Comparative Efficacy and Safety of Novel Therapeutic Drugs for Chronic Heart Failure: A Systematic Review and Network Meta-Analysis

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Research Article

Keywords: chronic heart failure, SGLT2, cardiovascular mortality, NTDs

Posted Date: October 25th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-962831/v1

Abstract

Recently, several novel therapeutic drugs (NTDs) were found to have therapeutic potential in treating chronic heart failure (CHF). This network meta-analysis aimed to compare and rank different NTDs in patients with CHF. We searched Medline/PubMed, Embase and Cochrane Library of Clinical Trials database through February 9, 2021, for RCTs comparing the NTDs with standard of care (SOC) in adult patients with CHF. Trials of angiotensin receptor-neprilysin inhibitor (ARNI), sodium-glucose transporter 2 (SGLT2) inhibitors, ivabradine, non-steroidal mineralcorticoid receptor antagonists (MRA), soluble guanylate cyclase (SGC) stimulators and cardiac myosin activators (CMA) were included. We performed a Bayesian network meta-analysis to indirectly compare the mortality, HF hospitalization and adverse events of the NTDs. Thirty-three studies enrolling 63614 patients were included in this analysis. The results showed none of the NTDs was associated with a significant superiority in reducing all-cause mortality, composite outcome of cardiovascular mortality or HF hospitalization and HF hospitalization alone. For cardiovascular mortality alone, ARNI was superior to ivabradine and CMA, while SGLT2 inhibitors were superior to CMA. For adverse events, SGLT2 inhibitors were associated with a lower risk of serious adverse events than ivabradine and CMA. ARNI and SGLT2 inhibitors were recommended as better choices in reducing CV mortality, while SGLT2 inhibitors performed better regarding serious adverse event.

Introduction

Heart failure (HF) remains a major cause of mortality and hospitalizations worldwide, affecting more than 30 million individuals globally[1]. Chronic heart failure (CHF) refers to a worsening and persistent stable state of HF, and is the most common form of HF leading to hospital admission, portending a poorer prognosis[2]. Over the past 3 decades, stepwise advancements have been made in pharmacological treatments for patients with CHF[3]. Current clinical guidelines recommend the combination of angiotensin converting enzyme inhibitors/angiotensin-receptor antagonists (ACEI/ARB), β-receptor blocker and mineralcorticoid receptor antagonist (MRA) as the cornerstone of pharmacological treatment for CHF[2]. Although the recommended treatments have been proven to improve the prognosis of CHF, the excess mortality and hospitalization rates still remain a pressing challenge[4,5].

Several new therapeutic drug classes have emerged within the recent decade that are expected to offer more effective treatments for heart failure[6–9]. The most representative drugs are sacubitril/valsartan and ivabradine. As a first-in-class angiotensin receptor-neprilysin inhibitor (ARNI), sacubitril/valsartan has been demonstrated to be superior than enalapril in improving clinical outcomes for heart failure in the PARADIGM-HF trial and the PARAGON-HF trial[10,11]. Ivabradine, a sinoatrial node modulator, has shown to increase survival of patients with stable chronic heart failure[12]. They were both recommended as new treatment options for patients with heart failure in the 2016 American College of Cardiology/American Heart Association (ACC/AHA) guidelines[13]. Additionally, trials have shown clinical superiority of sodium-glucose transporter 2 (SGLT2) inhibitors and vericiguat, a soluble guanylate cyclase (SGC) stimulator, when each was investigated against placebo in addition to standard-of-care (SOC) inclusive of renin-angiotensin-system inhibitors, β blockers, and MRAs[14]. Similar findings were recently reported for Omecamtiv mecarbil, the selective cardiac myosin activator (CMA)[15]. Furthermore, the novel non-steroidal MRA has demonstrated a better protective effect on cardiorenal function over eplerenone, and has entered the clinical development recently[16]. All these drugs have a possibility to enter therapeutic algorithms of heart failure in the future.

The NTDs exert benefits for heart failure to different extent according to the specific outcomes, leading to clinical uncertainty about the optimal treatment and the potential risks. A comprehensive understanding of the efficacy and safety profile of NTDs is now needed. However, there are no trials directly comparing the efficacy of these drug classes. When no head-to-head trial exists, network meta-analysis (NMA) provides an opportunity to indirectly compare the therapeutic benefits of multiple interventions based on a common comparator[17].

The purpose of this network meta-analysis was to compare the relative efficacy of ARNI, SGLT2 inhibitors, ivabradine, non-steroidal MRA, SGC stimulators, and CMA in reducing mortality and hospitalization outcomes in patients with heart failure and their relative safety profiles.

Methods

This systematic review and network meta-analysis has been conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement and the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses (PRISMA-NMA)[18,19], the details are provided in supplementary material (see Supplementary Table S1 online). The study protocol is available in the PROSPERO register (https://www.crd.york.ac.uk/prospero/; registration number: CRD42021235971).

Literature Search

A systematic literature search of Medline/PubMed, Embase, and Cochrane Library of Clinical Trials database was conducted to identify studies published up to February 9, 2021. The search strategies of each database are detailed in supplementary material (see Supplementary Table S2 online). The reference lists of included studies were reviewed to identify additional studies. Recent systematic reviews, meta-analysis, guidelines and conference proceedings were manually retrieved and reviewed for any trials that may be neglected.

