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CARDIOVASCULAR CARE (L ROEVER, SECTION EDITOR)

What We Learned With Recent Network Meta-analyses on Acute Heart Failure Care

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Abstract

Purpose of Review Acute heart failure remains a common and ominous clinical condition. Several interventions are currently available, with ensuing difficulties in prioritizing and formalizing decision-making. Network meta-analysis appears particularly promising to summarize the evidence base on competing interventions. We thus aimed to review, appraise, and summarize recent network meta-analyses on acute heart failure care.

Recent Findings We searched for recent network meta-analyses on acute heart failure care, retrieving five reviews, encompassing a total of 101 randomized trials and 19,085 patients. Three reviews focused on severe sepsis or septic shock, one review on shock-refractory ventricular arrhythmias, and one review on high-risk percutaneous coronary intervention. Quality of reporting and internal validity of the reviews was moderate, with common shortcomings on protocol registration and confounding appraisal. No single intervention or combo proved clearly superior for severe sepsis or septic shock, lidocaine appeared as the best strategy for shock-refractory ventricular arrhythmias, and medical therapy appeared most favorable for high-risk percutaneous coronary intervention.

Summary Recent network meta-analyses on acute heart failure begin to offer guidance for comparative effectiveness and improved clinical decision-making. Further synthesizing efforts are however needed to provide a more comprehensive and updated synthesis of the multitude of clinical alternatives for physicians caring for patients with acute heart failure.

Keywords Acute heart failure · Cardiogenic shock · Heart failure · Meta-analysis · Network meta-analysis · Overview of reviews

Introduction

The incidence, prevalence, and adverse outcomes of heart failure continue to gain ominous impact [1, 2]. Indeed, our successes at managing acute cardiovascular conditions has translated into a booming prevalence of chronic heart failure. Yet, acute heart failure poses even greater management challenges than chronic heart failure, as optimal decision-making must be accomplished in a limited time frame [3]. Specifically, in keeping with current definitions, acute heart failure is a recent onset clinical syndrome characterized by typical symptoms that may be accompanied by signs caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress [1].

Several interventions have been recommended or considered for acute heart failure, yet uncertainty persists on many of them [1, 3]. This has to do with difficulty in enrolling patients in randomized trials, but also with the fragmentation of interventions and clinical scenarios. Network meta-analysis is a methodological tool suitable for synthesizing complex evidence stemming from different randomized trials comparing alternative interventions for a common condition. Accordingly, network

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meta-analyses can be particularly useful to summarize randomized trials on acute heart failure care.

We thus aimed to provide a concise yet comprehensive overview of recent network meta-analyses on acute heart failure care, to inform clinical practitioners and guide further research efforts [4].

Methods

PubMed was searched on December 15, 2017, for network meta-analyses and mixed treatment comparisons published in scholarly peer-reviewed journals and focusing on the management of acute heart failure, cardiac shock, or cardiogenic shock with the following string: ((acute AND heart AND failure) OR (cardiogenic OR cardiac) AND shock)) AND ((network AND (meta-analysis* OR meta-analysis)) OR ((mixed AND treatment AND comparison*)). We adopted a broad selection approach, thus including reviews on acute heart failure as well as conditions leading, even indirectly, to cardiovascular insufficiency.

We abstracted key features of included reviews, as well as summarizing key findings and bibliometric indexes. Quality of reporting was appraised in keeping with the PRISMA statement on network meta-analysis [5•]. Internal validity was appraised in keeping with Biondi-Zoccai and Zarin et al. [6••, 7•], focusing on the following domains: search, selection, abstraction, appraisal, effect estimate, inconsistency estimate, and confounding estimate. Each domain was scored as validly, invalidly, or unclearly addressed. Results were tabulated without additionally summarizing efforts.

All reviewing activities were conducted by one expert reviewer (GBZ), and then independently checked by another reviewer (LG), with discrepancies resolved after consensus.

Results

We identified an initial set of 43 citations, with 5 being finally excluded because not using a network approach, 4 being a qualitative review, 8 being an observational study, 3 being a randomized trial report, 16 being an animal experimental study, and 2 focusing on cancer. Eventually, five network meta-analyses were shortlisted (Table 1), including a total of 101 randomized trials and 19,085 patients [8–12].

