatinine values were imputed using multiple imputation with a fully conditional specification method. After examining the interaction between variables, an interaction term for age and serum magnesium value was included in the propensity model. The balance of variables between groups was assessed using the standardized mean differences; variables were considered well balanced if the standardized mean differences ranged from -0.2 to 0.2. We used overlap weight instead of inverse probability weight to avoid the influence of observations with extreme weight on outcome.[81] The overlap weighting approach assigned each patient a weight proportional to his or her probability of being in the opposite treatment group, and we also observed the exact balance of covariates between the treatment groups. Further, a falsification endpoint was used to further evaluate for the presence or absence of bias in the model which evaluated the association between IV magnesium with patient outcomes after weighting. To achieve this, the association between IV magnesium and urinary tract infections (UTIs) or hip fractures was explored as both conditions are associated with increased frailty and poorer overall health unrelated to magnesium pathophysiology or the cardiovascular system.

Two-sided p-values <0.05 were considered statistically significant. All analyses were done with SAS 9.4 version (SAS Institute Inc).

This study was approved by the University of Alberta Research Ethics Board (Pro00010852). Given the nature of the study, with de-identified administrative data provided through Alberta Health Services, individual patient consent was not deemed necessary by the board.

2.3 RESULTS

2.3.1 Cohort characteristics

Our study included 78,957 episodes of hospitalization or ED visits for HF (in 42,763 patients followed for a median of 1.9 years [Interquartile range (IQR) 0-3.8] after their first episode of care), and in 58.7% episodes, serum magnesium was measured. The

median age of the patient cohort was 80 years (IQR 70, 87) with 47.2% of patients being female. Among 46,363 episodes during which magnesium was measured, patients had serum magnesium levels <0.75 mmol/L in 31.7% of episodes, between 0.75 - 0.95 mmol/L in 56.8% of episodes and >0.95 mmol/L in 11.5% of episodes. Episodes, where patients were tested for serum magnesium levels, were more likely to occur at a tertiary hospital (23.7% vs 5.7%; p<0.0001), were more likely to occur with patients who were admitted rather than discharged from the ED (69.1% vs 42.3%; p<0.0001) and had a longer length of stay (5 (IQR 1,11) vs 1 (IQR 1,5) days; p<.0001) (Table 1). Patients had higher BNP (858 (IQR 478, 1580) vs 746 (IQR 413, 1364); p<.0001) and NT-proBNP (1908 (IQR 696, 5528) vs 1420 (IQR 531, 3877); p<.0001) values in episodes with a magnesium test compared with episodes without a magnesium test (Table 1). Patients in episodes with a serum magnesium test also had more comorbidities according to the Charlson Comorbidity Index (5 (IQR 3, 7) vs 4 (IQR 2, 6); p<0.0001) than patients in episodes that did not feature a test (Table 1). However, there was no difference in potassium levels, medication use, or ejection fraction between the two groups.

2.3.2 Hypomagnesemia

Magnesium levels (per 0.02 mmol/L increase) were independently associated with mortality when they were less than 0.70 mmol/L [hazard ratio (HR) 0.99 (95% confidence interval (CI) 0.98-0.99); p<0.001] or greater than 0.86 mmol/L [HR 1.04 (95% CI 1.03-1.04); p<0.001] (Figure 1). Patients with hypomagnesemia were also more likely to be hospitalized rather than discharged from the ED compared with patients with normal magnesium levels and hypermagnesemia respectively (72.4% vs 67.8% vs 66.3%; p<0.0001) (Table 3). Patients with hypomagnesemia also had longer episodes (6 (IQR 1, 13) vs 5 (IQR 1, 10) vs 4 (1,10); p<0.0001) (Table 3). However, patients with hypomagnesemia had lower BNP (545 (IQR 198, 1220) vs 573 (IQR 214, 1238) vs 708 (IQR 238, 1680); p<0.0001) NT-proBNP levels (1830 (IQR 676, 5305) vs 1898 (IQR 696, 5385) vs 2209 (IQR 781, 7421); p<0.0001) than patients without hypomagnesemia, while having similar medication use, residence and potassium levels (Table 3).

2.3.3 IV magnesium

IV magnesium was given in 13.7% (n=6,333) of episodes that featured a serum magnesium test and in 30.3% (n=4451) of episodes with hypomagnesemia. Among patient episodes that received IV Mg (n=6,333), 70.3% (n=4,451) of episodes had magnesium levels <0.75 mmol/L, 27.5% (n=1,744) had magnesium levels 0.75-0.95 mmol/L and 2.2% (n=138) had magnesium levels above 0.95 mmol/L. In the patients who did not receive IV magnesium, but had a magnesium test there were 9010 deaths (2.6 per 100 person-months) and 13339 hospitalizations for any cause (5.8 per 100 person-months). Whereas, in the group of patients who received IV magnesium the number of deaths was 1539 (2.7 per 100 person-months) and the number of any cause hospitalizations was 2176 (5.8 per 100 person-months). Having an urban residence [aOR 1.55 (95% CI 1.42-1.69); p<0.001], visiting a tertiary hospital [aOR 1.35 (95% CI 1.26-1.45); p<0.001], and being admitted to the hospital [aOR 2.41 (95% CI 2.22-2.62); p<0.001] were associated with an increased likelihood of receiving IV magnesium (Table 5). Similarly, patients with coronary artery disease [aOR 1.13 (95% CI 1.06-1.21); p<0.001] and atrial fibrillation [aOR 1.17 (95% CI 1.09-1.25); p<0.001] were also more likely to receive IV magnesium (Table 5). Additionally, every 0.1 mmol/L reduction in serum magnesium concentration from 0.8 mmol/L was associated with a 308% increase in the likelihood of receiving IV magnesium [aOR 4.08 (95% CI 3.92-4.25); p<0.001] (Table 5). However, the use of beta blockers [aOR 0.83 (95% CI 0.77-0.90); p<0.001] was associated with a lower likelihood of receiving IV magnesium and other GDMTs such as MRAs and ACEi/ARB/ARNi trended towards a lower likelihood of receiving IV magnesium, but was not statistically significant (Table 5).

After weighting, receiving IV magnesium was associated with a higher 7 day mortality risk [HR 1.57 (95% CI 1.33-1.86); p<0.0001], that persisted in the 7-30 day period [HR 1.45 (95% CI 1.11-1.90); p=0.007] (Figure 3). Up to 60 days after the infusion of magnesium a pattern of mortality risk according to serum magnesium concentration was evident as patients with normal magnesium levels had a higher risk of death compared to both patients with hypomagnesemia and patients with

hypermagnesemia (Figure 3). IV magnesium was also associated with a higher risk of 7 day [HR 1.36 (95% CI 1.13-1.64); p<0.001] all-cause hospitalization and a reduction in the risk of 7 day all-cause ED visits [HR 0.62 (95% CI 0.50-0.78); p<0.001] after weighting (Figure 3). IV magnesium was associated with an increase in the likelihood of 30-60 day CV physician claims after weighting [HR 1.27 (95% 1.06-1.51); p=0.009] (Figure 3). IV Magnesium was not associated with CV or HF hospitalization, ED visits, or Physician claims at any time point after adjustment. Patient outcomes at all other time points were similar regardless of IV magnesium administration (Figure 3).

2.3.4 Falsification Endpoint:

IV magnesium therapy was not associated with increased or decreased risk of urinary tract infection (UTIs) or hip fractures at any time point, before or after adjustment with propensity weighting (Table 6).

2.4 DISCUSSION

2.4.1 Key findings

This study explored the factors and outcomes related to serum magnesium testing, hypomagnesemia, and IV magnesium supplementation in patients with acute HF, which to our knowledge no other study has done before. There are three key results from our study that warrant discussion. First, serum magnesium testing is associated with more testing, longer hospital stays, and worse patient conditions, and IV magnesium administration may have two main patterns of prescription. Second, serum magnesium levels are associated with increased mortality below 0.7 mmol/L, and hypomagnesemia is not associated with an increase in BNP or NT-proBNP levels. Finally, IV magnesium administration is associated with greater mortality, particularly when it is given to patients with normal serum magnesium levels.

2.4.2 Patterns in administration and testing

We determined that serum magnesium testing and IV magnesium replacement occur frequently in patients with heart failure in hospitals. Serum magnesium testing occurred more in patients with heart failure that appears more severe and with more comorbidities, patients with longer hospital stays, and patients being treated in tertiary hospitals. Patients who were tested for serum magnesium were also more likely to have been tested for other markers and electrolytes such as sodium, potassium, and creatinine. This suggests that testing was more likely to occur when patients appeared to have a worse condition and potentially as a part of a routine combination of tests. Conversely, the likelihood of receiving Intravenous magnesium supplementation was higher for patients with hypomagnesemia, patients who had atrial fibrillation, patients who were admitted rather than discharged, and patients who visited tertiary hospitals. This supports the presence of two main prescription patterns for IV magnesium: its association with hypomagnesemia suggests that it is often used to correct the magnesium balance, additionally, its increased use in patients with a heightened risk of arrhythmias such as patients with atrial fibrillation and the evidence of magnesium acting as an antiarrhythmic suggest its other main use to be as a prophylactic antiarrhythmic agent.

2.4.3 Hypomagnesemia

There is no consensus concerning the prognostic significance of hypomagnesemia in HF and limited agreement concerning the factors related to hypomagnesemia, but our study may provide some clarity concerning the factors and significance of hypomagnesemia in AHF. Our study found that hypomagnesemia was more likely in patients who were younger and female and that hypomagnesemia was associated with more hospitalizations, and longer hospital stays, but not higher BNP and NT-proBNP levels. Importantly, our study also found that serum magnesium concentrations were associated with mortality when they were below the level of 0.7 mmol/L and above the level of 0.86 mmol/L. In comparison to studies in the past which have found both evidence for and against an association between low magnesium levels and poor outcomes, our study took a data driven approach; previous studies generally grouped patients into categories of

hypomagnesemia, normal magnesemia, and hypermagnesemia or low and high serum magnesium and evaluated the association of these groups with poor outcomes.[55,57,59-65,78-79] This approach introduces some unnecessary assumptions and is the reason that there are a variety of definitions of hypomagnesemia that have been used in previous studies, but even when studies used similar definitions they often had varying mean serum magnesium concentrations in their groups.[59,64-65] For example, the EVEREST study, which was the only other study to evaluate the prognostic significance of serum magnesium in worsening heart failure, used a similar cutoff of 0.74 mmol/L to our data driven cut off of 0.7 mmol/L for the hypomagnesemic group, however the mean magnesium concentration in this group was 0.7 mmol/L which suggests that much of this group was not at a magnesium level which would be associated with worse future outcomes according to our results.[64] This may be one reason why their study did not find an association between hypomagnesemia and mortality in patients with worsening heart failure while our study did. In general, our study is able to avoid the problem of defining hypomagnesemia a priori and consequently, it provides stronger results, but cannot be compared directly with previous research.

While our study provides more evidence supporting the prognostic significance of magnesium in acute HF, it is still unclear whether serum magnesium is representative of total body magnesium balance which poses an important problem because while it is clear that magnesium is critical to the physiology of the cardiovascular system, it cannot be determined if the association between hypomagnesemia and poorer outcomes in patients with acute HF is due to a pathophysiological depletion of critical electrolytes or if hypomagnesemia is associated with poor outcomes for another reason such as a lack of high magnesium foods, which has more consistently been associated with worse outcomes, resulting in hypomagnesemia.[58,62,82-85] Consequently a greater understanding of the relationship between serum magnesium concentration and pathophysiological processes is necessary.

2.4.4 IV magnesium

Although previously there were no attempts to evaluate the efficacy of IV magnesium in reducing mortality and hospitalization in chronic or acute HF, some research evaluating the use of oral and IV magnesium supplementation to establish rhythmic, electrolytic, and hemodynamic control has been done in patients with HF.[52,55,57,79-80] Particularly well documented is the reduction in arrhythmic phenotypes and increases in serum magnesium concentration which result from IV magnesium infusion in patients with chronic and worsening HF.[52,55,57] While IV magnesium may be able to reduce arrhythmic phenotypes the results of our study suggest that IV magnesium may not address more dangerous arrhythmias as we were unable to find an impact on the mortality and morbidity risk for patients with acute HF at any time point with IV magnesium administration. In fact, there was a strong association between magnesium infusion and greater mortality risks at 7 and 30 days in our study after adjustment for known confounders. This was not observed in trials of IV magnesium infusion in patients with acute myocardial infarction like MAGIC and ISIS-5 which found no association between mortality and IV magnesium infusion.[71-72] As magnesium is a potent vasodilator and may have a role in modulating the central nervous system, it is possible that IV magnesium administration contributed to severe hypotension and respiratory depression in some patients, however, our results also indicate that the risk of mortality associated with IV magnesium infusion is largest for individuals with magnesium in the relatively normal range, and near neutral for individuals with hyper- and hypo- magnesemia which suggest that the association of IV magnesium with mortality is not dose related and may have a more complex pattern in AHF.[86] As the likelihood of IV magnesium administration was higher for individuals who were admitted to the hospital rather than discharged it is possible that IV magnesium was more likely to be administered to patients with a more severe condition. This would suggest that IV magnesium and patient outcomes may be associated with a mutual relationship with another variable. However, it is unlikely that a mortality benefit is hidden under an erroneous association between IV magnesium therapy and patient outcomes through effect modification after the extensive adjustment procedures followed. Additionally, a potential association between IV magnesium administration and health condition severity is tempered as an explanation for the mortality risk seen after IV

magnesium administration due to the lack of a similar association between IV magnesium administration and other factors (UTI's and Hip Fractures) which may be associated with health condition severity.[87-90] More research is needed to understand the association between IV magnesium and mortality in AHF.

2.4.5 Strengths and limitations

Our study has a number of strengths, but due to its observational and retrospective design, it also has some limitations. By using administrative health data from a single payer universal healthcare system our study population closely represents the characteristics of the general population and as a result, our study findings are easily generalizable to the general population. We addressed the influence of known confounders and factors influencing exposure risk through our propensity-weighted analysis and falsification endpoint analysis, but we also recognize that there may be unknown or unmeasured variables that may have impacted our results. Though the administrative health database did not have access to data on clinical characteristics of patients like blood pressure, New York Heart Association functional class, or ejection fraction in the case of some patients, we were able to access and account for other characteristics including laboratory tests like serum potassium, and natriuretic peptide levels.

2.4.6 Conclusion

We determined that nearly 59% of acute HF episodes had a serum magnesium test, with 31.7% having hypomagnesemia and IV magnesium infusion being given in 8% of all episodes and 13.7% of episodes that featured a serum magnesium test. This represents a significant portion of the AHF patient population which suggests that magnesium related tests and treatments are frequently prescribed. It is still unclear how important serum magnesium levels are to patient outcomes in heart failure and there is no evidence to suggest a patient benefit from IV magnesium treatment; on the contrary, our results indicate there may be significant harm associated with the treatment in patients with

acute HF, particularly patients with normal serum magnesium levels. It is critical then, to further evaluate the relationship between acute heart failure and magnesium balance and when and if IV magnesium's frequent use is justified in patients with acute HF.

Figures:

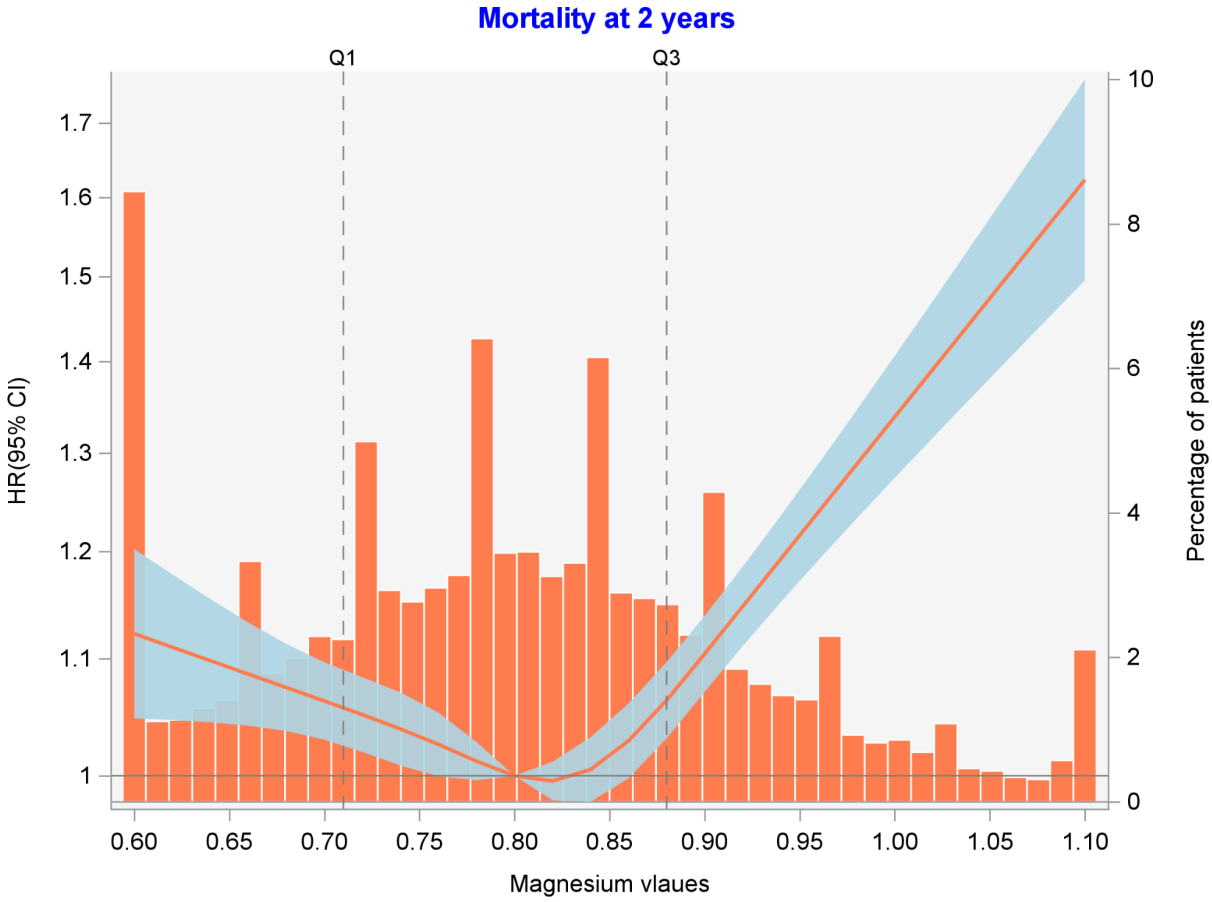


Figure 2.1. The proportion of patients at various magnesium concentrations with a hazard ratio curve for various magnesium concentrations at 2 years overlayed.