Study Selection

Two authors (Honghui Wu and Yalu Wen) independently screened studies for titles and abstracts. Further review of the full text was performed once necessary. Randomized controlled trials (RCTs) were considered eligible if they compared ARNI, SGLT2 inhibitors, ivabradine, non-steroidal MRA, SGC stimulators, or CMA with one another or with other drug classes of SOC, or placebo in adult patients with CHF. All studies had to provide at least 1 of the pre-specified primary, secondary, and safety outcomes. Studies were excluded if they were secondary analyses of RCTs, had no available trial register identifier, or had a follow-up of less than 4 weeks.

Outcomes

The pre-specified primary outcomes included all-cause mortality, composite outcome of cardiovascular (CV) mortality and HF hospitalization, the secondary outcomes included CV mortality, HF hospitalization, the safety outcomes were any adverse event, any serious adverse event and discontinuation due to adverse events.

Data Extraction

Two authors (Honghui Wu and Yalu Wen) independently extracted the numeric data of interest from eligible studies using a pre-established Microsoft Excel sheet. The extracted data included the study design, trial identifier, baseline patient characteristics (ie. Patient sample size, NYHA class, medication history, et al.), study drugs and doses, comparators, mean or median duration of follow up, and predefined outcomes. Finally, we further reviewed the available trial reports from ClinicalTrials.gov and extracted additional clinical events whenever necessary.

Risk of Bias Assessment

Two authors (Honghui Wu and Yalu Wen) assessed the risk of bias on 6 domains for individual studies, including selection bias (i.e. whether the random sequence generation and allocation sequence concealment were performed), performance bias (i.e. whether the blinding methods were used for participants and implementers), detection bias (i.e. whether the blinding methods were used for outcome evaluation), attrition bias (i.e. whether the complete outcome data were obtained), reporting bias(i.e. whether the results were reported selectively) and other bias. The Cochrane Collaboration risk of bias tool was used to conduct above assessment, the results for each domains were classified as low bias risk, moderate bias risk, high bias risk or unclear. The publication bias was assessed by Egger's test and was checked with the funnel plot[20].

Network Meta-Analysis

Network meta-analysis provided a method allowing indirect comparisons between multiple treatment to be made when there was few direct comparison evidence. Indirect treatment comparisons were achievable when one or more common comparators existed, with the assumption that the heterogeneity between studies was low.

We performed a Bayesian network meta-analysis using the gemtc package (version 0.8.8) on R software (version 4.0.4) to calculate the relative indirect comparative effects between the NTDs[21]. In a Bayesian framework, data extracted from eligible RCTs were converted as logarithm of hazard ratio (log[HR]) to be used to infer the posterior probability distribution based on the predefined prior probability distribution. For studies that did not report hazard ratio, the number of events and length of follow-up (in person-years) for each group were synthesized to estimate HRs using the poisson likelihood and log link[22]. The inference was performed by Monte Carlo Markov-chain (MCMC) methods, using 4 chains to simulate, including total 50,000 iterations. Subsequently, the Brooks-Gelman-Rubin trace plot were checked visually to confirm the convergence. We compared the goodness of fit of fixed-effects and random-effects models using the deviance information criterion (DIC) value, and then the models with smaller DIC value were selected (see Supplementary Table S6 online)[23]. Outputs were presented as hazard ratios (HRs) with 95% credible intervals (CrIs). We evaluated the transitivity assumption by checking the baseline patient characteristics similarity of various studies. We assessed the heterogeneity assumption by calculating the I^2 statistics, the I^2 value indicated the heterogeneity level between studies[24]. Consistence assumption could not be assessed because of no trial direct compare NTDs with each other was retrieved. For each outcomes, we presented the the rank probabilities of all treatments in a line chart, the values of surface under the cumulative ranking curves (SUCRA) were also calculated, which ranged from 0% (ranking worst) to 100% (ranking best).

Results

The process of literature search and screening is provided in Fig. 1. In total, 7553 records were identified from electronic databases, among which 2180 records were duplicated and were thereafter discarded. After screening the titles and abstracts, 608 articles remained for further full-text screening. Finally, 33 studies which compared ARNI (8 studies), SGLT2 inhibitors (10 studies), Ivabradine (4 studies), non-steroidal MRA (3 studies), SGCs (6 studies) or CMAs (2 studies) versus the SOC were considered eligible for the meta-analysis[10–12, 15,25–52] (Table 1). Each study included between 56 to 10917 patients with a mean follow-up duration ranging from 30 days to 35 months. More detailed basic characteristics of the included 33 studies were shown in supplementary material (see Supplementary Table S2 and Table S3 online).

Table 1
Main baseline characteristics of patients in included studies.

Drug type	Number of studies	Enrolled participants	Mean age (years)	Female (%)	Mean LVEF (%)	Diabetes (%)
ARNI vs SOC	8	17403	67.1	35.1	39.7	37.5
SGLT2i vs SOC	10	11021	67.0	25.5	30.9	52.1
Ivabradine vs SOC	4	17837	63.4	39.2	31.3	34.8
Non-steroidal MRA vs SOC	3	1519	71.5	22.3	29.1	56.1
SGC stimulator vs SOC	6	7154	68.2	28.2	34.6	46.9
CMA vs SOC	2	8680	64.4	21.0	26.7	40.3

Abbreviations: *ARNI*, angiotensin receptor-neprilysin inhibitors; *SGLT2i*, sodium-glucose transporter 2 inhibitors; *MRA*, mineralcorticoid receptor antagonists; *SGCs*, soluble guanylate cyclase; *CMA*, cardiac myosin activators; SOC, standard of care; LVEF, left ventricular ejection fraction.