Specifically, Lee et al. included 13 randomized trials with 2843 patients on different means for mechanical hemodynamic support during high-risk percutaneous coronary intervention with or without cardiogenic shock [11]. Khan and colleagues focused on 11 randomized trials and 5200 subjects receiving antiarrhythmics for shock-refractory ventricular arrhythmias [12] Belletti et al. [8], Gibbison and colleagues [9], and Zhou et al. [12] all focused on pharmacologic interventions for severe sepsis or septic shock, including, respectively, 33, 23, and 21 randomized trials, with 3470, 3753, and 3819 patients.

Quality of reporting was moderately high in the five reviews (Table 2), with major weaknesses in protocol registration, inconsistency appraisal, and confounding appraisal. Internal validity was moderately high as well (Table 3), despite some lapses on inconsistency assessment, and common deficiencies in confounding appraisal. In particular, only Belletti et al. appropriately checked for small study effects or publication bias as recommended with comparison-adjusted funnel plots, regression tests, or network meta-regression [6••,8].

The main findings of shortlisted reviews were in favor of lidocaine for shock-refractory ventricular arrhythmias and several vasopressors for severe sepsis and septic shock (Table 4). Conversely, no evidence of benefit was found for mechanical hemodynamic support in

Table 1 Recent network meta-analyses on acute heart failure

First author	Journal	Year	PubMed ID	Included studies	Included patients	Topic
Belletti	Journal of Critical Care	2017	27,660,923	33	3470	Vasoactive drugs in severe sepsis and septic shock
Gibbison	Critical Care	2017	28,351,429	23	3753	Corticosteroids in septic shock
Khan	Heart & Lung	2017	28,958,592	11	5200	Antiarrhythmics in shock-refractory ventricular arrhythmias
Lee	International Journal of Cardiology	2015	25,697,869	13	2843	Mechanical hemodynamic support during high-risk percutaneous coronary intervention
Zhou	Therapeutics and Clinical Risk Management	2015	26,203,253	21	3819	Vasopressors in septic shock

Table 2 Quality of reporting of recent network meta-analyses on acute heart failure

First author	Protocol and registration	Search	Selection	Abstraction	Appraisal	Included studies	Geometry	Inference	Inconsistency	Confounding	Funding	Conflicts of interest
Belletti	I	A	A	A	A	A	A	A	A	A	A	A
Gibbison	A	A	A	A	A	A	A	A	I	I	A	A
Khan	I	A	A	A	A	A	I	A	I	A	A	A
Lee	I	A	A	A	A	A	A	A	A	A	A	A
Zhou	I	A	A	A	A	A	A	A	A	A	I	A

Modified from the Preferred Reporting Items for Systematic Reviews and Meta-analyses-Network Meta-Analysis (PRISMA-NMA) checklist [5•]; *A*, adequately reported; *I*, inadequately reported

high-risk percutaneous coronary intervention or corticosteroids in septic shock. Bibliometric indexes and usage metrics, albeit confounded by journal and publication date, suggested that all network meta-analyses, except for Khan et al., were extensively quoted and disseminated (Table 5) [10].

Discussion

This focused overview of recent network meta-analyses on acute heart failure care highlights the potential benefits as well as drawbacks of this novel tool for complex evidence synthesis [6••]. Specifically, we were able to shortlist five recent network meta-analyses focusing on pharmacological and mechanical interventions in patients with acute heart failure [8–12]. These works appeared of moderately high quality in terms of reporting and internal validity. Their main findings highlighted the clinical usefulness of lidocaine and several vasopressors in, respectively, shock-refractory ventricular arrhythmias and severe sepsis or septic shock [8, 10, 12]. Conversely, they suggested that corticosteroids are not beneficial in septic shock, nor are mechanical hemodynamic support devices in high-risk percutaneous coronary intervention [9, 11].

Despite these apparent fruitful efforts, the actual elephant in the room is the paucity of network meta-analysis on acute heart failure care published in recent years, as well as the limited number and scope of randomized trials among included reviews. Indeed, several of the most important clinical decisions were not the focus of reviewing efforts (e.g., diagnostic approaches, diuretics, antithrombotics). In addition, most evidence networks were largely star-shaped, testifying the lack of comprehensive comparative data for any given intervention-condition combination [6••]. Even the sobering results in favor of lidocaine reported by Khan et al. [12] should be put into the broader perspective stemming from the non-significant findings of the large randomized trial led by Kudenchuk et al., despite its inclusion in the above network meta-analysis [13].