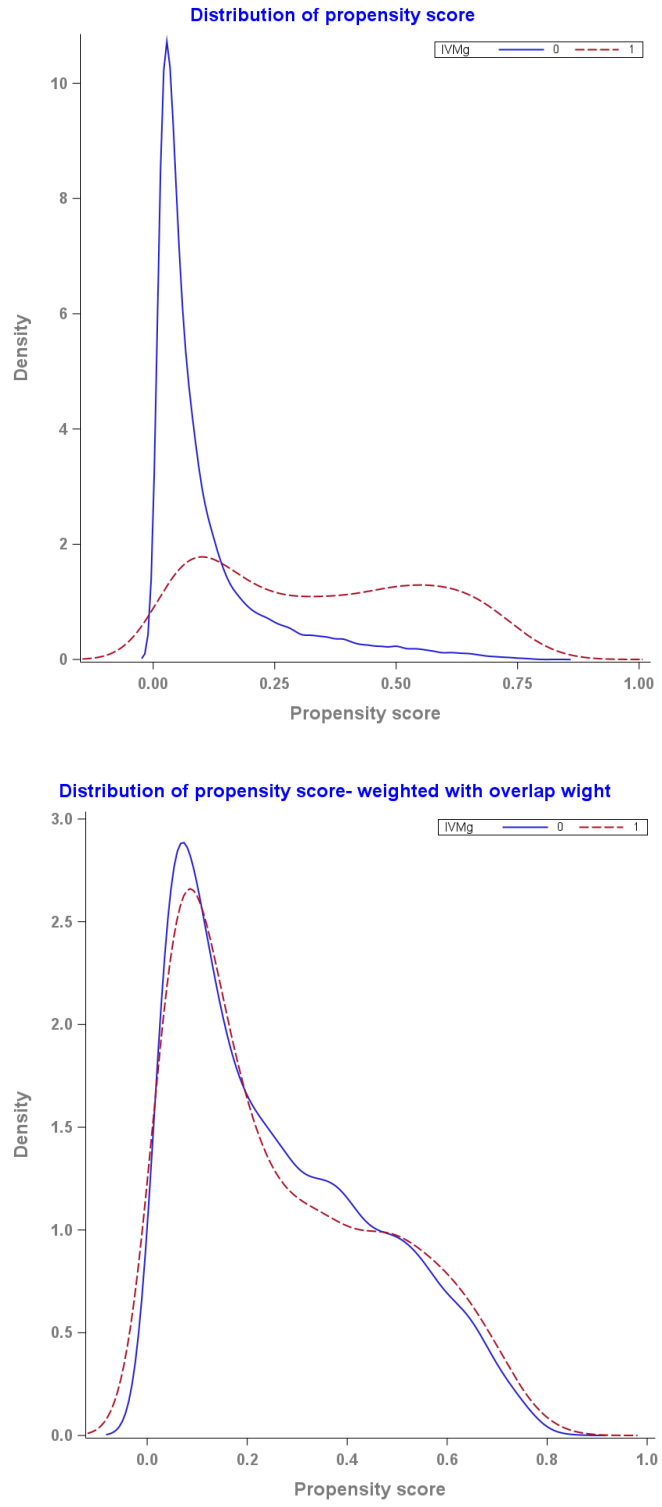
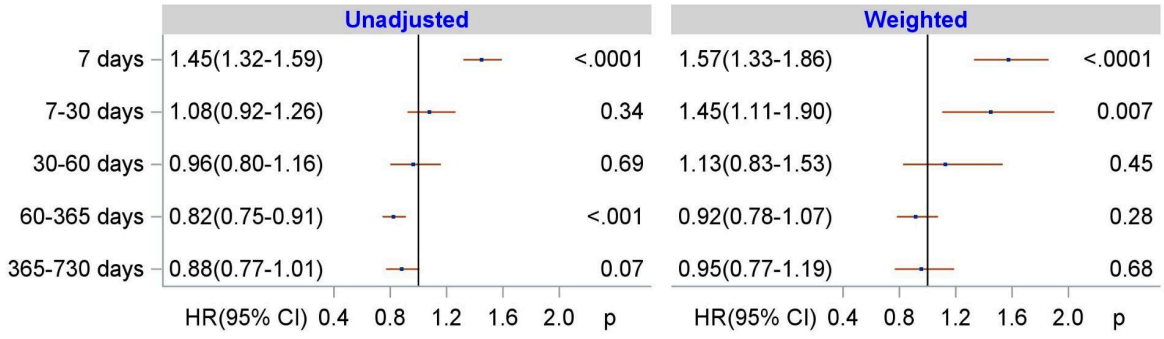
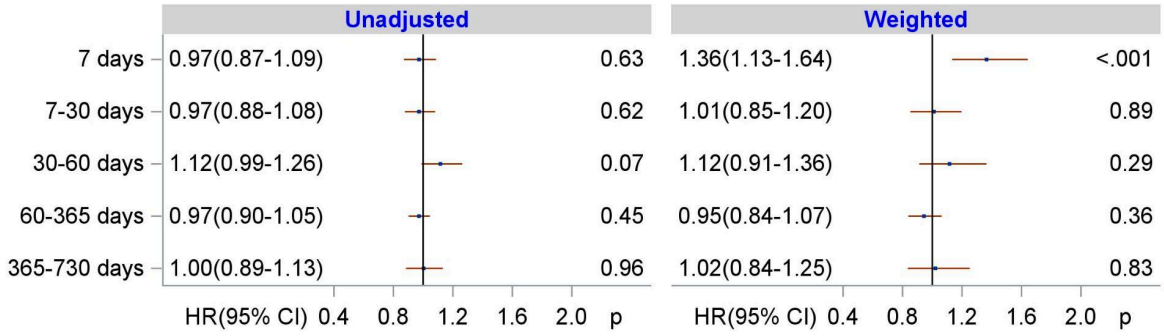


Figure 2.2. Propensity score distribution before and after overlap weighting

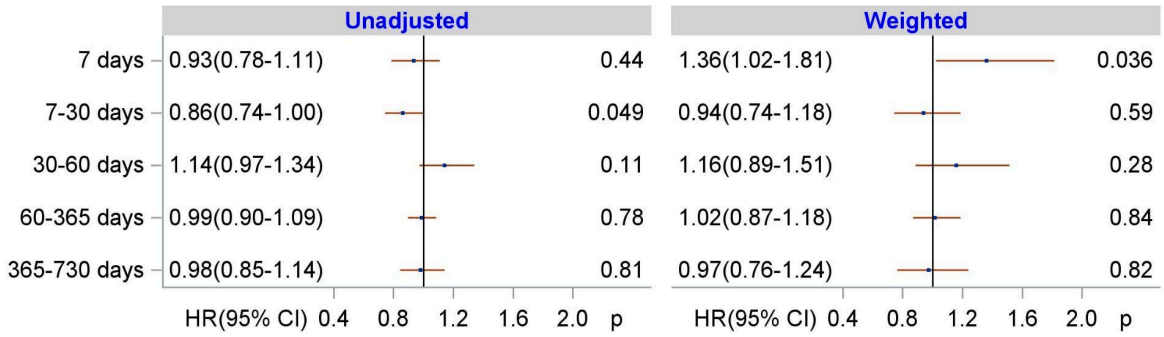
Mortality



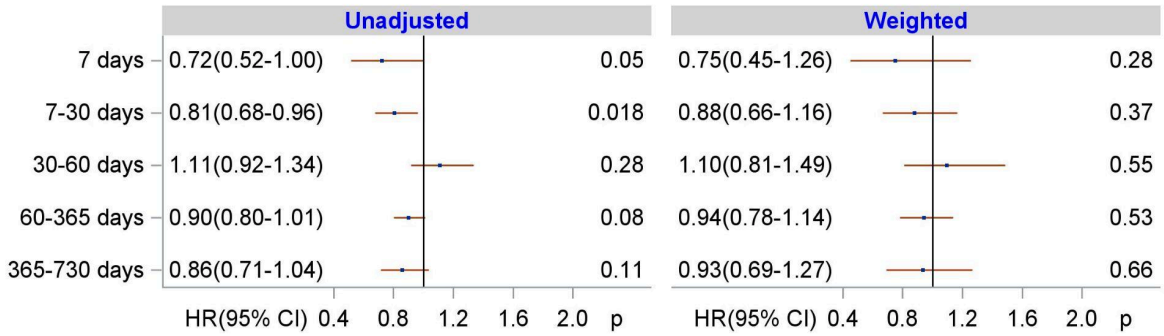
Hospitalization- Any cause



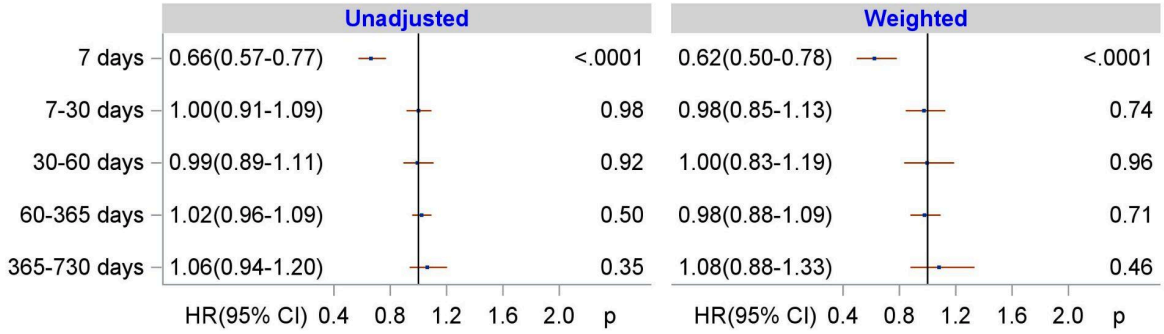
Hospitalization- CV



Hospitalization- HF

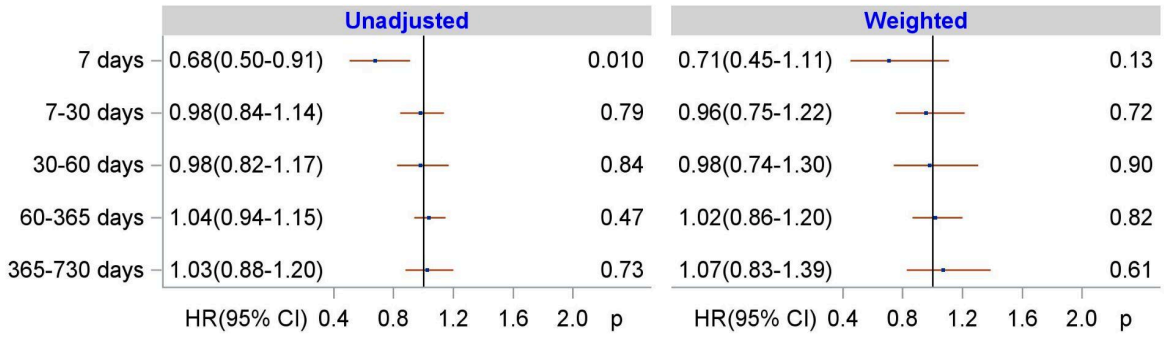


ED visit- Any cause

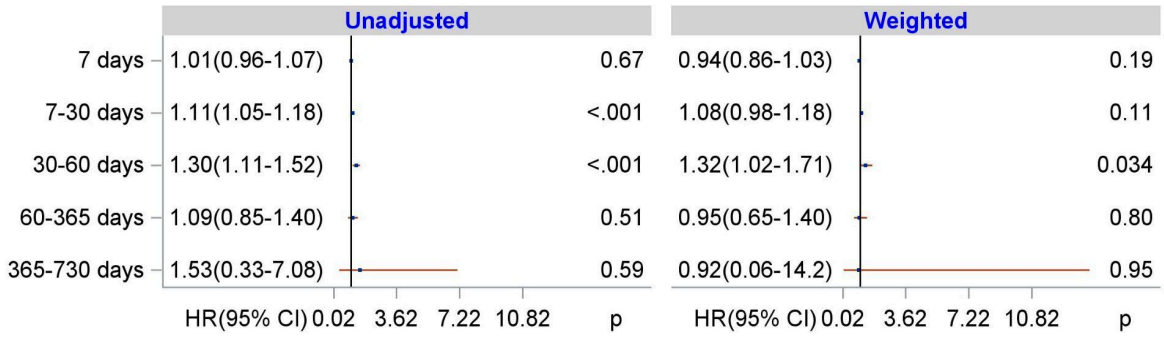


ED visit- CV

ED visit- HF



Physicians claims- Any cause



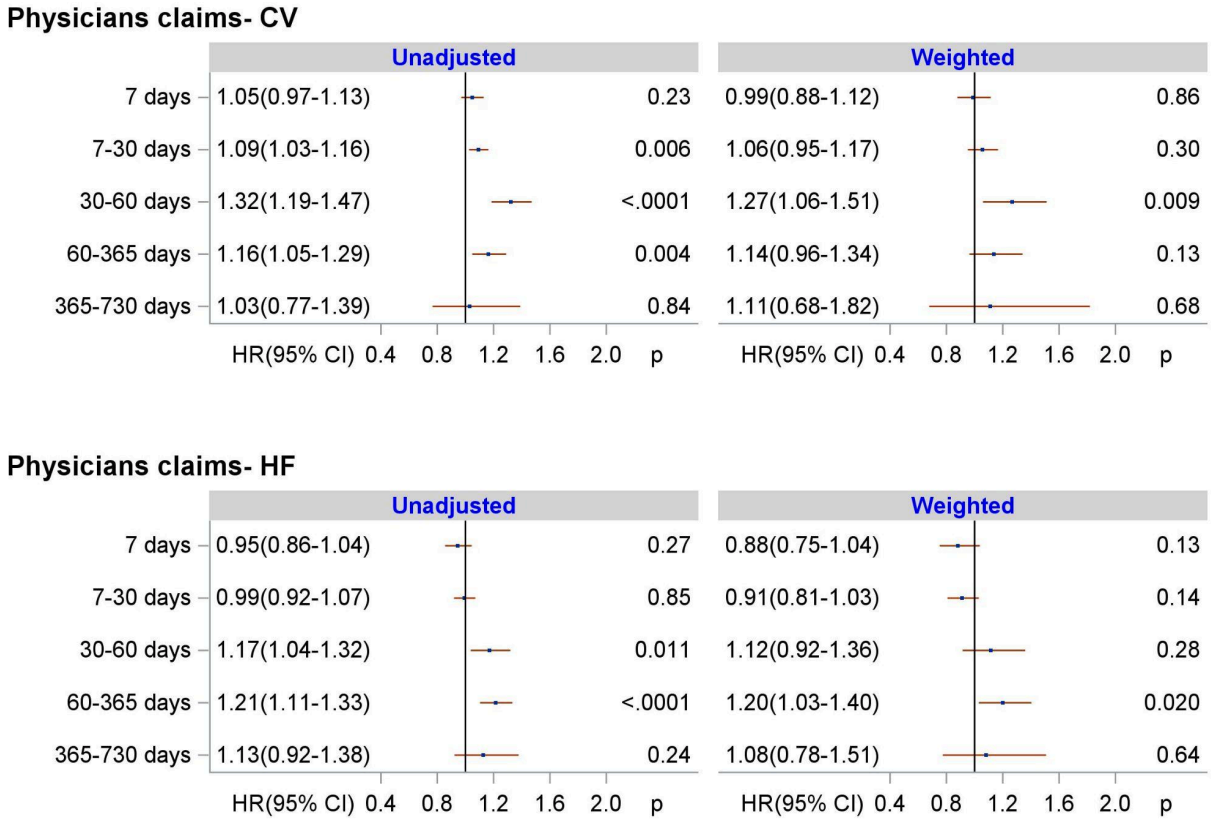


Figure 2.3: Forest plots with unadjusted and adjusted hazard ratios for patient outcomes after IV magnesium administration from the time-varying Cox proportional hazard model.

Abbreviations: ED, emergency department; CV, cardiovascular; HF, heart failure.

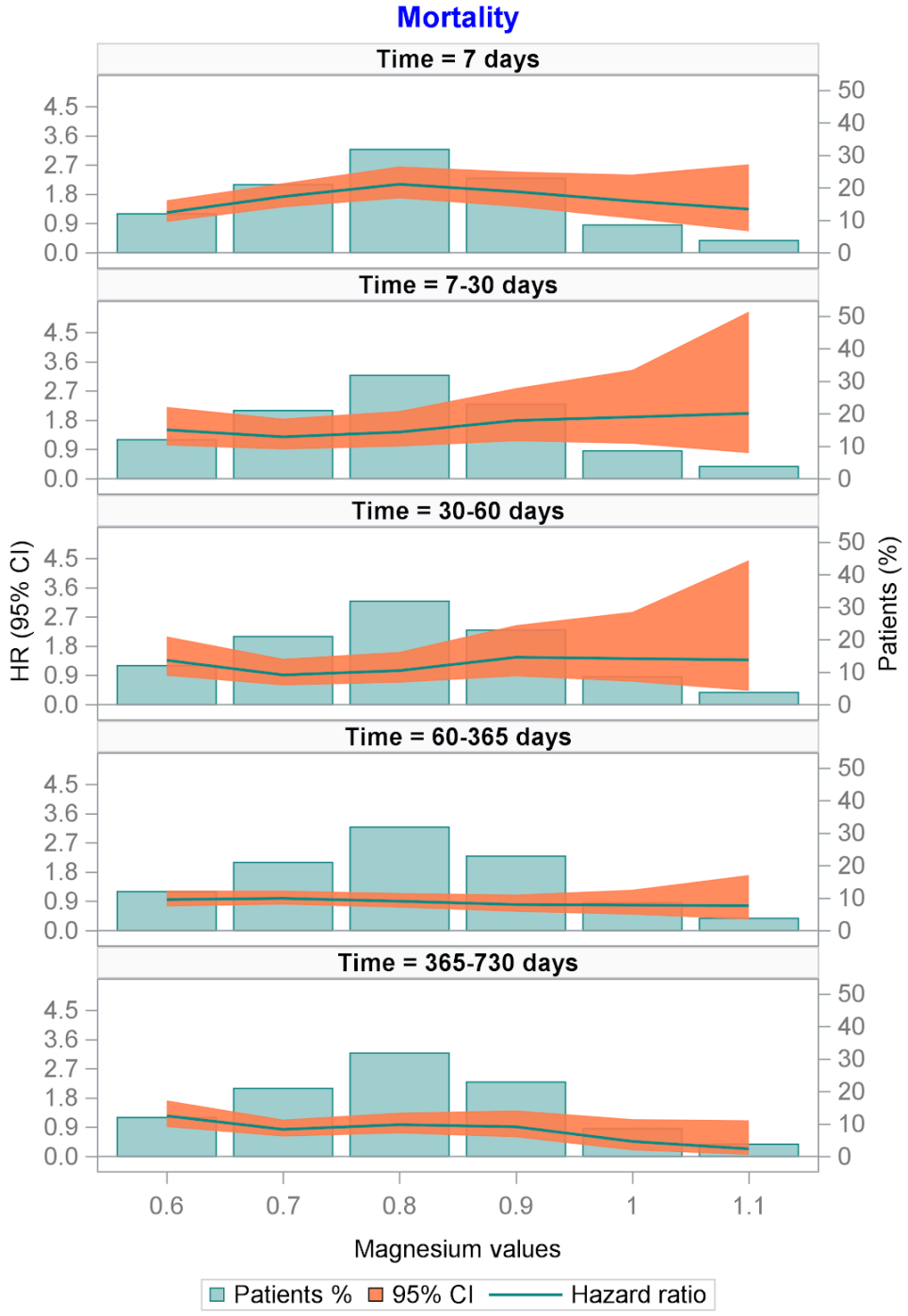


Figure 2.4. The proportion of patients who received IV magnesium at various magnesium concentrations with a hazard ratio curve for various magnesium concentrations at various overlayed.

Abbreviations: HR, hazard ratio; CI, confidence interval.

Tables:

Table 2.1. Characteristics of episodes with HF according to Magnesium testing.

Variable Label	Statistic	Episodes with no tests	Episodes with tests	p-value
Total N	N	32,594	46,363	
Age (years)	Median (IQR)	81 (72, 88)	80 (69, 87)	<.0001
Female Sex	n (%)	15,609 (47.9)	21,620 (46.6)	0.0005
Residence				
Rural	n (%)	10,692 (32.8)	7,938 (17.1)	<.0001
Urban	n (%)	21,902 (67.2)	38,425 (82.9)	
Tertiary hospital	n (%)	1,860 (5.7)	10,968 (23.7)	<.0001
Clinical setting				
Discharged from ED	n (%)	18,799 (57.7)	14,332 (30.9)	<.0001
Admitted	n (%)	13,795 (42.3)	32,031 (69.1)	
Length of episode	Median (IQR)	1 (1, 5)	5 (1, 11)	<.0001
Fiscal year				
2012	n (%)	4,033 (12.4)	4,955 (10.7)	<.0001
2013	n (%)	3,911 (12.0)	5,457 (11.8)	
2014	n (%)	4,166 (12.8)	5,855 (12.6)	
2015	n (%)	4,070 (12.5)	5,981 (12.9)	
2016	n (%)	4,147 (12.7)	6,351 (13.7)	
2017	n (%)	4,388 (13.5)	6,616 (14.3)	
2018	n (%)	4,566 (14.0)	6,858 (14.8)	
2019	n (%)	3,313 (10.2)	4,290 (9.3)	
HF subtype				
HFmrEF	n (%)	1,002 (3.1)	1,745 (3.8)	<.0001
HFpEF	n (%)	4,549 (14.0)	6,713 (14.5)	
HFrEF	n (%)	1,876 (5.8)	3,910 (8.4)	
Missing	n (%)	25,167 (77.2)	33,995 (73.3)	

Comorbidities				
Diabetes	n (%)	14,175 (43.5)	21,662 (46.7)	<.0001
Hypertension	n (%)	28,516 (87.5)	40,372 (87.1)	0.0887
Dyslipidemia	n (%)	5,798 (17.8)	9,125 (19.7)	<.0001
CAD	n (%)	17,153 (52.6)	24,709 (53.3)	0.0639
PVD	n (%)	5,451 (16.7)	7,429 (16.0)	0.0087
Atrial Fibrillation	n (%)	16,508 (50.6)	24,688 (53.2)	<.0001
Stroke/TIA	n (%)	19 (0.1)	53 (0.1)	0.0102
Thromboembolism	n (%)	4,940 (15.2)	7,052 (15.2)	0.8344
Asthma	n (%)	3,931 (12.1)	5,240 (11.3)	0.0011
COPD	n (%)	12,718 (39.0)	17,481 (37.7)	0.0002
Anemia	n (%)	8,858 (27.2)	14,130 (30.5)	<.0001
Cancer	n (%)	5,671 (17.4)	7,749 (16.7)	0.0116
Sleep Apnea	n (%)	3,079 (9.4)	4,965 (10.7)	<.0001
Depression	n (%)	6,111 (18.7)	9,365 (20.2)	<.0001
Dementia	n (%)	3,386 (10.4)	4,875 (10.5)	0.5677
Smoking	n (%)	3,958 (12.1)	6,060 (13.1)	0.0001
Charlson Comorbidity Index	Median (IQR)	4 (2, 6)	5 (3, 7)	<.0001
Medications				
ACEi	n (%)	17,328 (53.2)	24,400 (52.6)	0.1382
ARB	n (%)	10,815 (33.2)	15,136 (32.6)	0.1156
ARNi	n (%)	403 (1.2)	529 (1.1)	0.2216
MRA	n (%)	9,320 (28.6)	12,327 (26.6)	<.0001
ACEi/ARB/ARNi	n (%)	25,385 (77.9)	35,541 (76.7)	<.0001
Beta blocker	n (%)	23,250 (71.3)	33,320 (71.9)	0.1002
Digoxin	n (%)	4,426 (13.6)	5,995 (12.9)	0.0080
Statin	n (%)	18,681 (57.3)	27,237 (58.7)	<.0001
Imaging				
LVEF test	n (%)	7,427 (22.8)	12,368 (26.7)	<.0001
LVEF values	Median (IQR)	55 (40, 65)	53 (35, 65)	<.0001

Laboratory				
Hemoglobin	n (%)	29,734 (91.2)	46,219 (99.7)	<.0001
Hemoglobin, g/dl	Median (IQR)	12.1 (10.6, 13.5)	11.9 (10.3-13.4)	<.0001
Serum Creatinine	n (%)	29,989 (92.0)	46,273 (99.8)	<.0001
Serum creatinine value	Median (IQR)	106.0 (81.0, 146.0)	113.0 (85.0, 161.0)	<.0001
Sodium	n (%)	17,839 (54.7)	32,466 (70.0)	<.0001
Sodium value	Median (IQR)	139.0 (136.0, 142.0)	138.0 (135.0, 141.0)	<.0001
Potassium	n (%)	17,894 (54.9)	32,509 (70.1)	<.0001
Potassium value	Median (IQR)	4.0 (3.8, 4.3)	4.0 (3.0, 4.2)	<.0001
BNP	n (%)	4,067 (12.5)	17,813 (38.4)	<.0001
BNP value	Median (IQR)	746.0 (413.0, 1364.0)	858.0 (478.0, 1580.0)	<.0001
NTproBNP	n (%)	18,068 (55.4)	20,748 (44.8)	<.0001
NTproBNP value	Median (IQR)	1420.0 (531.0, 3877.0)	1908.0 (696.0, 5528.0)	<.0001

Abbreviations: IQR, interquartile range; ED, emergency department; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; CAD, coronary artery disease; PVD, peripheral vascular disease; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; LVEF, left ventricular ejection fraction; BNP, B-type natriuretic peptide; NTproBNP, N-type proBNP.