The network plot of all included studies is shown in Fig. 2. Nodes of the network represent treatments, and the sizes of the nodes are in proportion with the number of participants in each treatment. The thickness of connecting lines corresponds to the number of studies directly comparing the treatments. The network has a radial structure centralizing on the node of SOC with no closed loops, indicates that no direct comparison between NTDs is available.

Risk of Bias and Publication Bias

Most of the trials demonstrated a low risk of bias or an unclear risk of bias in all domains evaluated (see Supplementary Table S5 online), while 4 trials investigating ivabradine were considered to have a high risk of additional other bias. The funnel plots showed a basically inverted shape and exhibited a symmetrical distribution for all outcomes, suggesting absence of publication bias (see Supplementary Fig.S2 online).

Primary outcomes

All-cause mortality Because of the data on all-cause mortality were not available in all non-steroidal MRA related trials, a network meta-analysis was finally conducted among the other 6 treatments. Compared with SOC, all the available treatments tended to reduce the all-cause mortality of patients. ARNI (HR 0.90, 95%CI 0.82 to 0.97) and SGLT2 inhibitors (HR 0.88, 95%CI 0.79 to 0.98) were the most efficacious treatment in terms of reducing all-cause mortality. Intuitively, SGLT2 inhibitors seemed to be superior to other NDTs in reducing all-cause mortality, but there was no significant differences be found in the NMA-based indirect comparison results (Table 2).

Table 2
Results of network meta-analysis for all-cause mortality and a composite of CV death or HF hospitalization

Outcome	Comparator/Intervention	SOC	ARNI	SGLT2i	Ivabradine	Non-steroidal MRA	SGC stimulators	CMA
All-cause mortality	**SOC**	1	1.12 (1.03,1.21)	1.14 (1.02,1.27)	1.02 (0.94,1.11)	NA	1.02 (0.91,1.15)	1.00 (0.92,1.09)
	ARNI	0.9 (0.82,0.97)	1	1.02 (0.89,1.17)	0.91 (0.81,1.03)	NA	0.91 (0.79,1.05)	0.90 (0.8,1.01)
	SGLT2i	0.88 (0.79,0.98)	0.98 (0.85,1.12)	1	0.90 (0.78,1.03)	NA	0.89 (0.76,1.05)	0.88 (0.76,1.01)
	Ivabradine	0.98 (0.9,1.07)	1.09 (0.97,1.23)	1.12 (0.97,1.28)	1	NA	1 (0.86,1.15)	0.98 (0.87,1.1)
	Non-steroidal MRA	NA	NA	NA	NA	1	NA	NA
	SGCs	0.98 (0.87,1.11)	1.10 (0.95,1.27)	1.12 (0.95,1.32)	1.00 (0.87,1.16)	NA	1	0.98 (0.85,1.14)
	CMA	1 (0.92,1.09)	1.12 (0.99,1.26)	1.14 (0.99,1.31)	1.02 (0.91,1.15)	NA	1.02 (0.88,1.18)	1
CV death or HF hospitalization	**SOC**	1	1.18 (0.99,1.42)	1.34 (1.14,1.57)	1.09 (0.93,1.31)	NA	1.11 (0.92,1.43)	1.06 (0.82,1.36)
	ARNI	0.85 (0.7,1.01)	1	1.13 (0.89,1.44)	0.92 (0.73,1.2)	NA	0.94 (0.72,1.28)	0.9 (0.65,1.22)
	SGLT2i	0.75 (0.64,0.88)	0.88 (0.7,1.13)	1	0.81 (0.65,1.05)	NA	0.83 (0.65,1.12)	0.79 (0.58,1.07)
	Ivabradine	0.92 (0.76,1.08)	1.09 (0.83,1.38)	1.23 (0.96,1.54)	1	NA	1.03 (0.78,1.37)	0.98 (0.7,1.3)
	Non-steroidal MRA	NA	NA	NA	NA	1	NA	NA
	SGC stimulator	0.9 (0.7,1.09)	1.06 (0.78,1.38)	1.2 (0.89,1.54)	0.98 (0.73,1.28)	NA	1	0.95 (0.66,1.29)
	CMA	0.95 (0.73,1.22)	1.12 (0.82,1.54)	1.26 (0.93,1.71)	1.03 (0.77,1.42)	NA	1.05 (0.78,1.51)	1

All outcomes reported in hazard ratio (HR) for intervention vs comparator (row relative to column), and 95% credible intervals (CrI). Abbreviations: CV, cardiovascular; HF, heart failure; *ARNI*, angiotensin receptor-neprilysin inhibitors; *SGLT2i*, sodium-glucose transporter 2 inhibitors; *MRA*, mineralcorticoid receptor antagonists; *SGC*, soluble guanylate cyclase; *CMA*, cardiac myosin activators; SOC, standard of care; LVEF, left ventricular ejection fraction.