Table 2.2. Factors associated with Magnesium testing.

Variables	**aOR (95% CI)**	**p-value**
Age <75 years (per 5 years increase)	0.94(0.93-0.96)	<.0001
Age ≥75 years (per 5 years increase)	0.92(0.90-0.93)	<.0001
Sex- Males vs Females	1.05(1.01-1.08)	0.012
Residence- Urban vs Rural	2.07(1.99-2.15)	<.0001
Hospital- tertiary vs non-tertiary	2.54(2.41-2.68)	<.0001
Clinical setting- Admitted vs ED discharged	2.43(2.36-2.52)	<.0001
Fiscal year		<0.001
2013 vs 2012	1.13(1.06-1.21)	
2014 vs 2012	1.17(1.10-1.24)	
2015 vs 2012	1.22(1.15-1.30)	
2016 vs 2012	1.31(1.22-1.39)	
2017 vs 2012	1.31(1.23-1.40)	
2018 vs 2012	1.29(1.22-1.38)	
2019 vs 2012	1.16(1.08-1.25)	
Comorbidities		
Diabetes	1.07(1.03-1.11)	0.0003
Hypertension	0.96(0.91-1.02)	0.16
Hyperlipidemia	1.06(1.01-1.11)	0.022
Coronary artery disease	1.00(0.96-1.03)	0.85
Peripheral vascular disease	0.92(0.88-0.97)	0.001

Atrial fibrillation	1.16(1.12-1.20)	<.0001
Thromboembolism	1.00(0.95-1.05)	0.90
Asthma	0.89(0.85-0.94)	<.0001
Chronic obstructive pulmonary disease	0.98(0.95-1.02)	0.39
Anemia	1.08(1.04-1.12)	0.0002
Cancer	1.00(0.95-1.04)	0.93
Sleep Apnea	1.03(0.97-1.09)	0.31
Depression	0.99(0.95-1.04)	0.78
Dementia	1.03(0.97-1.09)	0.29
Smoking	1.04(0.99-1.10)	0.13
Medications		
ACEi/ARB/ARNi	0.94(0.90-0.98)	0.004
MRA	0.94(0.90-0.97)	0.001
Beta-blocker	0.96(0.93-1.00)	0.083
Digoxin	0.95(0.90-1.00)	0.065
Statin	1.00(0.97-1.04)	0.85

Abbreviations: aOR, adjusted odds ratio; ED, emergency department; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; LVEF, left ventricular ejection fraction; BNP, B-type natriuretic peptide; NTproBNP, N-type proBNP.

Table 2.3. Characteristics of patient episodes with hypomagnesemia (<0.75 mmol/L), normal magnesemia (0.75-0.95 mmol/L), and hypermagnesemia (>0.95 mmol/L).

Variable Label	Statistic	Magnesium <0.75 mmol/L	Magnesium 0.75-0.95 mmol/L	Magnesium >0.95 mmol	p-value
Total N	N	14,699	26,323	5,341	
Age	Median (IQR)	77 (68, 85)	80 (70, 87)	82 (73, 88)	<.0001
Female Sex	n (%)	7,365 (50.1)	11,909 (45.2)	2,346 (43.9)	<.0001
Residence					
Rural	n (%)	2,710 (18.4)	4,360 (16.6)	868 (16.3)	<.0001
Urban	n (%)	11,989 (81.6)	21,963 (83.4)	4,473 (83.7)	
Tertiary hospital	n (%)	3,676 (25.0)	6,122 (23.3)	1,170 (21.9)	<.0001
Clinical setting					
Discharged from ED	n (%)	4,053 (27.6)	8,481 (32.2)	1,798 (33.7)	<.0001
Admitted	n (%)	10,646 (72.4)	17,842 (67.8)	3,543 (66.3)	
Length of episode	Median (IQR)	6 (1, 13)	5 (1, 10)	4 (1, 10)	<.0001
Fiscal year					
2012	n (%)	1,522 (10.4)	2,846 (10.8)	587 (11.0)	<.0001
2013	n (%)	1,712 (11.6)	3,127 (11.9)	618 (11.6)	
2014	n (%)	2,035 (13.8)	3,225 (12.3)	595 (11.1)	
2015	n (%)	1,951 (13.3)	3,464 (13.2)	566 (10.6)	
2016	n (%)	2,028 (13.8)	3,591 (13.6)	732 (13.7)	
2017	n (%)	2,070 (14.1)	3,755 (14.3)	791 (14.8)	

2018	n (%)	2,169 (14.8)	3,844 (14.6)	845 (15.8)	
2019	n (%)	1,212 (8.2)	2,471 (9.4)	607 (11.4)	
HF type					
HFmEF	n (%)	638 (4.3)	953 (3.6)	154 (2.9)	<.0001
HFpEF	n (%)	2,332 (15.9)	3,746 (14.2)	635 (11.9)	
HFrEF	n (%)	1,317 (9.0)	2,268 (8.6)	325 (6.1)	
Missing	n (%)	10,412 (70.8)	19,356 (73.5)	4,227 (79.1)	
Comorbidities					
Diabetes	n (%)	8,457 (57.5)	10,782 (41.0)	2,423 (45.4)	<.0001
Hypertension	n (%)	13,030 (88.6)	22,547 (85.7)	4,795 (89.8)	<.0001
Hyperlipidemia	n (%)	2,992 (20.4)	5,024 (19.1)	1,109 (20.8)	0.0009
CAD	n (%)	7,816 (53.2)	13,922 (52.9)	2,971 (55.6)	0.0012
PVD	n (%)	2,412 (16.4)	4,047 (15.4)	970 (18.2)	<.0001
Atrial Fibrillation	n (%)	7,640 (52.0)	14,122 (53.6)	2,926 (54.8)	0.0003
Cerebrovascular-Stroke/TIA	n (%)	18 (0.1)	31 (0.1)	4 (0.1)	0.6571
Thromboembolism	n (%)	2,395 (16.3)	3,846 (14.6)	811 (15.2)	<.0001
Asthma	n (%)	1,710 (11.6)	2,936 (11.2)	594 (11.1)	0.3071
COPD	n (%)	6,000 (40.8)	9,585 (36.4)	1,896 (35.5)	<.0001
Anemia	n (%)	4,768 (32.4)	7,504 (28.5)	1,858 (34.8)	<.0001
Cancer	n (%)	2,465 (16.8)	4,390 (16.7)	894 (16.7)	0.9702

Sleep Apnea	n (%)	1,782 (12.1)	2,632 (10.0)	551 (10.3)	<.0001
Depression	n (%)	3,244 (22.1)	5,171 (19.6)	950 (17.8)	<.0001
Dementia	n (%)	1,465 (10.0)	2,844 (10.8)	566 (10.6)	0.0291
Smoking	n (%)	2,432 (16.5)	3,118 (11.8)	510 (9.5)	<.0001
Charlson Comorbidity Index	Median (IQR)	5 (3, 7)	4 (2, 6)	5 (3, 7)	<.0001
Medications					
ACEi	n (%)	7,980 (54.3)	13,562 (51.5)	2,858 (53.5)	<.0001
ARB	n (%)	4,822 (32.8)	8,372 (31.8)	1,942 (36.4)	<.0001
ARNi	n (%)	154 (1.0)	312 (1.2)	63 (1.2)	0.4355
MRA	n (%)	3,689 (25.1)	6,863 (26.1)	1,775 (33.2)	<.0001
ACEi/ARB/ARNi	n (%)	11,588 (78.8)	19,725 (74.9)	4,228 (79.2)	<.0001
Beta blocker	n (%)	10,678 (72.6)	18,585 (70.6)	4,057 (76.0)	<.0001
Digoxin	n (%)	1,788 (12.2)	3,390 (12.9)	817 (15.3)	<.0001
Statin	n (%)	9,178 (62.4)	14,923 (56.7)	3,136 (58.7)	<.0001
Imaging					
LVEF test	n (%)	4,287 (29.2)	6,967 (26.5)	1,114 (20.9)	<.0001
LVEF	Median (IQR)	53 (35, 65)	53 (34, 65)	53 (36, 65)	0.0335
Laboratory tests					
Hemoglobin test	n (%)	14,651 (99.7)	26,244 (99.7)	5,324 (99.7)	0.8939
Hemoglobin (g/dl)	Median (IQR)	11.8 (10.3, 13.3)	12.1 (10.5, 13.6)	11.3 (9.7, 12.9)	<.0001
Serum creatinine	n (%)	14,671 (99.8)	26,267 (99.8)	5,335 (99.9)	0.3127
Serum creatinine value	Median (IQR)	103.0 (79.0, 142.0)	111.0 (85.0, 155.0)	169.0 (122.0, 251.0)	<.0001

Sodium	n (%)	10,531 (71.6)	18,218 (69.2)	3,717 (69.6)	<.0001
Sodium value	Median (IQR)	138.0 (135.0, 141.0)	139.0 (136.0, 141.0)	138.0 (135.0, 141.0)	<.0001
Potassium	n (%)	10,542 (71.7)	18,239 (69.3)	3,728 (69.8)	<.0001
Potassium value	Median (IQR)	4.0 (3.0, 4.0)	4.0 (3.2, 4.2)	4.0 (4.0, 4.8)	<.0001
BNP	n (%)	5,562 (37.8)	10,365 (39.4)	1,886 (35.3)	<.0001
BNP value	Median (IQR)	544.6 (198.4, 1220.0)	572.8 (214.0, 1237.6)	708.1 (238.1, 1679.7)	<.0001
NTproBNP	n (%)	6,626 (45.1)	11,683 (44.4)	2,439 (45.7)	0.1435
NTproBNP value	Median (IQR)	1830.0 (676.0, 5305.0)	1898.0 (696.0, 5385.0)	2209.0 (781.0, 7421.0)	<.0001

Abbreviations: IQR, interquartile range; ED, emergency department; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; CAD, coronary artery disease; PVD, peripheral vascular disease; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; LVEF, left ventricular ejection fraction; BNP, B-type natriuretic peptide; NTproBNP, N-type proBNP.

Table 2.4. Factors associated with hypomagnesemia (<0.75 mmol/L).

Variables	**aOR (95% CI)**	**p-values**
Age <75 years (per 5 years increase)	0.96(0.95-0.98)	<.0001
Age ≥75 years (per 5 years increase)	0.89(0.87-0.91)	<.0001
Sex- Males vs Females	0.72(0.68-0.75)	<.0001
Residence- Urban vs Rural	0.93(0.87-0.99)	0.0171
Hospital- tertiary vs non-tertiary	1.06(1.00-1.11)	0.0332
Clinical setting- Admitted vs ED discharged	1.29(1.23-1.35)	<.0001
Fiscal year		<0.001
2013 vs 2012	1.04(0.96-1.14)	
2014 vs 2012	1.23(1.13-1.34)	
2015 vs 2012	1.07(0.98-1.17)	
2016 vs 2012	1.04(0.95-1.13)	
2017 vs 2012	1.02(0.93-1.11)	
2018 vs 2012	1.01(0.93-1.10)	
2019 vs 2012	0.88(0.80-0.97)	
Diabetes	1.83(1.74-1.93)	<.0001
Hypertension	1.12(1.04-1.21)	0.0025
Hyperlipidemia	0.92(0.86-0.97)	0.0054
Coronary artery disease	0.94(0.89-0.99)	0.0189
Peripheral vascular disease	0.98(0.92-1.04)	0.5132
Atrial fibrillation	1.07(1.02-1.12)	0.0081

Thromboembolism	1.05(0.99-1.12)	0.1286
Asthma	0.92(0.85-0.99)	0.0282
Chronic obstructive pulmonary disease	1.17(1.11-1.23)	<.0001
Anemia	1.11(1.05-1.17)	0.0001
Cancer	1.07(1.01-1.14)	0.0228
Sleep Apnea	0.98(0.90-1.05)	0.5242
Depression	1.05(0.99-1.11)	0.1264
Dementia	0.98(0.91-1.06)	0.6866
Smoking	1.25(1.16-1.34)	<.0001
ACEi/ARB/ARNi	1.11(1.04-1.17)	0.0007
Mineralocorticoid receptor antagonist	0.81(0.77-0.85)	<.0001
Beta-blocker	1.02(0.97-1.08)	0.3946
Digoxin	0.89(0.82-0.95)	0.001
Statin	1.11(1.06-1.18)	<.0001

Abbreviations: aOR, adjusted odds ratio; ED, emergency department; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; LVEF, left ventricular ejection fraction; BNP, B-type natriuretic peptide; NTproBNP, N-type proBNP.

Tables 2.5. Factors associated with IV Magnesium.

Variables	**aOR (95% CI)**	**p-value**
Age <75 years (per 5 years increase)	0.97 (0.95-0.99)	0.003
Age ≥75 years (per 5 years increase)	0.76 (0.73-0.78)	<0.001
Sex- Males vs Females	1.18 (1.10-1.26)	<0.001
Residence- Urban vs Rural	1.55 (1.42-1.69)	<0.001
Hospital- tertiary vs non-tertiary	1.35 (1.26-1.45)	<0.001
Clinical setting- Admitted vs ED discharged	2.41 (2.22-2.62)	<0.001
Fiscal year		<0.001
2013 vs 2012	1.07 (0.93-1.22)	
2014 vs 2012	1.23 (1.08-1.40)	
2015 vs 2012	1.26 (1.11-1.43)	
2016 vs 2012	1.19 (1.05-1.36)	
2017 vs 2012	1.28 (1.13-1.46)	
2018 vs 2012	1.38 (1.21-1.56)	
2019 vs 2012	1.46 (1.26-1.68)	
Mg level ≤1.1 (per 0.1 unit decrease)	1.28 (1.19-1.38)	<0.001
Mg level ≤0.8 (per 0.1 unit decrease)	4.08 (3.92-4.25)	<0.001
Diabetes	0.83 (0.77-0.89)	
Hypertension	0.89 (0.81-0.98)	0.024
Hyperlipidemia	0.93 (0.86-1.01)	0.091
Coronary artery disease	1.13 (1.06-1.21)	<0.001

Peripheral vascular disease	1.03 (0.94-1.12)	0.52
Atrial fibrillation	1.17 (1.09-1.25)	<0.001
Thromboembolism	0.98 (0.90-1.07)	0.65
Asthma	1.00 (0.90-1.10)	0.96
Chronic obstructive pulmonary disease	0.85 (0.80-0.92)	<0.001
Anemia	0.93 (0.86-0.99)	0.033
Cancer	1.00 (0.92-1.09)	0.98
Sleep Apnea	0.93 (0.84-1.02)	0.13
Depression	0.89 (0.83-0.97)	0.005
Dementia	0.94 (0.84-1.05)	0.27
Smoking	0.95 (0.87-1.04)	0.26
ACEi/ARB/ARNi	0.96 (0.89-1.05)	0.36
Mineralocorticoid receptor antagonist	0.93 (0.87-1.01)	0.078
Beta blocker	0.83 (0.77-0.90)	<0.001
Digoxin	0.91 (0.83-1.01)	0.075
Statin	0.97 (0.90-1.04)	0.37

Abbreviations: aOR, adjusted odds ratio; ED, emergency department; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; LVEF, left ventricular ejection fraction; BNP, B-type natriuretic peptide; NTproBNP, N-type proBNP.

Table 2.6. Association between falsification endpoints and IV magnesium administration.

	Unadjusted		Weighted	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Hospitalization- UTI				
7 days	1.79(0.91-3.50)	0.0892	2.61(0.68-9.97)	0.1604
7-30 days	1.07(0.51-2.27)	0.8546	0.76(0.20-2.89)	0.6873
30-60 days	1.33(0.62-2.87)	0.4591	1.28(0.34-4.85)	0.7197
60-365 days	0.81(0.57-1.16)	0.2588	0.84(0.48-1.48)	0.5563
365-730 days	0.84(0.55-1.29)	0.4249	0.54(0.27-1.08)	0.0819
Hospitalization- hip fracture				
30 days	0.51(0.07-3.95)	0.5214	1.19(0.03-45.0)	0.9241
30-60 days	0.88(0.26-2.95)	0.8356	0.69(0.10-4.92)	0.7135
60-365 days	0.94(0.53-1.65)	0.8227	1.16(0.46-2.94)	0.7532
365-730 days	0.68(0.31-1.49)	0.3333	0.62(0.20-1.91)	0.4028

Abbreviations: HR, hazard ratio; UTI, urinary tract infection.

Chapter 3 - A Network Meta-analysis of Health-Related Quality of Life in Patients Undergoing Pharmacological Treatment for Heart Failure with Reduced Ejection Fraction.

3.1 INTRODUCTION

3.1.1 Current Treatment for HFrEF

Heart failure (HF) is a complex, multifactorial end-stage clinical condition that affects more than 50 million people globally and is associated with frequent hospital and emergency department visits, reduced health-related quality of life (HRQoL) and high mortality rates.[91-92] In recent years the growing number of pharmacological treatments available for heart failure with reduced ejection fraction (HFrEF) such as angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), beta-blockers (BB), mineralocorticoid receptor antagonists (MRAs), digoxin, hydralazine-isosorbide dinitrate, ivabradine, angiotensin receptor–neprilysin inhibitors (ARNi), sodium glucose cotransporter-2 inhibitors (SGLT2i), vericiguat, and omecamtiv-mecarbil (OM) have allowed physicians to build treatment plans consisting of pharmacological agents that target multiple aspects of HFrEF which are titrated to levels that achieve a maximally positive effect on mortality and hospitalization risk.[3-4,15] However, a complete understanding of the effect of these agents together on HRQoL is not currently available.

3.1.2 A foundation for an RCT

While several systematic reviews and meta-analyses have previously shown the effect that various classes of drugs used to treat HFrEF have on HRQoL individually, there has not yet been an assessment of the effect of different agent combinations on quality of life which is more clinically relevant.[93-107] As a recent systematic review and network meta-analysis of pharmacological treatment effects on patient outcomes in HFrEF has shown evidence for the additive nature of these medications, evaluating the treatment effect of these combinations on HRQoL is feasible.[108] Since most patients with HFrEF are

prescribed numerous medications of various classes, which may or may not concurrently reduce the risk of mortality and increase HRQoL, understanding the effect of the most recommended and accepted medication combinations would facilitate understanding how another HF treatments like IV magnesium may influence quality of life in a similar patient population. Further, understanding how large the impact of effective HF treatment combinations are on quality of life would provide a baseline for determining a sample size and effectively interpreting the findings for a future study on the effects of IV magnesium on the quality of life experienced by patients during and after acute HF. As a result we conducted a systematic review and network meta analysis to estimate the aggregate impact of combinations of pharmacological therapies in adult patients with HFrEF.