CV mortality or HF Hospitalization As for the composite outcome of CV death or HF hospitalization, the non-steroidal MRA related trials were excluded once more for not reporting the relative outcome. All the other available treatments had the tendency to reduce the composite outcome when compared with SOC, but only SGLT2 inhibitors (HR 0.75, 95%CI 0.64 to 0.88) was associated with a significant reduction. Indirect comparisons of SGLT2 inhibitors with other NDTs showed no significant difference on the composite outcome (Table 2).

Secondary outcomes

CV mortality Both ARNI and SGLT2 inhibitors were associated with significant reductions in CV mortality when compared with SOC. It was worth noting that the ARNI not only had the best performance in decreasing the risk of CV mortality in direct comparisons, but also showed significant benefits over ivabradine (HR 0.85, 95%CI 0.74 to 0.97) and CMA (HR 0.84, 95%CI 0.73 to 0.96) in indirect comparisons. SGLT2 inhibitors were associated with reduced CV death events compared with CMA (HR 0.86, 95%CI 0.73 to 0.99). Non-steroidal MRA, it should be noted, showed the largest reduction in CV mortality both in direct and indirect comparison but of no statistical significance (Table 3).

Table 3
Results of network meta-analysis for CV mortality and HF hospitalization

Outcome	Comparator/Intervention	SOC	ARNI	SGLT 2i	Ivabradine	Non-steroidal MRA	SGC stimulators	CMA
CV mortality	**SOC**	1	1.19 (1.08,1.31)	1.16 (1.02,1.31)	1.01 (0.92,1.11)	1.43 (0.58,3.14)	1.04 (0.91,1.18)	0.99 (0.9,1.09)
	ARNI	0.84 (0.77,0.93)	1	0.97 (0.83,1.14)	0.85 (0.74,0.97)	1.2 (0.49,2.66)	0.88 (0.75,1.03)	0.84 (0.73,0.96)
	SGLT2i	0.87 (0.77,0.98)	1.03 (0.88,1.2)	1	0.87 (0.75,1.02)	1.23 (0.49,2.74)	0.9 (0.75,1.08)	0.86 (0.73,0.99)
	Ivabradine	0.99 (0.9,1.09)	1.18 (1.03,1.34)	1.15 (0.98,1.34)	1	1.41 (0.57,3.12)	1.03 (0.88,1.21)	0.98 (0.86,1.12)
	Non-steroidal MRA	0.7 (0.32,1.73)	0.83 (0.38,2.06)	0.81 (0.37,2.03)	0.71 (0.32,1.75)	1	0.73 (0.33,1.81)	0.7 (0.32,1.72)
	SGCs	0.96 (0.85,1.1)	1.14 (0.97,1.34)	1.11 (0.93,1.34)	0.97 (0.83,1.14)	1.37 (0.55,3.05)	1	0.95 (0.81,1.12)
	CMA	1.01 (0.92,1.11)	1.2 (1.05,1.37)	1.17 (1,1.37)	1.02 (0.89,1.17)	1.44 (0.58,3.18)	1.05 (0.89,1.24)	1
HF hospitalization	**SOC**	1	1.21 (1.03,1.51)	1.42 (1.18,1.68)	1.19 (1,1.49)	0.35 (0.01,2.34)	1.12 (0.91,1.47)	1.03 (0.78,1.37)
	ARNI	0.83 (0.66,0.97)	1	1.17 (0.86,1.47)	0.98 (0.75,1.28)	0.29 (0.01,1.93)	0.93 (0.68,1.26)	0.85 (0.58,1.17)
	SGLT2i	0.71 (0.6,0.85)	0.86 (0.68,1.16)	1	0.84 (0.66,1.14)	0.25 (0.01,1.68)	0.79 (0.61,1.12)	0.73 (0.53,1.03)
	Ivabradine	0.84 (0.67,0.99)	1.02 (0.78,1.34)	1.19 (0.88,1.51)	1	0.29 (0.01,1.98)	0.94 (0.7,1.29)	0.87 (0.59,1.2)
	Non-steroidal MRA	2.88 (0.43,100.19)	3.51 (0.52,122.01)	4.09 (0.6,141.28)	3.46 (0.51,120.61)	1	3.26 (0.48,112.33)	2.98 (0.43,103.56)
	SGC stimulator	0.89 (0.68,1.1)	1.08 (0.8,1.47)	1.26 (0.9,1.64)	1.06 (0.78,1.44)	0.31 (0.01,2.1)	1	0.92 (0.61,1.3)
	CMA	0.97 (0.73,1.29)	1.17 (0.86,1.71)	1.37 (0.97,1.91)	1.15 (0.84,1.69)	0.34 (0.01,2.31)	1.08 (0.77,1.63)	1

All outcomes reported in hazard ratio (HR) for intervention vs comparator (row relative to column), and 95% credible intervals (CrI). Abbreviations: CV, cardiovascular; HF, heart failure; *ARNI*, angiotensin receptor-neprilysin inhibitors; *SGLT2i*, sodium-glucose transporter 2 inhibitors; *MRA*, mineralcorticoid receptor antagonists; *SGC*, soluble guanylate cyclase; *CMA*, cardiac myosin activators; SOC, standard of care; LVEF, left ventricular ejection fraction.

HF hospitalization When compared with SOC, ARNI (HR 0.83, 95%CI 0.66 to 0.97), SGLT2 inhibitors (HR 0.71, 95%CI 0.6 to 0.85), ivabradine (HR 0.84, 95%CI 0.67 to 0.99) were associated with significant reduction in incidence of HF hospitalization. There were no significant differences among NDTs for HF hospitalization (Table 3).

Safety outcomes

None of the NTDs were associated with reduction in adverse events when compared with SOC or compared with each other (see Supplementary Table S7 online). With respect to serious adverse events, ARNI (HR 0.94, 95%CI 0.90 to 0.99) and SGLT2 inhibitors (HR 0.89, 95%CI 0.83 to 0.94) showed significantly reductions in the occurrence as compared to the SOC. In the NMA-based indirect comparisons, SGLT2 inhibitors exhibited a safer results than ivabradine (HR 0.92, 95%CI 0.85 to 0.99) and CMA (HR 0.84, 95%CI 0.91 to 0.99) in terms of the serious adverse events. Across NTDs, only ivabradine (HR1.14, 95%CI 1.0 to 1.3) showed a less acceptability than SOC, with a higher number of patients discontinued the trials due to adverse events. There was no significant difference in results of discontinuation due to adverse events in indirect comparisons among NTDs.

Treatment Ranking

Treatments with SGLT2 inhibitors got the highest SUCRA scores and were most likely to rank best for the primary outcomes and for HF hospitalization (88.5% for all-cause mortality, 94.2% for the composite outcome of CV death or HF hospitalization, and 93.5% for HF hospitalization), while ARNI ranked second best on the SUCRA scores for these outcomes (Table 4). For CV mortality, the ARNI was most likely to rank best (SUCRA score 81.8%), and non-steroidal MRA second best (SUCRA score 74.9%). For safety outcomes, SGLT2 inhibitors were most likely to rank best for serious adverse events (SUCRA score 92.3%), and non-steroidal MRA was most likely to rank best for adverse events (SUCRA score 90.2%) and discontinuation due to adverse events (SUCRA score 83.3%). Fig. 3 showed the ranking probabilities of treatments from best to worst on all outcomes.

Table 4
Network meta-analysis SUCRA scores for the cumulative ranking probabilities.

Outcomes	SOC	ARNI	SGLT2i	Ivabradine	Non-steroidal MRA	SGCs	CMA
All-cause mortality	24.1%	83.7%	88.5%	39.4%	NA	37.7%	26.6%
CV death or HF hospitalization	10.9%	67.7%	94.2%	42.7%	NA	50.4%	34.1%
CV death	25.1%	81.8%	74.5%	30.1%	74.9%	41.4%	22.2%
HF hospitalization	22.7%	69.5%	93.5%	65.4%	12.7%	52.0%	34.2%
AE	49.4%	31.6%	66.4%	25.6%	90.2%	50.3%	36.6%
SAE	12.4%	60.9%	92.3%	43.4%	48.5%	57.1%	35.4%
Discontinue due to AE	50.7%	71.2%	55.1%	13.3%	83.3%	12.3%	64.1%

Abbreviations: SUCRA, Surface under the cumulative ranking curve; CV, cardiovascular; HF, heart failure; AE,adverse events; SAE, serious adverse events; *ARNI*, angiotensin receptor-neprilysin inhibitors; *SGLT2i*, sodium-glucose transporter 2 inhibitors; *MRA*, mineralcorticoid receptor antagonists; *SGCs*, soluble guanylate cyclase stimulators; *CMA*, cardiac myosin activators; SOC, standard of care; LVEF, left ventricular ejection fraction.

Sensitive analysis

For each outcome, the fixed-effects model and the random-effects model were both used to evaluate the sensitivity of our conclusions, and the results from the two models were mainly congruent (see Supplementary Table S8 online). We also calculated the risk ratio (RR) with 95% confidence interval of our network meta-analysis comparisons, the results of which still did not affect our main findings (see Supplementary Table S9 online).

Discussion

CHF is the predominant reason of mortality and hospitalization worldwide, therefore, improving the length and quality of life remains the most important goal that must be taken into account when developing new drugs. To provide a perspective on the relative survival benefit of the promising new drug classes for CHF, we conducted a network meta-analysis of 33 trials to estimate the relative efficacy of the NTDs in reducing mortality, HF hospitalization rate, and adverse events. The results of this network meta-analysis may provide evidence to support the recommendation of superior drugs for treatment of CHF.

The results of our network meta-analysis did not indicate a significant superiority of one of the tested NTDs in terms of reducing all-cause mortality, composite outcome of CV death or HF hospitalization, and HF hospitalization alone. Although SGLT2 inhibitors performed well when compared to SOC for all above outcomes, these benefits were not sufficient enough to make significant differences with other drug classes. For CV death, additional survival benefits were found in ARNI over ivabradine and CMAs, and in SGLT2 inhibitors over CMAs, indicating that ARNI and SGLT2 inhibitors were the most efficacious treatment to reduce CV mortality. And there were no significant differences between these 2 superior drug classes. For safety outcomes, SGLT2 inhibitors were associated with additional reduction for serious adverse events compared to ivabradine and CMAs, while ivabradine was associated with an increased risk for discontinuation due to adverse events compared to ARNI and SOC. Despite the mostly non-significant differences, treatments with SGLT2 inhibitors maybe preferred over therapies with other new drug classes based on their association with lower mortality and their favorable serious adverse events profile as well as the highest SUCRA scores in most outcomes. ARNI followed, for the lowest CV mortality and the second highest SUCRA scores in most outcomes.