3.2 METHODS

3.2.1 Study design

Based on a prespecified study protocol and relying on frequentist statistical methods, we performed a systematic review and network meta-analysis. The results of the study are reported according to the PRISMA extension statement for systematic reviews incorporating network meta-analyses.

3.2.2 Search strategy, eligibility and selection criteria, and data collection

We performed a systematic search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials for randomized controlled trials published between January 1st 2021 and February 20th, 2024. Subject headings, MeSH terms, and /or keyword searches were based on the search terms used in a previous network meta-analysis (Tromp and Ouwerkerk et al).[108] In this study, previously used outcome parameters in Tromp and Ouwerkerk et al (e.g. mortality) were replaced with parameters related to quality of life including the scores assessed by the MLHFQ and KCCQ tools. The full search terms and protocol are outlined in the end of chapter 3.[108] Search results were

supplemented with the trials included in Tromp and Ouwerkerk et al. and trials included in related meta-analyses by other authors.[93-108]

We evaluated randomized controlled trials (RCT) that investigated the effects of GDMTs and other drugs which are effective in patients with HFrEF. Pharmacological agents considered included digoxin, hydralazine-isosorbide dinitrate (H-ISDN), ACEi, ARB, BB, MRA, ivabradine, ARNi, SGLT2i, vericiguat, and omecamtiv-mecarbil. Target studies were limited to adult populations (aged ≥18 years) with HFrEF, enrolled in the outpatient setting or after stabilization following hospitalization for HF who were assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) or the Minnesota Living With Heart Failure Questionnaire (MLHFQ) as these are reliable assessment tools which are most prevalent in contemporary clinical trials.[109-111] Studies were excluded when the entire study population was composed of patients with a concomitant diagnosis that likely had a major effect on quality of life outcomes of interest such as trials only including patients with diabetes. Studies that only investigated therapies for patients in acute HF episodes, studies that only compared agents within the same drug group, and studies that were not available in English were excluded.

Titles and abstracts of retrieved citations were screened independently by two investigators (R.M. and N.S.) to identify trial eligibility. The full texts of the trials which were deemed eligible were then independently screened by the same 2 investigators. Discrepancies were resolved by discussion and consensus at each step. Data from the final set of eligible trials after full text review were extracted by the same 2 authors, who double-checked each other's work for inconsistencies.

3.2.3 Outcomes

The primary outcome of interest of the study was the change in health-related quality of life assessed as the KCCQ Overall Summary Score (OSS) and the MLHFQ Overall score as these are the most commonly recorded score domains. The QoL scores from studies

using the KCCQ or MLHFQ were standardized based on a relevant clinical improvement conversion regression formula established by Nassif et al.[112]

MLWHF change = KCCQ OSS change * (-0.74902) – 2.92430

Using this formula, a common overall score was established and mean differences (MD) for the change in quality of life were calculated. Results are presented as a MD with 95% confidence intervals.

3.2.4 Network meta-analysis

We constructed network meta-analysis models using a frequentist framework through which we generated a random effects model. We assessed the change in quality of life scores for the individual components of the network compared with placebo and employed an additive component network meta-analysis model to evaluate the influence of individual treatment components as many treatments were combinations of a number of common components. This model assumes that the effect of treatment combinations is the sum of the effects of its components which has been accepted for similar network meta-analyses evaluating HFrEF therapies. Therefore, through this network meta-analysis we compared different combinations of treatments based on the treatment given and the background therapy within a trial. Treatment combinations that are not included in the network cannot be compared and a connected network is important for accurate results. We considered patients on background therapy if 50% of patients in the treatment arm were on that therapy at the time of enrollment in the trial. Given the mixed use of ARNi, ACEi, and ARBs in recent clinical trials, it was difficult to accurately place these patients on a background therapy of ARNi ACEi or ARB individually while it was clear that the use of ACEi/ARB/ARNi was high. To accurately represent the background therapies of the trial we considered these trials against a background of ARNi if more than 40% of the patients using ACEi/ARNi/ARB in either arm were on ARNi, if less than 40% were taking an ARNi then the background therapy was considered to be an ACEi.[113-122] We reported our findings as the MD for quality of life outcomes. Treatments were ranked

using the P-Score which is the frequentist equivalent of the surface under the cumulative ranking curve (SUCRA), both scores show the proportion of treatments that are worse than the treatment in question.[123]

3.2.5 Risk of bias and sensitivity analyses

We used a Cochrane Group risk of bias assessment tool (RoB2) to evaluate confidence in individual trials.[124] Using the August 2019 version of the RoB2, Each trial was assessed to determine the presence of bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported results. The risk-of-bias was classified as low risk, moderate risk (some concerns); or high risk (major concerns) of bias in each domain using a combination of signaling questions and tool algorithms which was used to inform a study risk-of-bias judgment. All studies were included regardless of their risk of bias to determine the confidence in individual comparisons according to the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework using the Confidence in Network Meta-Analysis (CINeMA).[125] The CINeMA framework considers 6 domains to assess confidence: 1) within-study bias; 2) reporting bias; 3) indirectness; 4) imprecision; 5) heterogeneity; and 6) incoherence. Within-study bias was assessed using the RoB2 study risk-of-bias assessment. Reporting bias was formally tested using the Egger test, which assesses the symmetry of funnel plots.[126] When this was found to be nonsignificant, we considered the risk of reporting bias as "low." Indirectness, which captures transitivity in the network, was assessed as low based on published guidelines. Imprecision compares the treatment effects included in the 95% CI with the range of equivalence using clinically important effects which were considered to be a change in score of 5. To assess heterogeneity, we calculated I^2 values.[127] I^2 values are calculated using the chi-square statistic and its *df* and represent the amount of inconsistency in the network. Incoherence captures transitivity, which stipulates that 2 treatments can be compared indirectly via an intermediate treatment node. If estimates from direct and indirect evidence disagree, transitivity does not hold and there is incoherence within the network. Incoherence was assessed through a visual evaluation of differences between evidence based on direct and indirect

comparisons in addition to a global test based on a random-effects design-by-treatment interaction model where a nonsignificant *P* value means that there is no incoherence. In our sensitivity analyses we further supported the validity of the standardization of KCCQ and MLHFQ overall scores, we separately analyzed trials that used the MLHFQ using the converted scores and the raw scores and compared these results. The random effects network meta-analysis was performed using the *netmeta* package in R (R Foundation); *P* values < 0.05 were considered statistically significant. Values that were not reported were imputed with the mean value from all studies or with values from studies with the most similar conditions (ie. length of follow up, background therapy) in the case of score standard deviations. Missing values were treated in the same way as they were treated in the original studies.

3.3 RESULTS

3.3.1 Characteristics of the included studies

After a search of MEDLINE, EMBASE, and Cochrane databases and the initial removal of duplicates we identified 988 studies. After title and abstract screening 922 studies were excluded (Figure 1), the full text of 66 studies were screened and 40 were included in the analysis.[113-122,128-157] These studies had a median of 273 (interquartile range (IQR) 105, 495) participants and together analyzed 40,832 patients who were mostly male (74.7%) with a mean LVEF of 27.9 and a median follow up time of 5.5 months (IQR 3,8). Of the 40 studies which were included, 35 were multi-center, 15 were multinational, and 20 used the MLHFQ and 20 used the KCCQ. 10 studies evaluated the impact of BBs on quality of life, while 9 studies evaluated the impact of SGLT2i, 5 studies evaluated ACEi compared to ARNi, 3 studies each evaluated ivabradine and OM, 2 studies each evaluated ACEi and ARB, 1 study each evaluated H-ISDN, vericiguat, digoxin, MRA, ARB compared to ACEi, and ARB compared to ARNi (Table 1).

3.3.2 Risk of bias and publication bias

The overall risk of bias was low as all studies were randomized, double-blind, placebo-controlled studies with most being multi-center (Table 2). Two studies had major concerns due to an imbalance in the number of missing patients between treatment groups without reported evidence that the outcomes of the missing participants were accounted for.[140,157] However, as one of the studies (SUGARDM-HF) did not report the OSS change of their treatment groups, this study was not included in the main analysis.[157] The other study with major concerns for bias, Willenheimer et al, was included in the main analysis, but sensitivity analyses showed that its removal did not significantly impact the main results.[140] There was no evidence of reporting bias for the outcome of change in quality of life (Egger test $p = 0.818$) (Figure 3). As the exclusion and inclusion criteria were very selective, indirectness was judged as low-very low. The minimally important clinical difference represents the minimum change which represents a noticeable improvement for a patient. In the KCCQ scale, a small clinical benefit has been defined as a change of 5 units, consequently, the effect size to evaluate the imprecision and heterogeneity in the study was defined as 5 units of score change in our study.[158] Due to the high variability in quality of life scores observed across all the studies there was a high level of imprecision in many treatment comparisons. Overall heterogeneity for the additive network meta-analysis model was high (I^2 61.9%). Incoherence was not significant and the confidence rating was high or moderate for all clinically relevant treatment comparisons. The confidence in the results of comparisons between treatments was generally lower for many of the comparisons which relied on smaller trials that had high variability and those that included data from the Willenheimer et al trial.[140]

3.3.3 Component analysis

Out of the 40 studies included in the NMA only 35 reported either the KCCQ OSS or the MLHFQ score;[114-122,128-149,153-156] these studies were included in the main analysis of change in quality of life measured through the change in OSS and converted MLHFQ scores (Figure 2). It was not possible to analyze the other domains of the KCCQ as there were

not enough studies to build an adequate network; 14, 14, and 8 studies reported the clinical summary score domain, the total symptom score domain, and the physical limitation score domain in sufficient detail for analysis respectively. The main analysis indicated that the therapies whose effect on quality of life was H-ISDN [MD 3.87 (95% CI -0.73-8.47)], however this effect was not significant. The treatment with the next largest effect was SGLT2i [MD 3.37 (95% CI 1.44-5.30)] which lead to the greatest improvement in quality of life, followed by Ivabradine [MD 3.26 (95% CI 0.08-6.43)], then ARNi [MD 2.62 (95% CI -3.24-8.47)] and then Vericiguat [MD 1.00 (95% CI -3.18-5.18)]. BB, ACEi, and ARB had a neutral impact on quality of life and Digoxin significantly reduced quality of life [MD -5.34 (95% CI -10.30 - -0.38)] (Figure 4).

3.3.4 Additive analysis

A combination of ARNi + BB + MRA + SGLT2i [MD 7.11 (95% CI -0.99-15.22)] had the largest effect on quality of life, but this effect was not significant. The combination of ARNi + BB + SGLT2i [MD 5.33 (95% CI 0.40-10.25)] was the most effective. Other combinations such as ACEi + BB + MRA + SGLT2i [MD 5.32 (95% CI -2.63-13.26)], ACEi + BB + MRA + Ivabradine [MD 5.24 (95% CI -3.07-13.55)], and ARNi + BB + MRA [MD 3.81 (95% CI -4.09-11.71)] also did not have a significant effect (Figure 5). Other combinations of ACEi/ARB/ARNi with BB and MRA generally had a neutral impact on quality of life and most combinations involving digoxin had a negative impact on quality of life even when paired with ACEi/ARB or BB. The P scores given in Table 3 demonstrate a similar pattern. The combination of ARNi + BB + MRA + SGLT2i did not improve quality of life significantly better than the combination of ACEi + BB + MRA + SGLT2i or the combination of ARNi + BB + SGLT2i, but was significantly more effective than a combination of ARNi + BB + MRA (Table 4).

3.3.5 Sensitivity Analysis

Two sensitivity analyses were conducted to supplement the main results of this study. The first sensitivity analysis evaluated the sensitivity of the results to the conversion of the

MLHFQ score to the KCCQ score scale. This was achieved by comparing a subnetwork with only trials that have converted scores to a subnetwork of only trials that have the original MLHFQ scores, and the result was largely the same (Figure 6). The second sensitivity analysis found that after removing studies which were determined to have major concerns in their results the primary analysis outcomes were largely the same (Figure 7).

3.4 DISCUSSION

3.4.1 Key Findings

This study evaluated the effect of interventions efficacious in heart failure with reduced ejection fraction on the health related quality of life experienced by patients with heart failure. Our study has two major findings which can inform the design of a study to evaluate the association between IV magnesium therapy and quality of life changes in patients with AHF. First, evidence with high confidence showed that a combination of ARNI + BB + MRA + SGLT2i had the largest impact on quality of life, but was not significant, instead, a combination of ARNi + BB + SGLT2i was the most effective at improving quality of life followed by a combination of ACEi + BB + MRA + SGLT2i respectively. Second, the addition of SGLT2i and Ivabradine to other treatment combinations significantly improved quality of life scores while the addition of digoxin to the treatment significantly reduced quality of life.

3.4.2 Additive network

The current guideline recommended therapy (GDMT) for heart failure with reduced ejection fraction involves the initiation and up titration of a combination of ARNi + BB + MRA + SGLT2i if possible as it is the most effective for improving survival however our study results could not confirm this combination is also the combination most effective for improving quality of life. We also could not confirm whether the replacement of SGLT2i with Vericiguat or ivabradine in combination with ACEi, BB, and MRA resulted in a change in quality of life as no significant difference in effect was found. The lack of significance for many results may not be an accurate reflection of the true effect of the treatment combinations and instead it could be due to the variability of the measure of

change in quality of life score and the lack of direct evidence for many of the comparisons. To our knowledge this is the first study to build a network meta-analysis for the evaluation of the efficacy of HFrEF interventions in improving quality of life, however, similar analyses evaluating these treatment combinations for their impact on mortality and hospitalization, which are outcomes that can influence quality of life, have found similar rankings of treatment combinations, but were often able to identify significant treatment effects.[159-161] Thus, while more direct comparisons and higher certainty evidence are needed, the current evidence together with the results of similar studies supports the immediate initiation and uptitration of a triple therapy of ARNI + BB + MRA or a quadruple therapy consisting of ARNi + BB + MRA, and SGLT2i for the majority of patients with HFrEF. These results also demonstrate the maximum mean quality of life benefit which can be expected from recommended pharmacological agent combinations, however more evidence is needed to determine if vericiguat or ivabradine can or should be added to quadruple therapy or used in combination with some parts of the quadruple therapy to increase quality of life for any subgroup of patients with HFrEF.

3.4.3 Component network

Concerning the effect of each treatment component individually, our results generally agree with previously conducted non-network based meta analyses. Results from recently conducted meta-analyses support our conclusions concerning the efficacy of SGLT2i and Ivabradine in improving quality of life as it has been demonstrated previously that SGLT2i and Ivabradine are both able to significantly improve quality of life.[162-164] Also, similar to the findings of past research, BB and ACEi did not have a significant impact on quality of life.[164] However, our study suggests that digoxin, which was previously shown to be neutral in its impact on quality of life, may significantly hinder quality of life.[164] Further, ARNi, ARB, and H-ISDN, which have been suggested to significantly improve quality of life did not have a statistically significant impact on quality of life in our study.[164-166] The impact of vericiguat on quality of life has not been evaluated previously, but in our study it did not have a significant impact. We were unable to assess the efficacy of OM or MRAs individually due to the lack of trials that evaluated the effect of the

interventions on the KCCQ OSS. Our results suggest that the addition of Ivabradine could be considered after GDMT is optimized, however, more evidence may be needed to determine the efficacy of Vericiguat and H-ISDN in improving quality of life before it is considered for addition to GDMT, particularly since only one trial evaluated the impact of H-ISDN and this trial only involved patients who self-identified as black.[142] Digoxin, however, should not be considered for addition to GDMT as it may result in a clinically meaningful reduction in quality of life. This may be the case due to the fact that particularly before the use of multiple imputation methods was computationally accessible, quality of life measurement practices heavily penalized treatment groups for patient deaths by imputing the worst score possible for missing data.[167-168] The DIG investigation - which was the only trial which evaluated digoxin directly in our study - used the worst score possible imputation method as a sensitivity analysis and patient scores using this method were found to be similar to the scores used in the main analysis which suggests that the imputed numbers may have been lower than the true scores of participants.[169] As digoxin may not reduce mortality in patients with HFrEF the potential toxicity and risks of digoxin treatment may not be compensated in the way that other medications such as ACEi and ARNi are, due to their beneficial effects on mortality. [108, 169-170] Consequently, digoxin, thought to be a treatment which improves quality of life, appears to reduce quality of life in our study when compared with other treatment options for HFrEF. This has implications for the assessment of IV magnesium which may also lack mortality reducing benefits.

3.4.4 Significance for assessment of IV magnesium

The conversion between the outcome measure of the study and the KCCQ OSS is direct so that the estimated MD of any treatment combination also describes the mean change in the KCCQ OSS which may be experienced by a patient who is initiated on this treatment. This means that patients who are initiated on a combination of ARNi + BB + MRA + SGLT2i may on average experience a small-medium clinically meaningful quality of life improvement and for combinations of ARNi + BB + SGLT2i, ACEi + BB + MRA + SGLT2i, or ACEi + BB + MRA + Ivabradine a small clinically meaningful quality of life

improvement may be experienced on average. This demonstrates that the effect size for recommended contemporary CHF intervention, which is a combination of multiple therapies, should lie somewhere between 3-7 mean units of change in the KCCQ. This is relevant for a future study of IV magnesium and will help determine the necessary sample size of such a study to prevent an over or under powered study. However, it's important to recognize that our network meta-analysis also revealed the extremely variable nature of the experience of quality of life in patients with CHF and our findings agree that the mean change is an incomplete description of the change in quality of life that may be experienced by a patient with heart failure. Patients are not likely to experience a mean improvement in quality of life, but rather a deterioration, no improvement or an improvement in quality of life; consequently it is suggested to summarize the intervention's impact on quality of life by considering and comparing the proportion of patients who experience a change of 5 units, 10 units and 20 units in the KCCQ - which have been defined by Spertus et al in their 2020 review as small, medium and large clinical changes respectively - in either direction in addition to the mean change in quality of life due to the intervention.[158] A future study evaluating magnesium therapy should consider evaluating quality of life using both measures. Another implication of the findings of our study is that the choice of quality of life measurement methodology would be critical to the accurate assessment of the study results. The use of a methodology which inappropriately penalizes the treatment group if it fails to reduce the risk of mortality in comparison with placebo would allow the direct quality of life benefits to be more clear for IV magnesium as it may not improve mortality and may in fact increase mortality.

3.4.5 Strengths and limitations

This is the largest and only study to evaluate the impact of combinations of treatments for heart failure with reduced ejection fraction on health related quality of life using a network meta analysis and systematic review methodology. It includes 40 placebo controlled, randomized, double blind trials, the majority of which are multi center trials and represents the best available evidence for the impact of efficacious HFrEF treatments

on patients' quality of life. The main analysis for the most clinically relevant treatment combinations largely relied on high confidence evidence with little detected bias. We conducted sensitivity analyses which showed that the conversion of scores from one score scale to the other and the bias that was detected in some studies did not influence the results of our study. However, many treatment combinations in our study did not have a statistically significant impact on quality of life likely due to the natural variability in quality of life experiences within study treatment groups and the lack of direct evidence for comparisons. Additionally, while the heterogeneity of the standard NMA model was low, the additive NMA model showed high heterogeneity which we partially compensated for by using a random effects model. Further, we were unable to account for the dosages of study treatments or the variability in length of follow up between studies. Thus, while our results should be interpreted with caution, these results are based on the best evidence currently available and provide clinically meaningful information.

3.4.6 Conclusion

The results of this study indicate the most effective treatment combinations and additional therapies for improving quality of life, this not only provides clinically meaningful information that can help patients and clinicians more effectively achieve patient goals, this will help inform the appropriate design and interpretation of a clinical trial for assessing the impact of IV magnesium on AHF.