Previous studies have demonstrated an association between SGLT2 inhibition and reduction of mortality and HF hospitalization rate in patients with diabetes[53,54]. Moreover, in subsequent trials, similar findings were observed in patients with established heart failure with or without diabetes. Specifically, Empagliflozin and Sotagliflozin displayed a superiority over SOC both in HFrHF and HFpHF[32,33,37], while Dapagliflozin demonstrated its benefits only in HFrEF[31,34,36] (trials assessing the effects of Dapagliflozin on HFpEF were ongoing and their data were unavailable). A recent meta-analysis found that the benefits of SGLT2 inhibitors were primarily driven by reduction on HF hospitalization rate, while their effects on CV mortality were modest[55]. Our results seem to be in line with these findings. The magnitude of the reduction in HF hospitalization rate (HR 0.75, 95%CI 0.64 to 0.88) was much greater than the reduction in CV mortality (HR 0.87, 95%CI 0.77 to 0.98). Accordingly, SGLT2 inhibitors were most likely to rank third best in reducing CV mortality, slightly inferior to ARNI and non-steroidal MRA. Such results may provide reference for clinical therapeutic decision for heart failure.

Sacubitril/valsartan, the only ARNI, was developed to combine neprilysin inhibitor sacubitril and angiotensin receptor blocker valsartan together with a design to minimize the risk of adverse effects[56]. The PARADIGM-HF and PARAGON-HF trials have demonstrated the superiority of ARNI over SOC in HFrEF and HFpEF respectively[10,11]. In 2016 AHA/ACC guidelines, Sacubitril/valsartan was recommended for patient with chronic HFrEF to reduce morbidity and mortality[13]. In this analysis, Sacubitril/valsartan was found to be a good alternative in CHF, especially for reducing CV mortality. Sacubitril/valsartan shared partially

overlapping mechanisms with SGC stimulators in increasing the level of cyclic guanosine monophosphate through natriuretic peptides enhancement[57]. However, SGC stimulators did not outperform SOC as expected in treating heart failure. Among the 3 included SGC stimulators (Riociguat, praliciguat and vericiguat), only vericiguat was investigated in a phase 3 trial with a large sample size. The phase 3 VICTORIA trial demonstrated vericiguat as a promising treatment for heart failure[49], indicating more dedicated trials for vericiguat were needed to collect comprehensive information.

Ivabradine is a novel heart rate lowering drug that specifically inhibits the cardiac If channels in the sinus node. The SHIFT and BEAUTIFUL trials have demonstrated that ivabradine can translate the reduction effect of heart rate into beneficial effects for improving the prognosis of heart failure[12,40]. However, these beneficial effects were limited to the patients with heart rate of 70 bpm or greater at baseline. In this analysis, when patients baseline characteristics were set to be in consistency with other drugs' trials, ivabradine showed no benefits on the prognostic in heart failure, except for the outcome of "HF hospitalization". An increased risk of discontinuation due to adverse events for Ivabradine was also observed in this analysis, the usage in partially inappropriate population (HR < 70 bmp) might explain why the acceptability of Ivabradine was lower.

Omecamtiv mecarbil was a first-in-class cardiac myosin activator, which selectively binding to cardiac myosin to augment cardiac contractility, thus improving myocardial function in patients with CHF[8]. Recently, the GALACTIC-HF trial failed to get expected results, no improvement on CV mortality and all-cause mortality was observed in Omecamtiv mecarbil[15]. In this analysis, Omecamtiv mecarbil, included as the only CMA, was not associated with any benefits in treating heart failure. For the outcome of CV mortality, we found an inferior performance of Omecamtiv mecarbil when compared to ARNI and SGLT2 inhibitors, which may herald a lower priority of this drug when considering the CV mortality as an important factor in clinical decision.

Due to lacking of large-sample multicenter trials, the available evidence from non-steroidal MRA trials seemed not strong enough. Despite all this, the existing data suggested that non-steroidal MRA may have therapeutic potential for some specific outcomes, especially for CV mortality and adverse events. The phase 3 trials FINEARTS-HF and JPRN-UMIN000037111 were now ongoing to investigated the effect of Finerenone and Esaxerenone in heart failure, respectively, which may provide more clear evidences.

To date, no head-to-head trial has directly compared the relative effects of these NTDs in heart failure. Our analysis may be a step forward in this direction with the help of the network meta-analysis statistical approach to conduct indirect comparison. The results may provide a reference for subsequent clinical practice and trial design. In this analysis, SGLT2 inhibitors were found to have the best SUCRA scores for most outcomes, indicating SGLT2 inhibitors may be the most promising treatment option for heart failure. It is important to stress that our findings are hypothesis generating, so more practical evidence is needed. Recently, FDA approved the use of dapagliflozin for treatment of HF, and it is anticipated that dapagliflozin will be added to guideline-directed medical therapy for HF in 2021 ACA/AHA heart failure guideline[58]. It is envisioned that more trials, including head-to-head trials, will be designed to investigate the role of SGLT2 inhibitors in patients with heart failure. Such trials could assist the determine of better therapeutic treatment algorithms, tailored to the appropriate population for each drug.

Limitations

This analysis has several limitations. First, we did not evaluate the consistency between direct and indirect evidences because there is no trials directly comparing these drug therapies, all the evidences were based on indirect comparisons. Second, the number of included trials investigating CMA was relatively small, so as the number of included patients in non-steroidal MRA trials, resulting in limited statistical power. Third, we did not evaluate the relative clinical efficacy and safety of individual drug types as well as individual doses. In our analysis, there is only 1 drug in most drug classes, except for SGLT2 inhibitors (containing dapagliflozin, empagliflozin and sotagliflozin) and SGC stimulators (containing Riociguat, Praliciguat and Vericiguat), and their between-study heterogeneity is low, suggesting little variability of treatment effects exist within drug classes. Fourth, the trials enrolled different patients with a broad spectrum of heart failure, as well as different percentages of SOC drugs. Although the heterogeneity between study populations still allowed a reliable comparisons, more subgroup analysis should be conducted in future studies.

Conclusions

In this network meta-analysis, none of the NTDs was associated with a significant superiority in terms of reducing all-cause mortality, composite outcome of CV death or HF hospitalization, and HF hospitalization alone, while SGLT2 inhibitors ranked best for these outcomes. For CV mortality alone, treatment with ARNI was superior to ivabradine and CMA, while SGLT2 inhibitors were superior to CMA. For adverse events, treatment with SGLT2 inhibitors were associated with a lower risk of serious adverse event than ivabradine and CMA.

Declarations

Data availability

All data generated or analysed during this study are included in this published article (and its Supplementary Information files).

Acknowledgements

This study was supported by the National Natural Science Foundation of China (No.81974541)

Author contributions

Xiaohui Yang contributed to the conception of the study.

Honghui Wu and Yalu Wen designed the study, performed the research and collected the data.

All authors analysed the data and were involved in writing the manuscript.

Competing Interests

The authors declare no competing interests.

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Figures

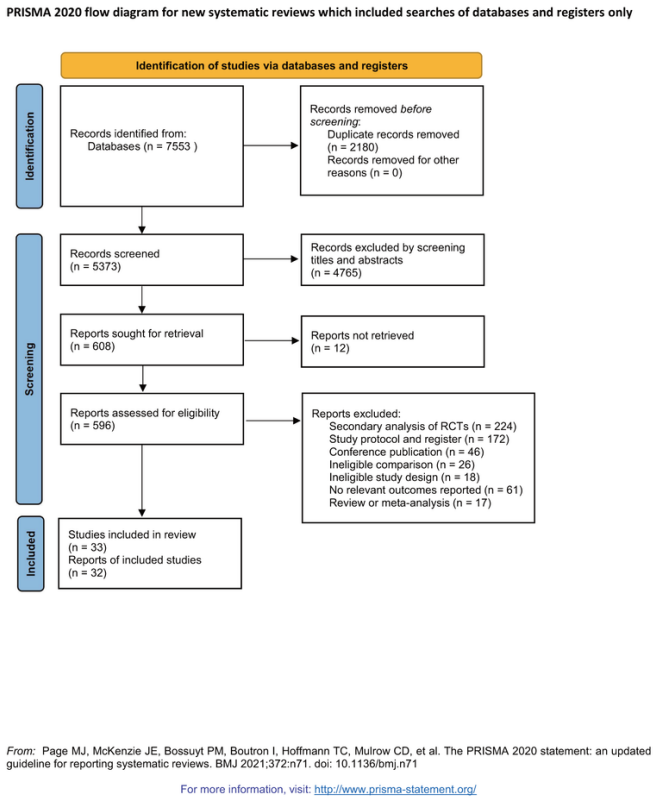

Figure 1

PRISMA flow diagram of study selection process Abbreviations: RCT, randomized controlled trial.