Figures:

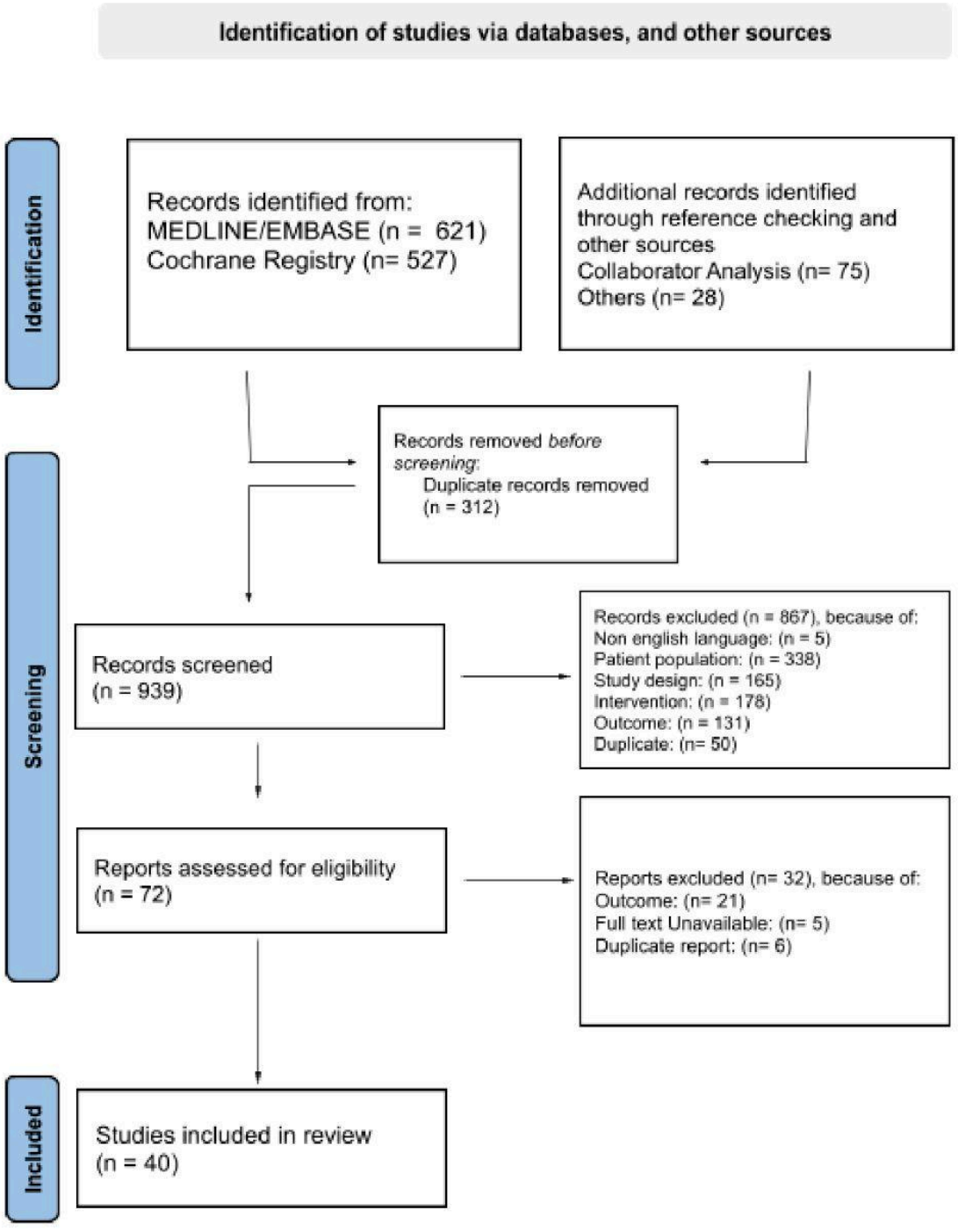


Figure 3.1. PRISMA flowchart.

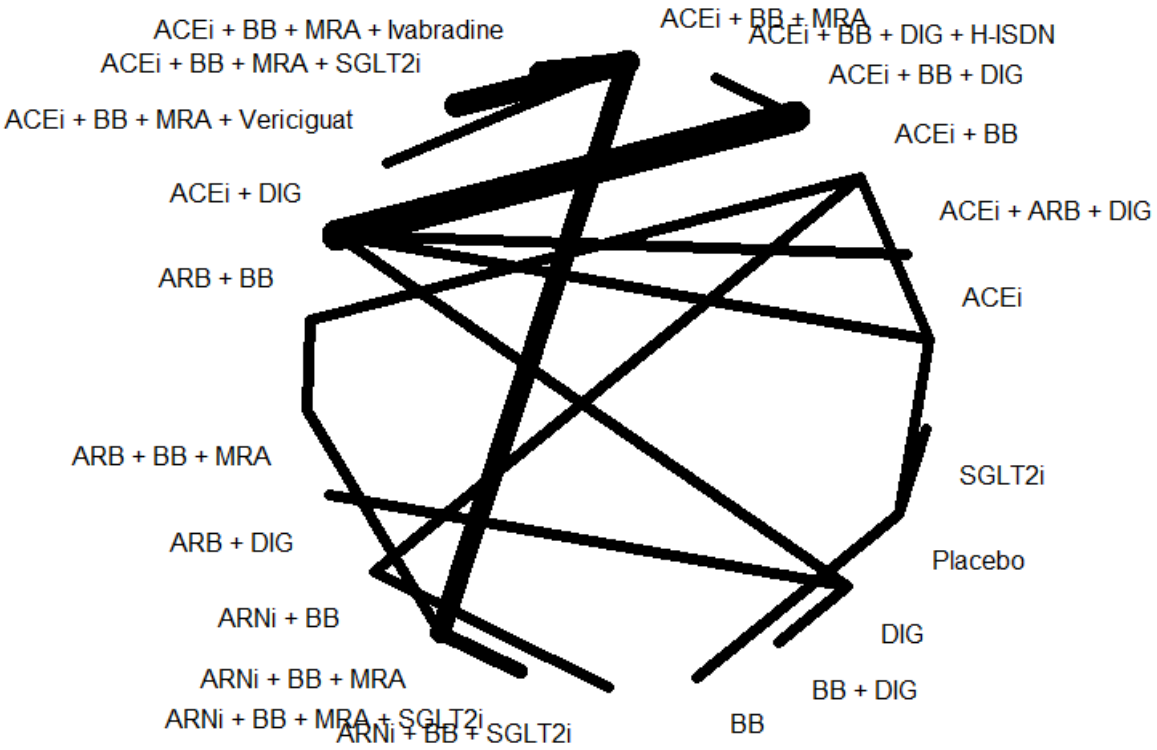


Figure 3.2. Network connection diagram for change in quality of life outcome.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; Dig, digoxin; H-ISDN, hydralazine–isosorbide dinitrate; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor

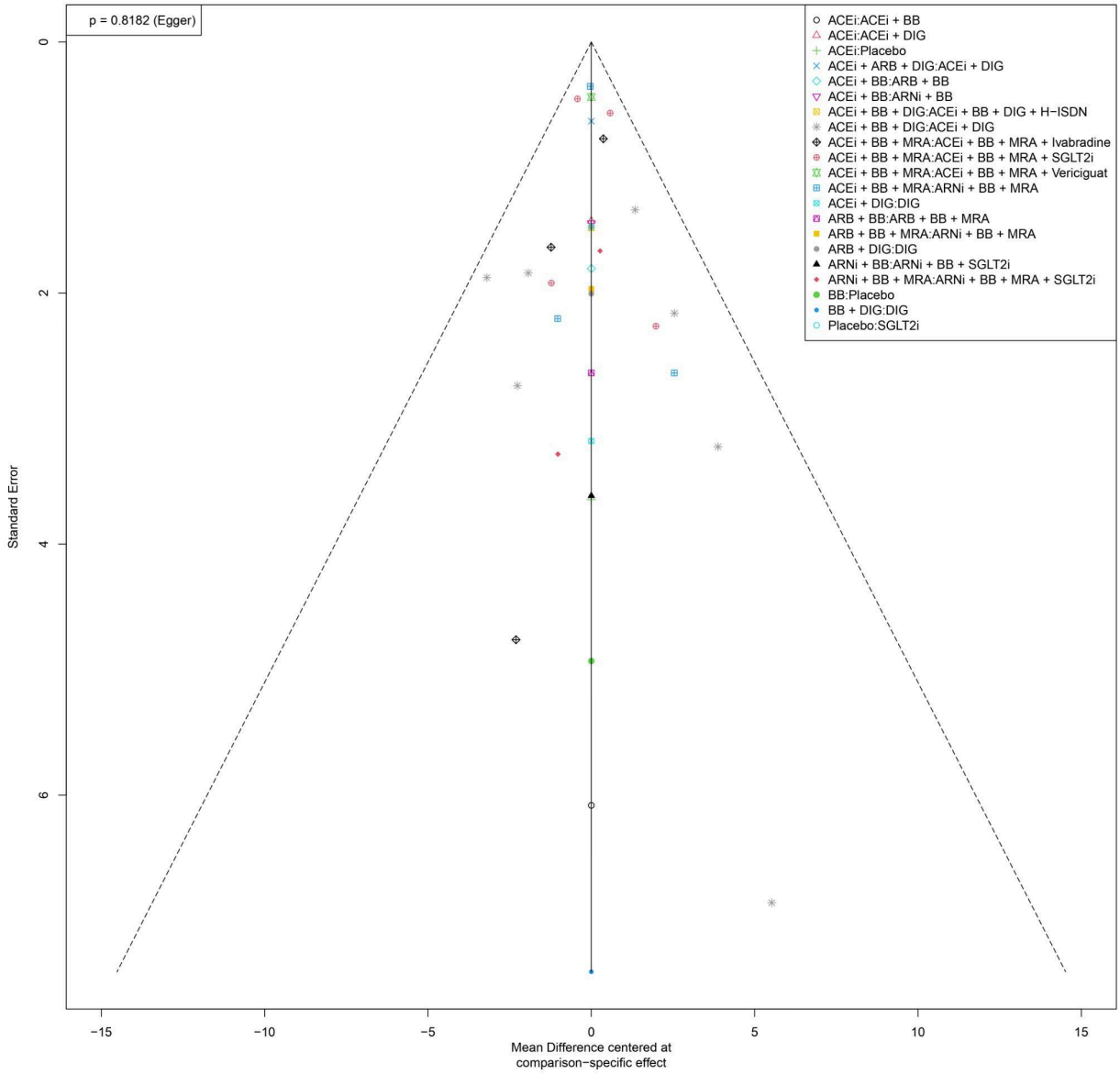


Figure 3.3. Funnel plots for quality of life outcome.

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; Dig, digoxin; H-ISDN, hydralazine–isosorbide dinitrate; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor

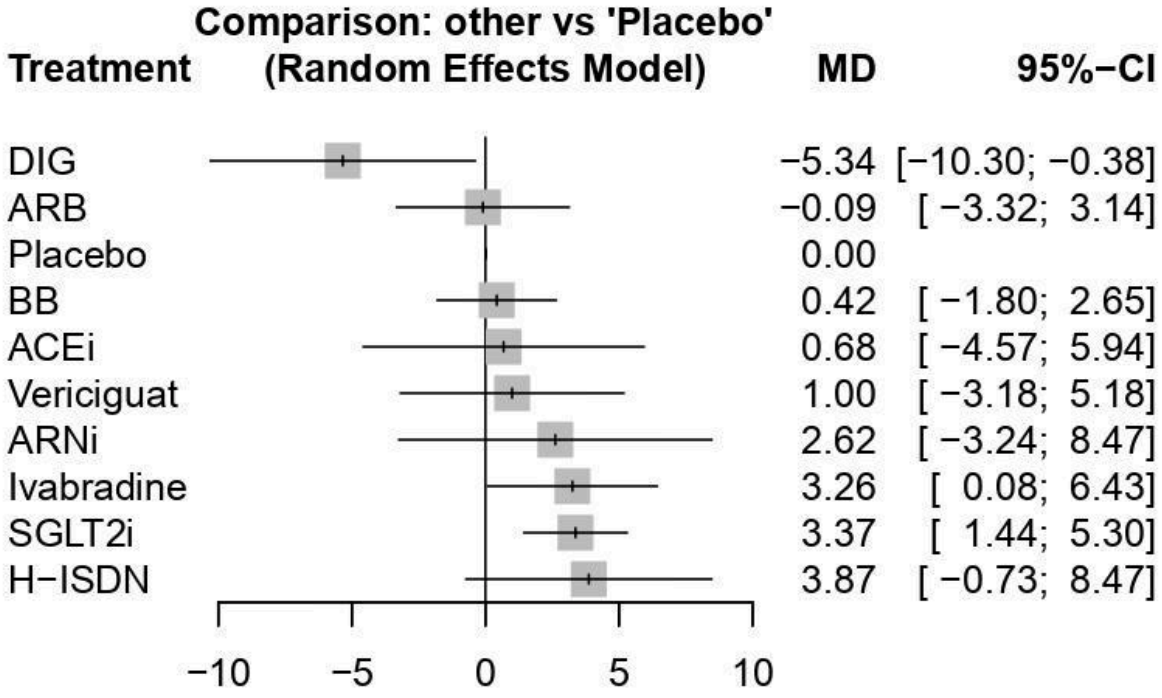


Figure 3.4. Forest Plot Showing the Mean Difference in Quality of Life Score Change Against Placebo.

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; Dig, digoxin; H-ISDN, hydralazine–isosorbide dinitrate; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor

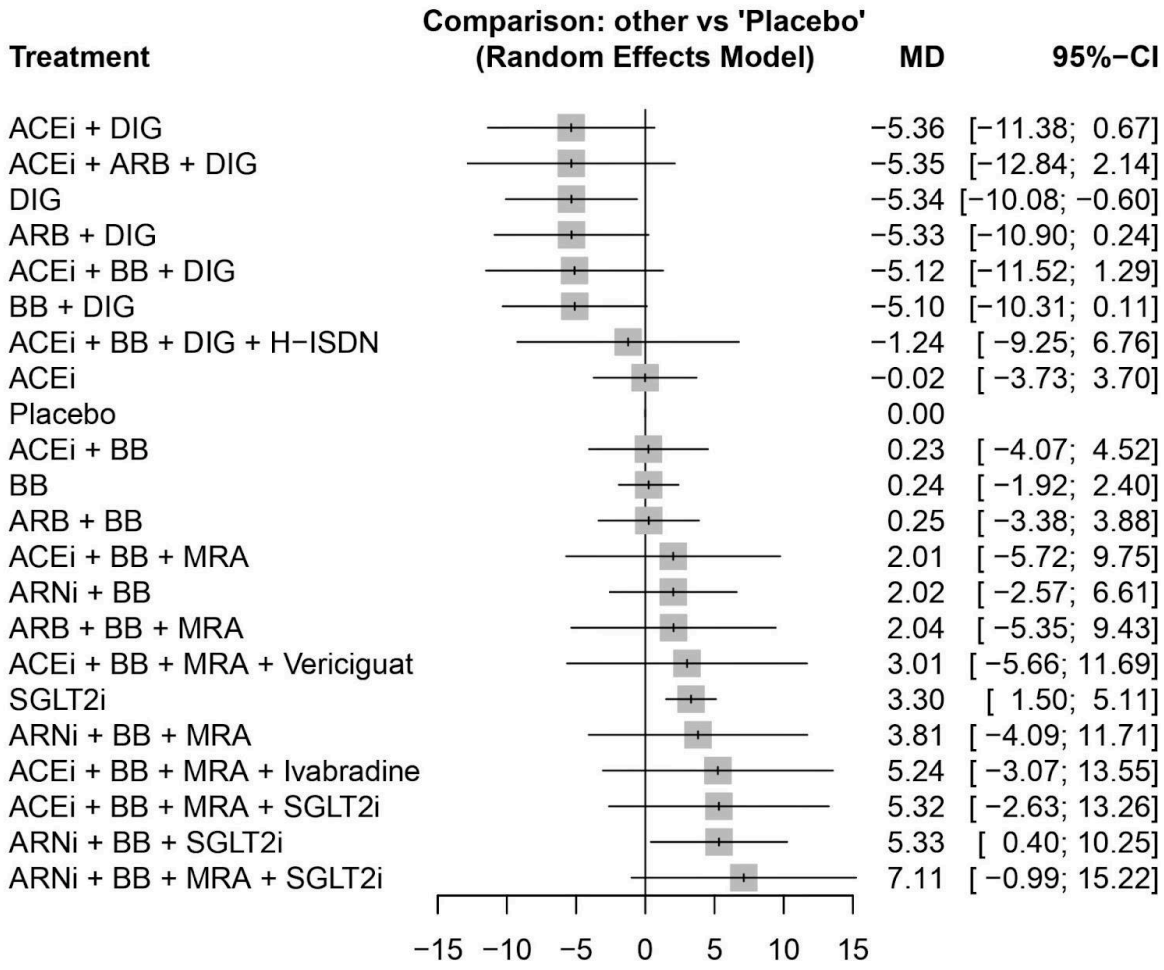


Figure 3.5. Forest plot showing the mean difference in quality of life score change of treatments in the additive network meta analysis against placebo.

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; Dig, digoxin; H-ISDN, hydralazine–isosorbide dinitrate; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor

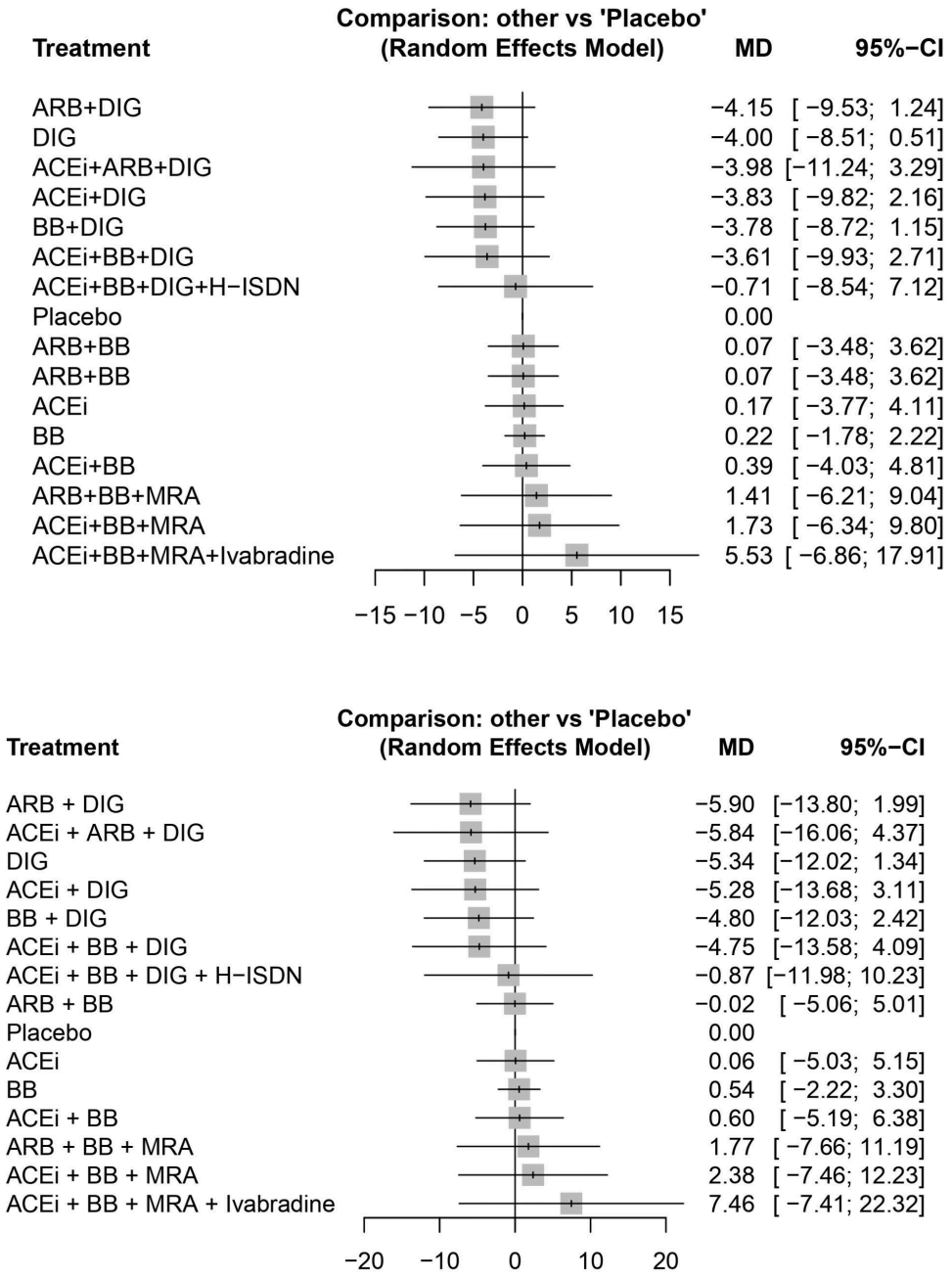


Figure 3.6. Forest plot showing the mean difference in quality of life Score for various treatments only in studies which used the MLHFQ score (A) and only in studies which used the MLHFQ score and were subsequently converted to KCCQ (B).