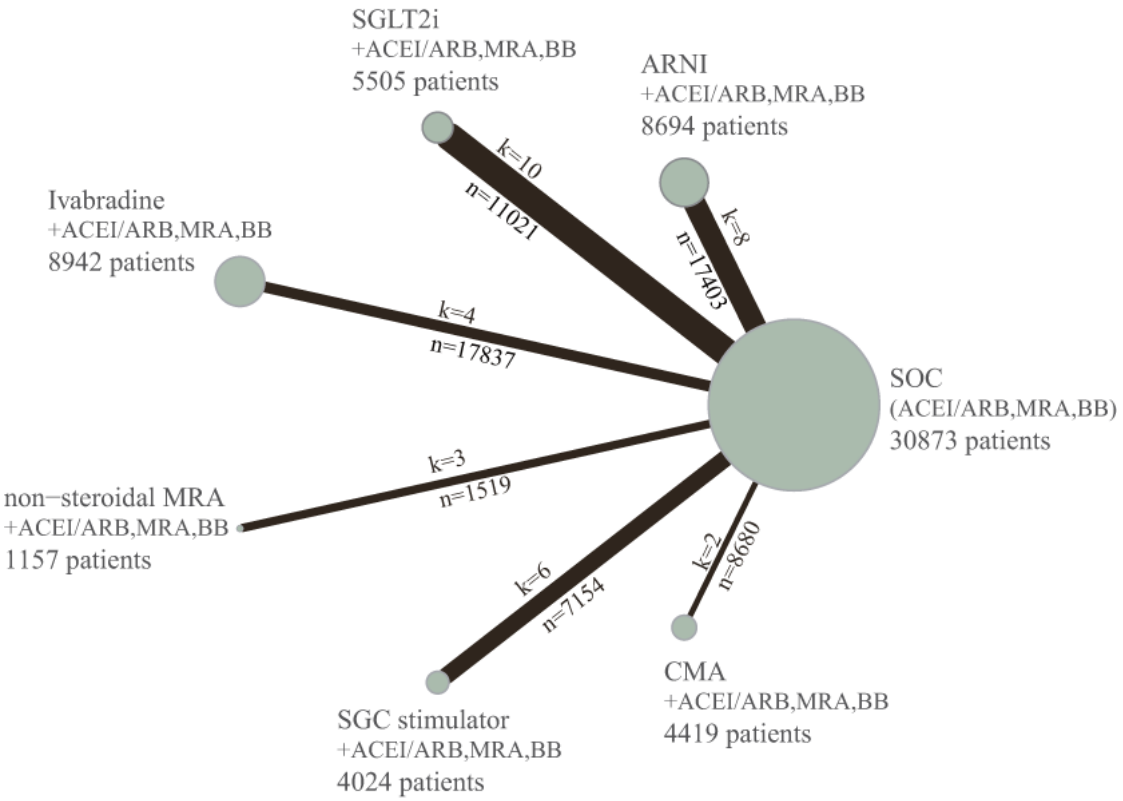

Figure 2

Network Plot for All Studies Graphical representation of network for all included trials. The sizes of the nodes are in proportion with the number of participants in each treatment. The thickness of connecting lines corresponds to the number of studies directly comparing the treatments. Abbreviations: ARNI, angiotensin receptor-neprilysin inhibitors; SGLT2i, sodium-glucose transporter 2 inhibitors; MRA, mineralcorticoid receptor antagonists; SGC, soluble guanylate cyclase; CMA, cardiac myosin activators; SOC, standard of care; ACEI, angiotensin converting enzyme inhibitors; ARB,angiotensin-receptor antagonists; BB,β-receptor blocker

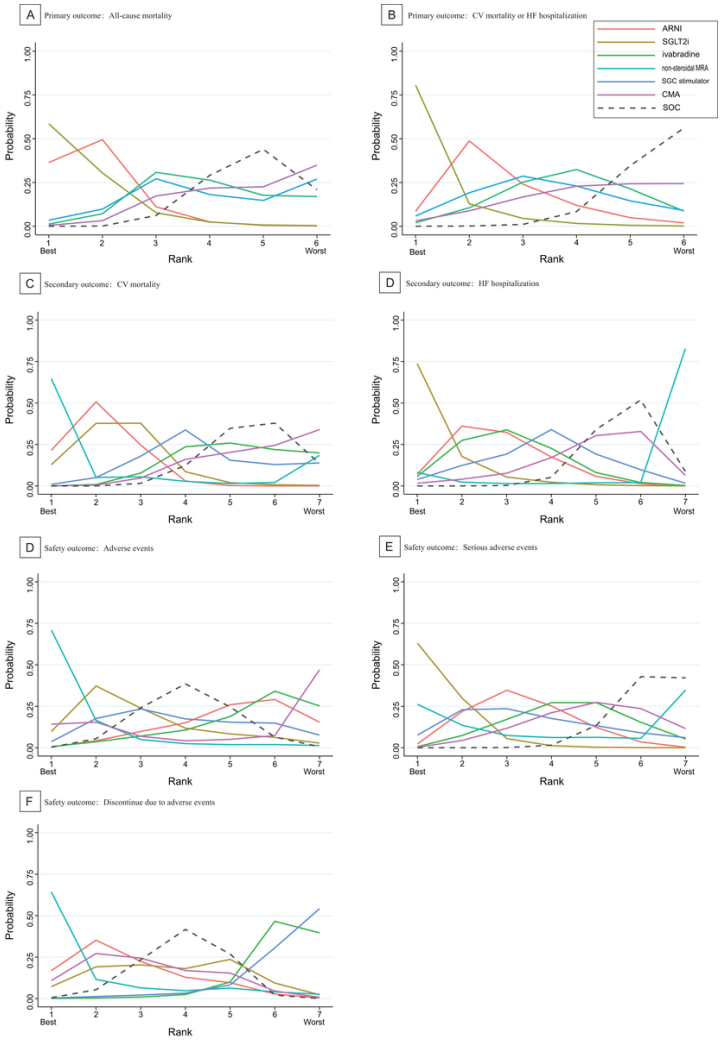

Figure 3

Ranking plots for all outcomes Ranking plots for primary, secondary and safety outcomes are stratified by treatment. Each line represents 1 drug class and shows the probability of its ranking from best to worst. The peak of the line represents the rank that the drug is most likely to be for each given outcome. Abbreviations: ARNI, angiotensin receptor-neprilysin inhibitors; SGLT2i, sodium-glucose transporter 2 inhibitors; MRA, mineralcorticoid receptor antagonists; SGC, soluble guanylate cyclase; CMA, cardiac myosin activators; SOC, standard of care

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