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; DIG, digoxin; H-ISDN, hydralazine–isosorbide dinitrate; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor

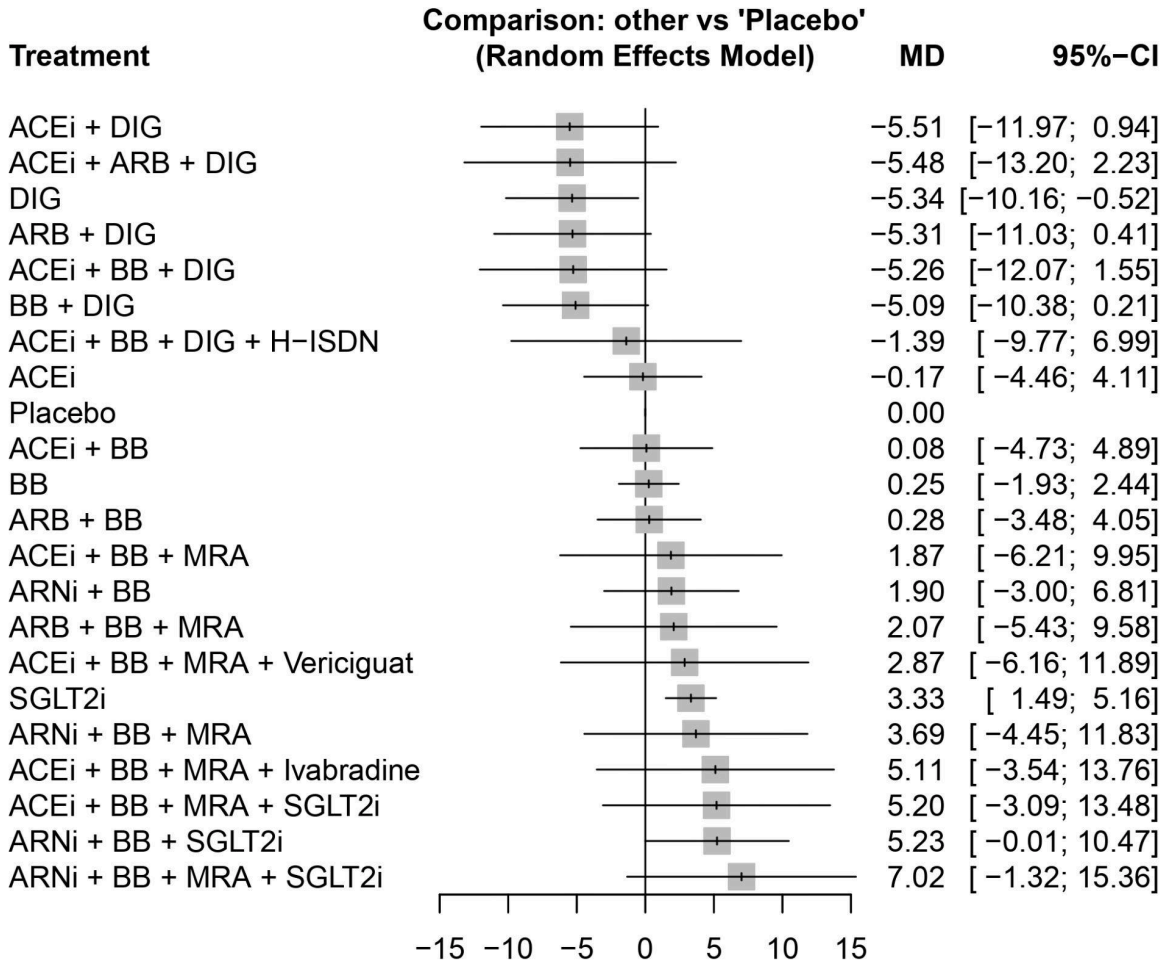


Figure 3.7. Forest plot showing the mean difference in quality of life Score for various Treatments after the removal of studies with major concerns of bias.

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; DIG, digoxin; H-ISDN, hydralazine–isosorbide dinitrate; MRA, mineralocorticoid receptor antagonist;

Tables:

Table 3.1. Study characteristics and outcomes by treatment arm

	Treatment	Follow up	N randomized	Mean MLHFQ score change	Mean KCCQ overall summary score (OSS) change	Mean KCCQ total symptom score (TSS) change	Mean KCCQ clinical summary score (CSS) change	Number of participants discontinuing the drug in the group
Pollock et al 1990	DIG	3	7	-6	4.11	NR	NR	4
	BB+DIG	3	12	-21	24.13	NR	NR	2
Widimsky et al 1995	DIG	3	48	-8	6.78	NR	NR	6
	ACEi+DIG	3	48	-13	13.45	NR	NR	4
	ACEi+DIG	3	53	-8	6.78	NR	NR	2
	ACEi+DIG	3	51	-6	4.11	NR	NR	4
	ACEi+DIG	3	48	-9	8.11	NR	NR	6
Bristow et al 1996	ACEi+DIG	6	84	-7.3	5.84	NR	NR	11
	ACEi+BB+DIG	6	83	-7.9	6.64	NR	NR	3
	ACEi+BB+DIG	6	89	-7.3	5.84	NR	NR	10
	ACEi+BB+DIG	6	89	-5.5	3.44	NR	NR	5
Packer et al 1996	ACEi+DIG	6	145	-3.7	1.04	NR	NR	30
	ACEi+BB+DIG	6	133	-5.5	3.44	NR	NR	19
Colucci et al 1996	ACEi+DIG	12	134	-4.9	2.64	NR	NR	14
	ACEi+BB+DIG	12	232	-2.4	-0.70	NR	NR	17
Cohn et al 1997	ACEi+DIG	3	35	-8.8	7.84	NR	NR	4
	ACEi+BB+DIG	3	70	-11.6	11.58	NR	NR	8
Goldstein et al 1999	ACEi+DIG	6	19	-4.84	2.56	NR	NR	3

	ACEi+BB+DIG	6	42	-8.87	7.94	NR	NR	9
Hjalmarson et al 2000	ACEi+DIG	1	339	0.2	-4.17	NR	NR	NR
	ACEi+BB+DIG	12	331	-0.7	-2.97	NR	NR	NR
Granger et al 2000	DIG	3	91	-4	1.44	NR	NR	12
	ARB+DIG	3	179	0	-3.90	NR	NR	31
Beanlands et al 2000	Placebo	3	21	1	-5.24	NR	NR	1
	BB	3	19	4	-9.24	NR	NR	1
De Milliano et al 2001	ACEi	6	11	-4.1	1.57	NR	NR	1
	ACEi+BB	6	43	-6.8	5.17	NR	NR	4
Hutcheon et al 2002	Placebo	2.5	37	-5.4	3.31	NR	NR	2
	ACEi	2.5	36	-4.8	2.50	NR	NR	5
Willenheimer et al 2002	ARB+BB	3	70	-0.7	-2.97	NR	NR	6
	ACEi+BB	3	71	-0.9	-2.70	NR	NR	14
Lader et al 2003	ACEi	12	291	-5	2.77	NR	NR	NR
	ACEi+DIG	12	298	-1	-2.57	NR	NR	NR
Taylor et al 2004	ACEi+BB+DIG	10	532	-2.7	-0.30	NR	NR	NR
	ACEi+BB+DIG+H-ISDN	10	518	-5.6	3.57	NR	NR	NR
Majani et al 2004	ACEi+DIG	23	1506	2.4	-7.11	NR	NR	NR
	ACEi+ARB+DIG	23	1504	0.4	-4.44	NR	NR	NR
Edes et al 2005	ACEi+DIG	12	126	-10.78	10.49	NR	NR	0
	ACEi+BB+DIG	12	134	-9.23	8.42	NR	NR	0
Chan et al 2007	ARB+BB	12	25	-10.96	10.73	NR	NR	1
	ARB+BB+MRA	12	23	-12.3	12.52	NR	NR	2
Ekman et al 2011	ACEi+BB+MRA	12	976	NR	4.3	3.6	3.3	NR
	ACEi+BB+MRA+Ivabradine	12	968	NR	6.7	4.6	5	NR

Abdel-Salam et al 2015	ACEi+BB+MRA	3	23	-8.6	7.58	NR	NR	0
	ACEi+BB+MRA+Ivabradine	3	20	-12.4	12.65	NR	NR	0
Lewis et al 2017	ACEi+BB+MRA	8	3826	NR	-0.14	−0.61	-0.29	NR
	ARNi+BB+MRA	8	3797	NR	1.13	0.53	0.64	NR
Nassif et al 2019	ACEi+BB+MRA	3	132	NR	1.9	-0.5	0.5	12
	ACEi+BB+MRA+SGLT2i	3	131	NR	5.2	4.5	4.2	11
Desai et al 2019	ACEi+BB	3	233	NR	4.2	NR	NR	17
	ARNi+BB	3	231	NR	8.7	NR	NR	16
McMurray et al 2019	ACEi+BB+MRA	8	2371	NR	4	3.3	3	249
	ACEi+BB+MRA+SGLT2i	8	2373	NR	6.5	6.1	6	258
Jensen et al 2020	ACEi+BB+MRA	3	95	NR	1.9	1.1	0.5	1
	ACEi+BB+MRA+SGLT2i	3	95	NR	2	3.2	3.3	0
Felker et al 2020	ACEi+BB+MRA	5	149	NR	NR	5	4.1	4
	ACEi+BB+MRA+OM	5	149	NR	NR	9.9	7	12
	ACEi+BB+MRA+OM	5	150	NR	NR	6.6	6.3	5
Abraham et al 2021	ARNi+BB+MRA	3	156	NR	6.4	3.65	4.82	13
	ARNi+BB+MRA+SGLT2i	3	156	NR	9.65	7.29	8.2	15
Santos-Gallego et al 2021	ARNi+BB	6	42	NR	1.9	NR	NR	2
	ARNi+BB+SGLT2i	6	42	NR	21	NR	NR	2

Tsutsui et al 2021	ACEi+BB+MRA	6	113	NR	NR	NR	-3.49	13
	ARNi+BB+MRA	6	112	NR	NR	NR	-2.22	11
Khandwalla et al 2020	ACEi+BB+MRA	2	70	NR	4.19	NR	NR	8
	ARNi+BB+MRA	2	70	NR	2.89	NR	NR	5
Lee et al 2021	ACEi+BB+MRA	9	53	NR	NR	4.2	NR	0
	ACEi+BB+MRA+SGLT2i	9	52	NR	NR	0.7	NR	5
Teerlink et al 2021	ACEi+BB+MRA	6	3072	NR	NR	6.3	NR	50
	ACEi+BB+MRA+OM	6	3076	NR	NR	5.8	NR	41
Butler et al 2021	ACEi+BB+MRA	12	1867	NR	5	5	4	335
	ACEi+BB+MRA+SGLT2i	12	1863	NR	6.5	6.75	5.5	303
Halle et al 2021	ACEi+BB+MRA	3	98	NR	5.84	4.75	4.92	7
	ARNi+BB+MRA	3	103	NR	8.11	8.29	7.33	4
Mann et al. 2021	ARB+BB+MRA	6	168	NR	10.8	NR	NR	36
	ARNi+BB+MRA	6	167	NR	11.8	NR	NR	49
Ye et al 2022	ACEi+BB+MRA	8	172	NR	5	NR	3	13
	ACEi+BB+MRA+Ivabradine	8	170	NR	9	NR	7	13
Palau et al 2022	ARNi+BB+MRA	3	45	-2.6	-0.43	NR	NR	0
	ARNi+BB+MRA+SGLT2i	3	45	-6	4.11	NR	NR	0

Spertus et al 2022	Placebo	3	91	NR	6.6	4.2	3.9	18
	SGLT2i	3	90	NR	9.8	9.1	7.5	13
Butler et al 2022	ACEi+BB+MRA	4	2524	NR	6.8	7.3	6.3	565
	ACEi+BB+MRA+Vericiguat	4	2526	NR	7.8	6.3	6.3	610
Lewis et al 2022	ARNi+BB+MRA	5	91	NR	NR	1.8	NR	6
	ARNi+BB+MRA+OM	5	185	NR	NR	0.3	NR	21

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; DIG, digoxin; H-ISDN, hydralazine–isosorbide dinitrate; MRA, mineralocorticoid receptor antagonist;

Table 3.2. Risk of bias 2 assessment domain and overall scores for all included studies.

Unique ID	Experimental	Comparator	Study Design	D1	D2	D3	D4	D5	Overall
Pollock et al 1990	BB	Placebo	DB, SC	0	0	1	0	0	Some Concerns
Widimsky et al 1995	ACEi	Placebo	DB, MC	0	0	0	0	0	Low risk
Bristow et al 1996	BB	Placebo	DB, MC	0	0	0	0	0	Low risk
Packer et al 1996	BB	Placebo	DB, MC	0	0	0	0	0	Low risk
Colucci et al 1996	BB	Placebo	DB, MC	0	0	0	0	0	Low risk
Cohn et al 1997	BB	Placebo	DB, MC	0	0	0	0	0	Low risk

Goldstein et al 1999	BB	Placebo	DB, MC	0	0	1	0	0	Some Concerns
Hjalmarson et al 2000	BB	Placebo	DB, MC	0	0	1	0	0	Some Concerns
Granger et al 2000	ARB	Placebo	DB, MC	0	0	1	0	0	Some Concerns
Beanlands et al 2000	BB	Placebo	DB, MC	0	0	0	0	0	Low Risk
De Milliano et al 2001	BB	Placebo	DB, MC	1	0	0	0	0	Some Concerns
Hutcheon et al 2002	ACEi	Placebo	DB, SC	0	0	0	0	0	Low Risk
Willenheimer et al 2002	ACEi	ARB	DB, MC	0	0	2	0	0	Major Concerns
Lader et al 2003	DIG	Placebo	DB, MC	0	0	0	0	0	Low Risk
Taylor et al 2004	H-ISDN	Placebo	DB, MC	0	0	0	0	0	Low Risk
Majani et al 2004	ARB	Placebo	DB, MC	0	0	0	0	0	Low Risk
Edes et al 2005	BB	Placebo	DB, MC	0	0	0	0	0	Low Risk
Chan et al 2007	ARB+MRA	ARB	DB, SC	0	0	0	0	0	Low Risk
Ekman et al 2011	Ivabradine	Placebo	DB, MC	0	0	0	0	0	Low Risk
Abdel-Salam et al 2015	Ivabradine	Placebo	DB, SC	0	0	0	0	0	Low Risk
Lewis et al 2017	ARNi	ACEi	DB, MC	0	0	0	0	0	Low Risk
Nassif et al 2019	SGLT2i	Placebo	DB, MC	0	0	0	0	0	Low Risk
Desai et al 2019	ARNi	ACEi	DB, MC	0	0	0	0	0	Low Risk
McMurray et al 2019	SGLT2i	Placebo	DB, MC	0	0	0	0	0	Low Risk
Jensen et al 2020	SGLT2i	Placebo	DB, MC	0	0	0	0	0	Low Risk

Felker et al 2020	OM	Placebo	DB, MC	0	0	0	0	0	Low Risk
Abraham et al 2021	SGLT2i	Placebo	DB, MC	0	0	0	0	0	Low Risk
Santos-Gallego et al 2021	SGLT2i	Placebo	DB, SC	0	0	0	0	0	Low Risk
Tsutsui et al 2021	ARNi	ACEi	DB, MC	0	0	0	0	0	Low Risk
Khandwalla et al 2020	ARNi	ACEi	DB, MC	0	0	1	0	0	Some Concerns
Lee et al 2021	SGLT2i	Placebo	DB, MC	1	0	2	0	0	Major Concerns
Teerlink et al 2021	OM	Placebo	DB, MC	0	0	0	0	0	Low Risk
Butler et al 2021	SGLT2i	Placebo	DB, MC	0	0	1	0	0	Some Concerns
Halle et al 2021	ARNi	ACEi	DB, MC	0	0	0	0	0	Low Risk
Mann et al. 2021	ARNi	ARB	DB, MC	0	0	1	0	0	Some Concerns
Ye et al 2022	Ivabradine	Placebo	DB, MC	0	0	0	0	0	Low Risk
Palau et al 2022	SGLT2i	Placebo	DB, MC	0	0	1	0	0	Some Concerns
Spertus et al 2022	SGLT2i	Placebo	DB, MC	0	0	0	0	0	Low Risk
Butler et al 2022	Vericiguat	Placebo	DB, MC	0	0	0	0	0	Low Risk
Lewis et al 2022	OM	Placebo	DB, MC	0	0	0	0	0	Low Risk

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; DIG, digoxin; H-ISDN, hydralazine–isosorbide dinitrate; MRA, mineralocorticoid receptor antagonist;

Table 3.3. P scores of each component

Treatment combination	P-score
ARNi + BB + MRA + SGLT2i	0.948
ARNi + BB + SGLT2i	0.859
ACEi + BB + MRA + SGLT2i	0.842
ACEi + BB + MRA + Ivabradine	0.831
SGLT2i	0.739
ARNi + BB + MRA	0.727
ACEi + BB + MRA + Vericiguat	0.655
ARNi + BB	0.642
ARB + BB + MRA	0.579
ACEi + BB + MRA	0.566
BB	0.481
ARB + BB	0.48
ACEi + BB	0.473
Placebo	0.46
ACEi	0.454
ACEi + BB + DIG + H-ISDN	0.415
BB + DIG	0.154
ACEi + BB + DIG	0.149
ACEi + ARB + DIG	0.143
ARB + DIG	0.137
DIG	0.136
ACEi + DIG	0.131

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; DIG, digoxin; H-ISDN, hydralazine–isosorbide dinitrate; MRA, mineralocorticoid receptor antagonist;

Table 3.4. Estimates of relative differences in treatment effect on quality of life of treatment combinations presented as the estimate of the difference between the treatment combination in the column versus the treatment combination in the respective row.

	ACEi + BB + DIG + H-ISDN	ACEi + BB + MRA	ACEi + BB + MRA + Ivabradine	ACEi + BB + MRA + SGLT2i	ACEi + BB + MRA + Vericiguat	ARNi + BB + MRA	ARNi + BB + MRA + SGLT2i	ARNi + BB + SGLT2i
ACEi	-1.23 (-8.32-5.86); 0.7345	2.03 (-4.75-8.82); 0.5575	5.26 (-2.17-12.69); 0.1653	5.34 (-1.69-12.36); 0.1364	3.03 (-4.81-10.87); 0.4487	3.83 (-3.34-11); 0.2957	7.13 (-0.26-14.52); 0.0587	5.34 (1.7-8.99); 0.0041
ACEi + ARB + DIG	4.11 (-1.92-10.13); 0.1818	7.36 (-1.42-16.14); 0.1002	10.59 (1.3-19.88); 0.0254	10.67 (1.7-19.63); 0.0197	8.36 (-1.26-17.98); 0.0884	9.16 (0.13-18.18); 0.0467	12.46 (3.26-21.67); 0.008	10.67 (4.09-17.26); 0.0015
ACEi + BB	-1.47 (-8.22-5.29); 0.67	1.79 (-4.64-8.22); 0.5857	5.02 (-2.09-12.13); 0.1666	5.09 (-1.59-11.78); 0.1351	2.79 (-4.75-10.33); 0.4683	3.58 (-3.25-10.42); 0.3043	6.89 (-0.18-13.96); 0.0562	5.1 (2.16-8.04); 7e-04
ACEi + BB + DIG	3.87 (-0.94-8.68); 0.1146	7.13 (-0.86-15.12); 0.0804	10.36 (1.81-18.91); 0.0175	10.43 (2.24-18.63); 0.0126	8.13 (-0.78-17.04); 0.0736	8.92 (0.6-17.25); 0.0356	12.23 (3.71-20.75); 0.0049	10.44 (4.86-16.02); 2e-04
ACEi + BB + DIG + H-ISDN	1	3.26 (-6.07-12.59); 0.4937	6.49 (-3.32-16.3); 0.1948	6.56 (-2.94-16.06); 0.1758	4.26 (-5.86-14.38); 0.4097	5.05 (-4.56-14.67); 0.3029	8.36 (-1.42-18.14); 0.094	6.57 (-0.8-13.93); 0.0805
ACEi + BB + MRA	-3.26 (-12.59-6.07); 0.4937	1	3.23 (0.2-6.26); 0.0368	3.3 (1.5-5.11); 3e-04	1 (-2.93-4.93); 0.6179	1.8 (-0.52-4.11); 0.1292	5.1 (2.16-8.04); 7e-04	3.31 (-3.76-10.38); 0.3589
ACEi + BB + MRA + Ivabradine	-6.49 (-16.3-3.32); 0.1948	-3.23 (-6.26--0.2); 0.0368	1	0.07 (-3.45-3.6); 0.9672	-2.23 (-7.19-2.73); 0.3783	-1.44 (-5.25-2.38); 0.4612	1.87 (-2.35-6.09); 0.3855	0.08 (-7.61-7.78); 0.9837
ACEi + BB + MRA + SGLT2i	-6.56 (-16.06-2.94); 0.1758	-3.3 (-5.11--1.5); 3e-04	-0.07 (-3.6-3.45); 0.9672	1	-2.3 (-6.63-2.02); 0.2961	-1.51 (-4.45-1.43); 0.314	1.8 (-0.52-4.11); 0.1292	0.01 (-6.83-6.84); 0.9986

ACEi + BB + MRA + Vericiguat	-4.26 (-14.38-5.86); 0.4097	-1 (-4.93-2.93); 0.6179	2.23 (-2.73-7.19); 0.3783	2.3 (-2.02-6.63); 0.2961	1	0.8 (-3.77-5.36); 0.7326	4.1 (-0.81-9.01); 0.1014	2.31 (-5.78-10.4); 0.5756
ACEi + DIG	4.11 (-1.16-9.38); 0.1261	7.37 (-0.91-15.65); 0.081	10.6 (1.78-19.42); 0.0184	10.68 (2.2-19.15); 0.0135	8.37 (-0.79-17.53); 0.0734	9.17 (0.57-17.76); 0.0367	12.47 (3.69-21.26); 0.0054	10.68 (4.7-16.66); 5e-04
ARB + BB	-1.49 (-9.03-6.04); 0.6977	1.76 (-5.48-9.01); 0.6332	5 (-2.86-12.85); 0.2127	5.07 (-2.4-12.54); 0.1834	2.76 (-5.48-11.01); 0.511	3.56 (-3.8-10.92); 0.3428	6.86 (-0.71-14.44); 0.0756	5.08 (1.08-9.07); 0.0128
ARB + BB + MRA	-3.28 (-13.19-6.63); 0.5162	-0.02 (-3.36-3.31); 0.9886	3.21 (-1.3-7.72); 0.1635	3.28 (-0.51-7.07); 0.0902	0.98 (-4.18-6.13); 0.7107	1.77 (-1.79-5.34); 0.3302	5.08 (1.08-9.07); 0.0128	3.29 (-4.29-10.86); 0.395
ARB + DIG	4.09 (-2.15-10.33); 0.1989	7.35 (-1.58-16.27); 0.1067	10.58 (1.15-20); 0.0279	10.65 (1.54-19.76); 0.0219	8.35 (-1.41-18.1); 0.0935	9.14 (0.13-18.16); 0.0468	12.45 (3.25-21.64); 0.008	10.66 (4.09-17.22); 0.0015
ARNi + BB	-3.26 (-10.41-3.88); 0.3704	-0.01 (-6.84-6.83); 0.9986	3.22 (-4.26-10.7); 0.3982	3.3 (-3.77-10.37); 0.3607	0.99 (-6.89-8.88); 0.805	1.79 (-4.64-8.22); 0.5857	5.09 (-1.59-11.78); 0.1351	3.3 (1.5-5.11); 3e-04
ARNi + BB + MRA	-5.05 (-14.67-4.56); 0.3029	-1.8 (-4.11-0.52); 0.1292	1.44 (-2.38-5.25); 0.4612	1.51 (-1.43-4.45); 0.314	-0.8 (-5.36-3.77); 0.7326	1	3.3 (1.5-5.11); 3e-04	1.52 (-5.17-8.2); 0.6566
ARNi + BB + MRA + SGLT2i	-8.36 (-18.14-1.42); 0.094	-5.1 (-8.04--2.16); 7e-04	-1.87 (-6.09-2.35); 0.3855	-1.8 (-4.11-0.52); 0.1292	-4.1 (-9.01-0.81); 0.1014	-3.3 (-5.11--1.5); 3e-04	1	-1.79 (-8.22-4.64); 0.5857
ARNi + BB + SGLT2i	-6.57 (-13.93-0.8); 0.0805	-3.31 (-10.38-3.76); 0.3589	-0.08 (-7.78-7.61); 0.9837	-0.01 (-6.84-6.83); 0.9986	-2.31 (-10.4-5.78); 0.5756	-1.52 (-8.2-5.17); 0.6566	1.79 (-4.64-8.22); 0.5857	1
BB	-1.49 (-9.2-6.22); 0.7058	1.77 (-5.66-9.2); 0.6401	5 (-3.02-13.03); 0.2217	5.08 (-2.57-12.72); 0.1931	2.77 (-5.63-11.18); 0.5179	3.57 (-4.03-11.17); 0.3576	6.87 (-0.94-14.68); 0.0847	5.08 (0.65-9.52); 0.0246

BB + DIG	3.86 (-2.22-9.93); 0.2138	7.11 (-1.7-15.93); 0.1138	10.34 (1.02-19.67); 0.0297	10.42 (1.42-19.42); 0.0233	8.11 (-1.54-17.76); 0.0994	8.91 (-0.05-17.87); 0.0513	12.21 (3.07-21.35); 0.0088	10.42 (3.93-16.92); 0.0017
DIG	4.1 (-2.35-10.55); 0.2131	7.35 (-1.72-16.43); 0.1122	10.58 (1.02-20.15); 0.0301	10.66 (1.41-19.91); 0.024	8.35 (-1.53-18.24); 0.0978	9.15 (-0.07-18.37); 0.0517	12.45 (3.06-21.85); 0.0093	10.67 (3.82-17.51); 0.0022
Placebo	-1.24 (-9.25-6.76); 0.7608	2.01 (-5.72-9.75); 0.6099	5.24 (-3.07-13.55); 0.2161	5.32 (-2.63-13.26); 0.1894	3.01 (-5.66-11.69); 0.496	3.81 (-4.09-11.71); 0.3447	7.11 (-0.99-15.22); 0.0854	5.33 (0.4-10.25); 0.0342
SGLT2i	-4.55 (-12.76-3.66); 0.2774	-1.29 (-9.23-6.65); 0.7502	1.94 (-6.56-10.44); 0.6548	2.01 (-5.72-9.75); 0.6099	-0.29 (-9.15-8.57); 0.9488	0.5 (-7.6-8.61); 0.9029	3.81 (-4.09-11.71); 0.3447	2.02 (-2.57-6.61); 0.388

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; DIG, digoxin; H-ISDN, hydralazine–isosorbide dinitrate; MRA, mineralocorticoid receptor antagonist;

Table 3.5. Cinema framework domain summary for all included comparisons

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
ACEi:ACEi+BB	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi:ACEi+DIG	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi:Placebo	1	No concerns	Low risk	Some concerns	Major concerns	No concerns	No concerns	Low
ACEi+ARB+DIG:ACEi+DIG	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+BB:ARB+BB	1	Major concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Low
ACEi+BB:ARNi+BB	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+BB+DIG:ACEi+BB+DIG+H-ISDN	1	No concerns	Low risk	Some concerns	No concerns	No concerns	No concerns	Moderate
ACEi+BB+DIG:ACEi+DIG	7	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+BB+MRA:ACEi+BB+MRA+Ivabradine	3	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+BB+MRA:ACEi+BB+MRA+SGLT2i	4	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+BB+MRA:ACEi+BB+MRA+Vericiguat	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+BB+MRA:ARNi+BB+MRA	3	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+DIG:DIG	1	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
ARB+BB:ARB+BB+MRA	1	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ARB+BB+MRA:ARNi+BB+MRA	1	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate

ARB+DIG:DIG	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
ARNi+BB:ARNi+BB+SGLT2i	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ARNi+BB+MRA:ARNi+BB+MRA+SGLT2i	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
BB:Placebo	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
BB+DIG:DIG	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
Placebo:SGLT2i	1	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
ACEi:ACEi+ARB+DIG	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi:ACEi+BB+DIG	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi:ACEi+BB+DIG+H-ISDN	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi:ACEi+BB+MRA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi:ACEi+BB+MRA+Ivabradine	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi:ACEi+BB+MRA+SGLT2i	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi:ACEi+BB+MRA+Vericiguat	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi:ARB+BB	0	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
ACEi:ARB+BB+MRA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi:ARB+DIG	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi:ARNi+BB	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
ACEi:ARNi+BB+MRA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi:ARNi+BB+MRA+SGLT2i	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low

ACEi:ARNi+BB+SGLT2i	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi:BB	0	No concerns	Low risk	Some concerns	Major concerns	No concerns	No concerns	Moderate
ACEi:BB+DIG	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi:DIG	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi:SGLT2i	0	No concerns	Low risk	Some concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+ARB+DIG:ACEi+BB	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+ARB+DIG:ACEi+BB+DIG	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
ACEi+ARB+DIG:ACEi+BB+DIG+H-ISDN	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
ACEi+ARB+DIG:ACEi+BB+MRA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+ARB+DIG:ACEi+BB+MRA+Ivabradine	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
ACEi+ARB+DIG:ACEi+BB+MRA+SGLT2i	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
ACEi+ARB+DIG:ACEi+BB+MRA+Vericiguat	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+ARB+DIG:ARB+BB	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+ARB+DIG:ARB+BB+MRA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+ARB+DIG:ARB+DIG	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+ARB+DIG:ARNi+BB	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+ARB+DIG:ARNi+BB+MRA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low

ACEi+ARB+DIG:ARNi+BB+MRA+SGLT2i	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+ARB+DIG:ARNi+BB+SGLT2i	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+ARB+DIG:BB	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+ARB+DIG:BB+DIG	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
ACEi+ARB+DIG:DIG	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+ARB+DIG:Placebo	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
ACEi+ARB+DIG:SGLT2i	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB:ACEi+BB+DIG	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB:ACEi+BB+DIG+H-ISDN	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB:ACEi+BB+MRA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB:ACEi+BB+MRA+Ivabradine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB:ACEi+BB+MRA+SGLT2i	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB:ACEi+BB+MRA+Vericiguat	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB:ACEi+DIG	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB:ARB+BB+MRA	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
ACEi+BB:ARB+DIG	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
ACEi+BB:ARNi+BB+MRA	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low

ACEi+BB:ARNi+BB+MRA+SGLT2i	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB:ARNi+BB+SGLT2i	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+BB:BB	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB:BB+DIG	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB:DIG	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB:Placebo	0	Some concerns	Low risk	Some concerns	Major concerns	No concerns	No concerns	Very low
ACEi+BB:SGLT2i	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+DIG: ACEi+BB+MRA	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
ACEi+BB+DIG: ACEi+BB+MRA+Ivabradine	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+DIG: ACEi+BB+MRA+SGLT2i	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+DIG: ACEi+BB+MRA+Vericiguat	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+DIG: ARB+BB	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
ACEi+BB+DIG: ARB+BB+MRA	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+DIG: ARB+DIG	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+DIG: ARNi+BB	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
ACEi+BB+DIG: ARNi+BB+MRA	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+DIG: ARNi+BB+MRA+SGLT2i	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate

ACEi+BB+DIG: ARNi+BB+SGLT2i	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+BB+DIG: BB	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+DIG: BB+DIG	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+BB+DIG: DIG	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+DIG: Placebo	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+DIG: SGLT2i	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+BB+DIG +H-ISDN:ACEi +BB+MRA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+DIG +H-ISDN:ACEi +BB+MRA+Ivabradine	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+DIG +H-ISDN:ACEi +BB+MRA+SGLT2i	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+DIG +H-ISDN:ACEi +BB+MRA+Vericiguat	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+DIG +H-ISDN:ACEi +DIG	0	No concerns	Low risk	Some concerns	No concerns	Some concerns	No concerns	Moderate
ACEi+BB+DIG +H-ISDN:ARB +BB	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+DIG +H-ISDN:ARB +BB+MRA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+DIG +H-ISDN:ARB +DIG	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High

ACEi+BB+DIG +H-ISDN:ARNi +BB	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+DIG +H-ISDN:ARNi +BB+MRA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+DIG +H-ISDN:ARNi +BB+MRA+SG LT2i	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
ACEi+BB+DIG +H-ISDN:ARNi +BB+SGLT2i	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+BB+DIG +H-ISDN:BB	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+DIG +H-ISDN:BB+ DIG	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+DIG +H-ISDN:DIG	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+DIG +H-ISDN:Place bo	0	No concerns	Low risk	Some concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+DIG +H-ISDN:SGLT 2i	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+MR A:ACEi+DIG	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
ACEi+BB+MR A:ARB+BB	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
ACEi+BB+MR A:ARB+BB+M RA	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
ACEi+BB+MR A:ARB+DIG	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
ACEi+BB+MR A:ARNi+BB	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
ACEi+BB+MR A:ARNi+BB+M RA+SGLT2i	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High

ACEi+BB+MRA:ARNi+BB+SGLT2i	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
ACEi+BB+MRA:BB	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+MRA:BB+DIG	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+MRA:DIG	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
ACEi+BB+MRA:Placebo	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+MRA:SGLT2i	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+MRA+Ivabradine:ACEi+BB+MRA+SGLT2i	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+BB+MRA+Ivabradine:ACEi+BB+MRA+Vericiguat	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+BB+MRA+Ivabradine:ACEi+DIG	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+MRA+Ivabradine:ARB+BB	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+MRA+Ivabradine:ARB+BB+MRA	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+MRA+Ivabradine:ARB+DIG	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
ACEi+BB+MRA+Ivabradine:ARNi+BB	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+MRA+Ivabradine:ARNi+BB+MRA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+BB+MRA+Ivabradine:A	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate

RNi+BB+MRA +SGLT2i								
ACEi+BB+MR A+Ivabradine:A RNi+BB+SGLT 2i	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+BB+MR A+Ivabradine:B B	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+MR A+Ivabradine:B B+DIG	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+MR A+Ivabradine: DIG	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+MR A+Ivabradine:P lacebo	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+MR A+Ivabradine:S GLT2i	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+MR A+SGLT2i:ACE i+BB+MRA+Ve riciguat	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+BB+MR A+SGLT2i:ACE i+DIG	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+MR A+SGLT2i:ARB +BB	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+MR A+SGLT2i:ARB +BB+MRA	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+MR A+SGLT2i:ARB +DIG	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
ACEi+BB+MR A+SGLT2i:AR Ni+BB	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+MR A+SGLT2i:AR Ni+BB+MRA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High

ACEi+BB+MRA+SGLT2i:ARNi+BB+MRA+SGLT2i	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+MRA+SGLT2i:ARNi+BB+SGLT2i	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+BB+MRA+SGLT2i:BB	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+MRA+SGLT2i:BB+DIG	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+MRA+SGLT2i:DIG	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+MRA+SGLT2i:Placebo	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+MRA+SGLT2i:SGLT2i	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+MRA+Vericiguat:ACEi+DIG	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+MRA+Vericiguat:ARB+BB	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+MRA+Vericiguat:ARB+BB+MRA	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
ACEi+BB+MRA+Vericiguat:ARB+DIG	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
ACEi+BB+MRA+Vericiguat:ARNi+BB	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+MRA+Vericiguat:ARNi+BB+MRA	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+BB+MRA+Vericiguat:ARNi+BB+MRA+SGLT2i	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High

ACEi+BB+MRA+Vericiguat:ARNi+BB+SGLT2i	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+BB+MRA+Vericiguat:BB	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+MRA+Vericiguat:BB+DIG	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+MRA+Vericiguat:DIG	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+BB+MRA+Vericiguat:Placebo	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+BB+MRA+Vericiguat:SGLT2i	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+DIG:ARB+BB	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
ACEi+DIG:ARB+BB+MRA	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+DIG:ARB+DIG	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+DIG:ARNi+BB	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
ACEi+DIG:ARNi+BB+MRA	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+DIG:ARNi+BB+MRA+SGLT2i	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
ACEi+DIG:ARNi+BB+SGLT2i	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ACEi+DIG:BB	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ACEi+DIG:BB+DIG	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
ACEi+DIG:Placebo	0	No concerns	Low risk	Some concerns	Some concerns	No concerns	No concerns	Moderate
ACEi+DIG:SGLT2i	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High

ARB+BB:ARB+DIG	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
ARB+BB:ARNi+BB	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
ARB+BB:ARNi+BB+MRA	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ARB+BB:ARNi+BB+MRA+SGLT2i	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ARB+BB:ARNi+BB+SGLT2i	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
ARB+BB:BB	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARB+BB:BB+DIG	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARB+BB:DIG	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low
ARB+BB:Placebo	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARB+BB:SGLT2i	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARB+BB+MRA:ARB+DIG	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
ARB+BB+MRA:ARNi+BB	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ARB+BB+MRA:ARNi+BB+MRA+SGLT2i	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ARB+BB+MRA:ARNi+BB+SGLT2i	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
ARB+BB+MRA:BB	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARB+BB+MRA:BB+DIG	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARB+BB+MRA:DIG	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
ARB+BB+MRA:Placebo	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARB+BB+MRA:SGLT2i	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low

ARB+DIG:ARNi+BB	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ARB+DIG:ARNi+BB+MRA	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
ARB+DIG:ARNi+BB+MRA+SGLT2i	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
ARB+DIG:ARNi+BB+SGLT2i	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ARB+DIG:BB	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARB+DIG:BB+DIG	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
ARB+DIG:Placebo	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ARB+DIG:SGLT2i	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ARNi+BB:ARNi+BB+MRA	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARNi+BB:ARNi+BB+MRA+SGLT2i	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARNi+BB:BB	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARNi+BB:BB+DIG	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARNi+BB:DIG	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
ARNi+BB:Placebo	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARNi+BB:SGLT2i	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARNi+BB+MRA:ARNi+BB+SGLT2i	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
ARNi+BB+MRA:BB	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARNi+BB+MRA:BB+DIG	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARNi+BB+MRA:DIG	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate

ARNi+BB+MRA:Placebo	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARNi+BB+MRA:SGLT2i	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARNi+BB+MRA+SGLT2i:ARNi+BB+SGLT2i	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
ARNi+BB+MRA+SGLT2i:BB	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARNi+BB+MRA+SGLT2i:BB+DIG	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARNi+BB+MRA+SGLT2i:DIG	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate
ARNi+BB+MRA+SGLT2i:Placebo	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARNi+BB+MRA+SGLT2i:SGLT2i	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARNi+BB+SGLT2i:BB	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ARNi+BB+SGLT2i:BB+DIG	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
ARNi+BB+SGLT2i:DIG	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ARNi+BB+SGLT2i:Placebo	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
ARNi+BB+SGLT2i:SGLT2i	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High
BB:BB+DIG	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Moderate
BB:DIG	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
BB:SGLT2i	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
BB+DIG:Placebo	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
BB+DIG:SGLT2i	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low

DIG:Placebo	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate
DIG:SGLT2i	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; DIG, digoxin; H-ISDN, hydralazine–isosorbide dinitrate; MRA, mineralocorticoid receptor antagonist;

3.5 SEARCH TERMS:

MEDLINE(R)/EMBASE search
Date of search: Feb 28 2023
1. exp Heart Failure/
2. Cardiomyopathy, Dilated/
3. (heart failure or cardiac failure or cardiac insufficiency or cardiomyopath$).tw.
4. ((cardi$ or myocard$) adj2 (failure$ or insufficien$)).tw.
5. OR/1-4
6. exp angiotensin receptor-neprilysin inhibitor/ OR ARNI
7. LCZ696 OR LCZ 696 OR LCZ-696 OR valsartan adj6 sacubitril OR valsartan adj6 sacubitril OR valsartan sacubitril OR valsartan-sacubitril OR sacubitril adj6valsartan OR sacubitril valsartan OR sacubitril-valsartan
8. exp dipeptidyl carboxypeptidase inhibitor/ OR exp Angiotensin-Converting Enzyme Inhibitors/
9. (angiotensin converting enzyme inhibitor OR ACEI OR ACEI OR antagonist$ OR inhibitor$ benazepril OR captopril OR enalapril OR fosinopril OR imidapril OR lisinopril OR moexipril OR perindopril OR quinapril OR ramipril OR trandolapril OR zofenopril OR alacepril OR cilazapril OR spirapril OR delapril).mp.
10. exp beta adrenergic receptor blocking agent/ OR exp Adrenergic beta-Antagonists/
11. (beta blocker$ OR BB OR acebutolol OR atenolol OR betaxolol OR bisoprolol OR carvedilol OR labetalol OR metoprolol OR nadolol OR nebivolol OR penbutolol OR pindolol OR propranolol OR sotalol OR timolol).mp.
12. exp aldosterone antagonist/
13. (aldosterone antagonist$ OR mineralocorticoid-receptor antagonist OR MRA OR eplerenone OR spironolactone).mp.
14. exp angiotensin receptor antagonist/
15. (angiotensin receptor blocker$ OR angiotensin receptor antagonist$ OR ARB OR azilsartan OR candesartan OR eprosartan OR irbesartan OR losartan OR olmesartan OR telmisartan OR valsartan).mp.

16. sodium-glucose co-transporter 2 OR SGLT2 OR SGLT2 inhibitor* OR sodium glucose adj6 inhibitor* OR (SGLT2 inhibitor*) OR sodium-glucose adj6 inhibitor* OR Sodium-Glucose Transporter 2 OR sodium glucose-cotransporter 2 OR sodium-glucose co-transporter$ OR sodium glucose-cotransporter$
17. (dapagliflozin OR empagliflozin).mp.
18 exp ivabradine plus metoprolol/ or exp ivabradine/ or exp carvedilol plus ivabradine/
19 (Omecamtiv mecarbil OR CK-1827452 OR Omecamtiv OR mecarbil)
20 (Vericiguat OR guanylate cyclase stimulator OR guanylate cyclase stimulator)
21. (Hydralazine-Isosorbide Dinitrate OR Hydralazine-Isosorbide adj6 Dinitrate OR Hydralazine Isosorbide Dinitrate OR Hydralazine adj6 Isosorbide adj6 Dinitrate)
22. OR/6-21
23. "randomized controlled trial".pt.
24. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
25. (retraction of publication or retracted publication).pt.
26. OR/23-25
27. "Quality of Life"/
28. (kansas city cardiomyopathy questionnaire or kccq)
29. ("minnesota living with heart failure questionnaire" or mlhfq)
30. ("quality of life" or qol or hrqol)
31. OR/27-30
32. 22 AND 31
33. (animals not humans).sh.
34. ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.
35. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.
36. 33 OR 34 OR 35
37. 26 NOT 36
38. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
39. RETRACTED ARTICLE/
40. OR/38-39
41. (animal$ not human$).sh,hw.
42. (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/
43. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/
44. OR/41-43
45. 40 NOT 44
46. 37 OR 45
47. 5 AND 32 AND 46
48. limit 47 to (human and yr="2020-Current" and (adult <18 to 64 years> or aged <65+ years>))

MEDLINE(R)/EMBASE search
Date of search: Feb 20 2024

1. exp Heart Failure/
2. Cardiomyopathy, Dilated/
3. (heart failure or cardiac failure or cardiac insufficiency or cardiomyopath$).tw.
4. ((cardi$ or myocard$) adj2 (failure$ or insufficien$)).tw.
5. OR/1-4
6. exp angiotensin receptor-neprilysin inhibitor/ OR ARNI
7. LCZ696 OR LCZ 696 OR LCZ-696 OR valsartan adj6 sacubitril OR valsartan adj6 sacubitril OR valsartan sacubitril OR valsartan-sacubitril OR sacubitril adj6valsartan OR sacubitril valsartan OR sacubitril-valsartan
8. exp dipeptidyl carboxypeptidase inhibitor/ OR exp Angiotensin-Converting Enzyme Inhibitors/
9. (angiotensin converting enzyme inhibitor OR ACEI OR ACEI OR antagonist$ OR inhibitor$ benazepril OR captopril OR enalapril OR fosinopril OR imidapril OR lisinopril OR moexipril OR perindopril OR quinapril OR ramipril OR trandolapril OR zofenopril OR alacepril OR cilazapril OR spirapril OR delapril).mp.
10. exp beta adrenergic receptor blocking agent/ OR exp Adrenergic beta-Antagonists/
11. (beta blocker$ OR BB OR acebutolol OR atenolol OR betaxolol OR bisoprolol OR carvedilol OR labetalol OR metoprolol OR nadolol OR nebivolol OR penbutolol OR pindolol OR propranolol OR sotalol OR timolol).mp.
12. exp aldosterone antagonist/
13. (aldosterone antagonist$ OR mineralocorticoid-receptor antagonist OR MRA OR eplerenone OR spironolactone).mp.
14. exp angiotensin receptor antagonist/
15. (angiotensin receptor blocker$ OR angiotensin receptor antagonist$ OR ARB OR azilsartan OR candesartan OR eprosartan OR irbesartan OR losartan OR olmesartan OR telmisartan OR valsartan).mp.
16. sodium-glucose co-transporter 2 OR SGLT2 OR SGLT2 inhibitor* OR sodium glucose adj6 inhibitor* OR (SGLT2 inhibitor*) OR sodium-glucose adj6 inhibitor* OR Sodium-Glucose Transporter 2 OR sodium glucose-cotransporter 2 OR sodium-glucose co-transporter$ OR sodium glucose-cotransporter$
17. (dapagliflozin OR empagliflozin).mp.
18 exp ivabradine plus metoprolol/ or exp ivabradine/ or exp carvedilol plus ivabradine/
19 (Omecamtiv mecarbil OR CK-1827452 OR Omecamtiv OR mecarbil)
20 (Vericiguat OR guanylate cyclase stimulator OR guanylate cyclase stimulator)
21. (Hydralazine-Isosorbide Dinitrate OR Hydralazine-Isosorbide adj6 Dinitrate OR Hydralazine Isosorbide Dinitrate OR Hydralazine adj6 Isosorbide adj6 Dinitrate)
22. OR/6-21
23. "randomized controlled trial".pt.
24. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
25. (retraction of publication or retracted publication).pt.
26. OR/23-25
27. "Quality of Life"/
28. (kansas city cardiomyopathy questionnaire or kccq)

29. ("minnesota living with heart failure questionnaire" or mlhfq)
30. ("quality of life" or qol or hrqol)
31. OR/27-30
32. 22 AND 31
33. (animals not humans).sh.
34. ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.
35. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.
36. 33 OR 34 OR 35
37. 26 NOT 36
38. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
39. RETRACTED ARTICLE/
40. OR/38-39
41. (animal$ not human$).sh,hw.
42. (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/
43. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/
44. OR/41-43
45. 40 NOT 44
46. 37 OR 45
47. 5 AND 32 AND 46
48. limit 47 to (human and yr="2023-Current" and (adult <18 to 64 years> or aged <65+ years>))

Cochrane Clinical Trial search

Date of search: Feb 28 2023

#1 MeSH descriptor: [Heart Failure] explode all trees
#2 MeSH descriptor: [Cardiomyopathy, Dilated] explode all trees
#3 (heart failure or cardiac failure or cardiac insufficiency or cardiomyopath$):ti,ab,kw (Word variations have been searched)
#4 #1 or #2 or #3
#5 (LCZ696 or LCZ 696 or LCZ-696 or valsartan adj6 sacubitril or valsartan adj6 sacubitril or valsartan sacubitril or valsartan-sacubitril or sacubitril adj6valsartan or sacubitril valsartan or sacubitril-valsartan):ti,ab,kw
#6 MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees
#7 (angiotensin converting enzyme inhibitor or ACEI or ACEI or antagonist$ or inhibitor$ benazepril or captopril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril or zofenopril or alacepril or cilazapril or spirapril or delapril):ti,ab,kw (Word variations have been searched)
#8 MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees

#9 (beta blocker$ or BB or acebutolol or atenolol or betaxolol or bisoprolol or carvedilol or labetalol or metoprolol or nadolol or nebivolol or penbutolol or pindolol or propranolol or sotalol or timolol):ti,ab,kw (Word variations have been searched)
#10 MeSH descriptor: [Mineralocorticoid Receptor Antagonists] explode all trees
#11 (aldosterone antagonist$ or mineralocorticoid-receptor antagonist or MRA or eplerenone or spironolactone):ti,ab,kw (Word variations have been searched)
#12 MeSH descriptor: [Angiotensin Receptor Antagonists] explode all trees
#13 (angiotensin receptor blocker$ or angiotensin receptor antagonist$ or ARB or azilsartan or candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or valsartan):ti,ab,kw (Word variations have been searched)
#14 MeSH descriptor: [Sodium-Glucose Transporter 2 Inhibitors] explode all trees
#15 (sodium-glucose co-transporter 2 or SGLT2 or SGLT2 inhibitor* or sodium glucose adj6 inhibitor* OR (SGLT2 inhibitor*) or sodium-glucose adj6 inhibitor* or Sodium-Glucose Transporter 2 or sodium glucose-cotransporter 2 or sodium-glucose co-transporter$ or sodium glucose-cotransporter$):ti,ab,kw (Word variations have been searched)
#16 (dapagliflozin or empagliflozin):ti,ab,kw
#17 MeSH descriptor: [Ivabradine] explode all trees
#18 (ivabradine plus metoprolol or ivabradine or exp carvedilol plus ivabradine):ti,ab,kw
#19 (Omecamtiv mecarbil or CK-1827452 or Omecamtiv or mecarbil):ti,ab,kw
#20 (Vericiguat OR guanylate cyclase stimulator OR guanylate cyclase stimulator):ti,ab,kw
#21 (Hydralazine-Isosorbide Dinitrate OR Hydralazine-Isosorbide adj6 Dinitrate OR Hydralazine Isosorbide Dinitrate OR Hydralazine adj6 Isosorbide adj6 Dinitrate):ti,ab,kw
#22 MeSH descriptor: [Quality of Life] explode all trees
#23 (kansas city cardiomyopathy questionnaire or kccq):ti,ab,kw
#24 ("minnesota living with heart failure questionnaire" or mlhfq):ti,ab,kw
#25 ("quality of life" or qol or hrqol):ti,ab,kw
#26 #22 or #25 or # 23 or #24
#27 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
#28 #4 and #26 and #27
#29 human not animal
#30 #28 and #29
#31 #30 in trials
#32 #31 (limit from 2020)

Cochrane Clinical Trial search

Date of search: Feb 20 2024
#1 MeSH descriptor: [Heart Failure] explode all trees
#2 MeSH descriptor: [Cardiomyopathy, Dilated] explode all trees
#3 (heart failure or cardiac failure or cardiac insufficiency or cardiomyopath$):ti,ab,kw (Word variations have been searched)
#4 #1 or #2 or #3

#5 (LCZ696 or LCZ 696 or LCZ-696 or valsartan adj6 sacubitril or valsartan adj6 sacubitril or valsartan sacubitril or valsartan-sacubitril or sacubitril adj6valsartan or sacubitril valsartan or sacubitril-valsartan):ti,ab,kw
#6 MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees
#7 (angiotensin converting enzyme inhibitor or ACEI or ACEI or antagonist$ or inhibitor$ benazepril or captopril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril or zofenopril or alacepril or cilazapril or spirapril or delapril):ti,ab,kw (Word variations have been searched)
#8 MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
#9 (beta blocker$ or BB or acebutolol or atenolol or betaxolol or bisoprolol or carvedilol or labetalol or metoprolol or nadolol or nebivolol or penbutolol or pindolol or propranolol or sotalol or timolol):ti,ab,kw (Word variations have been searched)
#10 MeSH descriptor: [Mineralocorticoid Receptor Antagonists] explode all trees
#11 (aldosterone antagonist$ or mineralocorticoid-receptor antagonist or MRA or eplerenone or spironolactone):ti,ab,kw (Word variations have been searched)
#12 MeSH descriptor: [Angiotensin Receptor Antagonists] explode all trees
#13 (angiotensin receptor blocker$ or angiotensin receptor antagonist$ or ARB or azilsartan or candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or valsartan):ti,ab,kw (Word variations have been searched)
#14 MeSH descriptor: [Sodium-Glucose Transporter 2 Inhibitors] explode all trees
#15 (sodium-glucose co-transporter 2 or SGLT2 or SGLT2 inhibitor* or sodium glucose adj6 inhibitor* OR (SGLT2 inhibitor*) or sodium-glucose adj6 inhibitor* or Sodium-Glucose Transporter 2 or sodium glucose-cotransporter 2 or sodium-glucose co-transporter$ or sodium glucose-cotransporter$):ti,ab,kw (Word variations have been searched)
#16 (dapagliflozin or empagliflozin):ti,ab,kw
#17 MeSH descriptor: [Ivabradine] explode all trees
#18 (ivabradine plus metoprolol or ivabradine or exp carvedilol plus ivabradine):ti,ab,kw
#19 (Omecamtiv mecarbil or CK-1827452 or Omecamtiv or mecarbil):ti,ab,kw
#20 (Vericiguat OR guanylate cyclase stimulator OR guanylate cyclase stimulator):ti,ab,kw
#21 (Hydralazine-Isosorbide Dinitrate OR Hydralazine-Isosorbide adj6 Dinitrate OR Hydralazine Isosorbide Dinitrate OR Hydralazine adj6 Isosorbide adj6 Dinitrate):ti,ab,kw
#22 MeSH descriptor: [Quality of Life] explode all trees
#23 (Kansas City Cardiomyopathy Questionnaire or kccq):ti,ab,kw
#24 ("minnesota living with heart failure questionnaire" or mlhfq):ti,ab,kw
#25 ("quality of life" or qol or hrqol):ti,ab,kw
#26 #22 or #25 or # 23 or #24
#27 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
#28 #4 and #26 and #27
#29 human not animal
#30 #28 and #29
#31 #30 in trials
#32 #31 (limit from 2023)

Chapter 4 - Summary, Conclusion, and Recommendations

4.1 OVERVIEW OF RESEARCH

In a set of two experiments we evaluated the impact of serum magnesium levels and IV magnesium supplementation on patient outcomes in acute heart failure and established the effect size of modern treatment combinations on quality of life and important limitations that will inform the design and interpretation of a future analysis of IV magnesium supplementation. Our first experiment evaluated the patterns and frequency of serum magnesium testing and IV magnesium supplementation through a retrospective cohort study design. Through this experiment we also evaluated the association between patient outcomes and IV magnesium and hypomagnesemia. Our study involved the collection and analysis of data from 42,763 patients and 78,957 patient episodes of ED visit or hospitalization over the course of 8 years from 2012 until 2020. We used a combination of descriptive statistics, multivariable binary logistic regression models, and time varying multivariable cox regression with overlap weighting to explore the data. Concurrently, in our second experiment we evaluated the impact of different HFrEF pharmacological treatment classes on quality of life both separately and in combination to determine the effect size of accepted HF treatments on quality of life. In this study we built a network meta analysis based on a frequentist model which included 40 studies that used the KCCQ or MLHFQ scores, but 5 studies were not analyzed due to insufficient data. We built an additive network in addition to the standard model and explored both random and variable effects in both. We also explored the sensitivity of the results of the conversion of MLHFQ scores to KCCQ scores and evaluated the results for bias.

4.2 SUMMARY OF RESULTS:

4.2.1 Study 1

Our analysis found that serum magnesium testing, hypomagnesemia and IV magnesium administration occurred frequently. Serum magnesium testing occurred in 58.7% of episodes and it was more common in tertiary hospitals, patients who were admitted to the

hospital rather than discharged, patients with higher natriuretic peptide levels, and patients with longer stays. Serum magnesium testing did not occur more frequently in patients with lower or higher potassium levels. The testing established that 31.7% of all patient episodes were hypomagnesemic. These patients were more likely to be hospitalized rather than discharged from the ER compared to patients who were not hypomagnesemic, they were also more likely to have a longer stay than patients who were not hypomagnesemic. We also found that with every 0.02 mmol/L unit decrease in serum magnesium level from 0.7 mmol/L and every 0.02 mmol/L unit increase in serum magnesium level from 0.86 mmol/L the risk of mortality at 2 years from the event increased significantly.

IV magnesium was given in 13.7% of all patient episodes and in the episodes in which it was given 70.2% of the patients had hypomagnesemia. Patients who visited a tertiary hospital, patients who were admitted instead of being discharged from the ER, patients with certain comorbidities and patients with hypomagnesemia were more likely to receive IV magnesium. After overlap weighting, IV magnesium was associated with higher risk of mortality at 7 until 30 days, but not any time points afterwards. Patients with normal magnesium levels had the highest risk of mortality after receiving IV magnesium. Patients with serum magnesium levels below (0.6 mmol/L) and patients with hypermagnesemia (0.95 mmol/L) who received IV magnesium did not have an increased risk of mortality compared with patients who did not receive IV magnesium at 7-30 days. Patients who received IV magnesium had a higher likelihood of any cause hospitalization at 7 days and lower likelihood of any cause ED visits at 7 days after overlapping weighting, but not at any other time point. IV magnesium was not associated with an increase in the likelihood of either falsification endpoint.

4.2.2: Study 2

Our network meta analysis included 40,832 patients across 40 clinical trials with a median follow up time of 5.5 months. All of the included studies were placebo controlled and double blinded, while the vast majority were also multi-center trials. We were only

able to analyze the effect of the various pharmacological treatment classes on the KCCQ overall summary score. Our study results showed that the individual therapies which lead to the greatest improvement in quality of life were SGLT2i, then Ivabradine, then ARNi. BB, ACEi, vericiguat and ARB had a neutral impact on quality of life and Digoxin significantly reduced quality of life. Only 1 trial evaluated H-ISDN so its impact on quality of life should be interpreted cautiously. A combination of ARNi + BB + SGLT2i was the most effective at improving quality of life. ARNi + BB + MRA + SGLT2i were shown to increase quality of life most, but their impact was not significant and this combination was followed by a combination of ACEi + BB + MRA + SGLT2i, then ACEi + BB + MRA + Ivabradine, and then ARNi + BB + MRA. Other combinations of ACEi/ARB/ARNi with BB and MRA generally had a neutral impact on quality of life and most combinations involving digoxin had a negative impact on quality of life even when paired with ACEi/ARB or BB. As the reported MD of the study translated directly to change in the KCCQ OSS score the effect size of the most effective treatment was determined to be 5.33 units of change on the KCCQ OSS scale and other effective treatments had effect sizes ranging from 3.01-7.11 units of change. The results had high variability and as a result the importance of supplementing the mean change in QoL score with data on the proportions of patients who experienced small, medium and large changes in quality of life was revealed. Further, the significance of using a methodology which did not inappropriately penalize a treatment group for mortality was shown as digoxin, which was known to reduce hospitalization risk and worsening heart failure risk, yielded a negative impact on quality life; this was likely due to a combination of the toxicity and adverse effects of digoxin with penalization due to the lack of improvement in mortality risk compared to placebo. These results were found to have high strength of evidence based on the GRADE criteria measured through the CINeMA framework. Additionally, sensitivity analyses showed that the inclusion of studies with major concerns for bias did not impact the outcome and that the results were not sensitive to the conversion of the MLHFQ scores to the KCCQ scale.

4.3 CONCLUSION:

The treatments used to improve the outcomes of patients with HF vary significantly in their physiological mechanisms and their efficacy. Often these treatments are combined to attempt to gain the largest benefit possible and occasionally treatments which are not sufficiently understood become a regular part of the treatment regimen. IV magnesium administration and serum magnesium testing have largely followed this pattern because while there is no evidence that their use improves the outcomes of patients with acute HF their use in thousands of patient hospitalization episodes suggests that they are a routine part of care. Our experiments have shown that hypomagnesemia may be associated with worse long term outcomes for patients with acute heart failure, but it is not clear if this is related to the physiological impact of magnesium in the cardiovascular system or if this is because hypomagnesemia is associated with another factor such as a low magnesium diet which is also associated with poor outcomes. A prospective study which can accurately evaluate and adjust factors like diet is necessary to determine if hypomagnesemia truly causes an increased risk of mortality.

Further, this study revealed that IV magnesium may follow a few patterns of administration: it may be administered to reduce the likelihood and severity of arrhythmias or it may be used to replace serum magnesium in hypomagnesemia. However it does not seem to reduce mortality in either case and in fact seems to be associated with a greater risk of short term mortality particularly when it may be used as to reduce the risk of arrhythmias as the risk associated with IV magnesium administration was seemingly highest for individuals with normal magnesium levels and much lower for individuals with low or high magnesium levels. This pattern also suggests that the physiological mechanism of IV magnesium sulfate which results in increased mortality may not be dose dependent as in the case of a dose dependent relationship it would be expected that the increased risk of mortality following magnesium administration would be highest in the patients with a high serum magnesium concentration. The difference in response compared to individuals with low and high magnesium who had a lower risk of mortality, but not a neutral relationship, may also suggest that IV magnesium is not being

used in the correct patient subgroups or that IV magnesium administration is associated with another factor like health condition severity which is itself associated with worse patient outcomes. In either case further research is required. IV magnesium was also associated with an increased risk of any cause hospitalizations at 7 days and a decrease in risk of any cause ED visits. It is not clear what relationship IV magnesium has with hospitalization or ED visits.

Whether IV magnesium has any significant positive impact on patient quality of life during and following an AHF episode which could justify its continued and frequent use is unknown. In order to further evaluate the IV magnesium therapy in acute heart failure through an RCT we would need to know what the expected effect of such a therapy is and through our network meta-analysis we were able to determine that a reasonable effect size estimate is somewhere between 3-7. Our findings also showed that an RCT to evaluate the effect of IV magnesium should consider measuring the change in quality of life both through a measurement of mean change of quality of life score and a measurement of the proportion of patients undergoing a small, medium and large clinical change both towards improvement and deterioration. Additionally, a future study should cautiously select the methodology used to analyze missing scores due to death as this may obscure the direct quality of life benefit provided by IV magnesium.

4.4 RECOMMENDATIONS FOR FUTURE RESEARCH:

- The effect of IV magnesium on subgroups of patients with various serum magnesium levels: to determine where IV magnesium is most effective and to determine where it is most detrimental, a study to evaluate the effect of IV magnesium in various subgroups of patients with AHF is necessary.
- The association between IV magnesium outcomes and markers of heart failure severity and progression: to more fully understand the impact of IV magnesium administration in heart failure it would be necessary to evaluate the association between the administration of IV magnesium and heart failure severity markers.

This would allow for a better understanding of the physiological impact of magnesium infusion on potential short term damage which may occur in the cardiovascular system during AHF.

- An RCT to examine the effect of IV magnesium on quality of life: to determine whether or not IV magnesium should have a role in AHF therapy due to a positive impact on quality of life we would need to conduct an RCT. Currently, it would not be possible to evaluate quality of life through a retrospective study design as quality of life information is not accessible in current health databases.
- An RCT to examine the effect of IV magnesium in AHF: while our study provides strong evidence that IV magnesium is harmful in AHF an RCT would allow us to isolate the relationship between IV magnesium and patient outcomes in AHF which would give stronger and more reliable results, particularly if further research replicates the results of our study.
- Oral magnesium supplementation for patients at high risk of AHF: efforts to evaluate the efficacy of oral magnesium supplementation have been focused largely on chronic heart failure and have not sufficiently explored the effect of oral magnesium supplementation on patient outcomes. Thus, more research is necessary to evaluate the impact of oral magnesium supplementation on patient outcomes in AHF.

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