Our operative choice of including in our overview of reviews also network meta-analyses on severe sepsis or septic shock merits further elaboration. Specifically, we chose to include these reviews [8, 9, 12] for a number of reasons. First, pathophysiologically, most cases of severe sepsis/septic shock are associated with at least mild diastolic and systolic dysfunction, thus making them pertinent for any review on acute heart failure [14]. Second, low blood pressure is common in acute heart failure and the optimal management of low blood pressure in severe sepsis/septic shock may indeed inform on the optimal management of low blood pressure in acute heart failure. Third, infection can often complicate acute heart failure, creating

Table 3 Internal validity of recent network meta-analyses on acute heart failure

First author	Search	Selection	Abstraction	Appraisal	Effect estimate	Inconsistency	Confounding
Belletti	V	V	V	V	V	V	V
Gibbison	V	V	V	V	V	U	U
Khan	V	V	V	V	V	U	U
Lee	V	V	V	V	V	V	I
Zhou	V	V	V	V	V	V	U

Modified from Biondi-Zoccai [6••]; *I*, invalid; *U*, unclear; *V*, valid

a clinical conundrum consisting of sepsis and heart failure, which may benefit from details on the optimal management of severe sepsis/septic shock. Yet, the reader should be aware that none of the included reviews provided details on cardiac systolic or diastolic dysfunction, thus clearly limited the external validity of these reviews.

From a more technical viewpoint, it remains disappointing that after several years of outstanding recommendations, no review was registered pre hoc (e.g., in the University of York Centre for Reviews and Dissemination PROSPERO system) [15]. In addition, inconsistency appraisal was not universally and explicitly performed. Similarly important drawbacks were apparent for small study effects, which were either not appraised at all or inappropriately checked in most reviews [6••, 16••]. Finally, network meta-regression approaches were never used, at odds with their potential for sensitivity analyses and hypothesis generation [17].

Implications for Research and Practice

Despite the above reporting and methodological limitations, it is interesting to notice that almost all reviews were already highly successful either in terms of peer usage or scholarly citation, confirming the appeal of network meta-analyses for practitioners as well as researchers [18]. Yet, such success should not distract our shared efforts to improve the methods and scope of network meta-analyses in acute heart failure care, as ample room for improvement persists. More poignantly, we can infer from the present overview that several vasopressors may be beneficial for severe sepsis and septic shock, in particular norepinephrine and levosimendan, that lidocaine is useful for shock-refractory ventricular arrhythmias, and that no mechanical hemodynamic support device is currently beneficial for high-risk percutaneous coronary intervention, irrespective of the presence of cardiogenic shock.

Table 4 Main findings of recent network meta-analyses on acute heart failure

First author	Summary of findings	Additional results
Belletti	Dobutamine, epinephrine, levosimendan, norepinephrine plus dobutamine and vasopressin appeared associated with better survival than placebo in severe sepsis and septic shock.	Rank analysis showed that levosimendan had the highest probability of being the best treatment. Mild inconsistency was found only for the terlipressin, vasopressin, and norepinephrine comparison.
Gibbison	No intervention including corticosteroids appeared better than placebo or alternative interventions on the spectrum of clinical outcomes for septic shock.	Hydrocortisone boluses and infusions appeared superior to methylprednisolone boluses and placebo in shock reversal.
Khan	Lidocaine appeared better for survival to hospital discharge for shock-refractory ventricular arrhythmias in comparison to amiodarone, MgSO4, or placebo.	Rank analysis showed that lidocaine had the highest probability of being the best treatment for survival to hospital discharge.
Lee	Intra-aortic balloon pump or percutaneous ventricular assist devices did not appear better for survival in comparison to medical therapy or alternative interventions for high-risk percutaneous coronary intervention with or without cardiogenic shock.	Percutaneous ventricular assist devices appeared worse than alternative interventions, and intra-aortic balloon pump appeared worse than medical therapy for bleeding.
Zhou	No intervention proved incrementally beneficial for improving survival in septic shock, including epinephrine, epinephrine plus norepinephrine, dobutamine plus norepinephrine, dobutamine plus terlipressin, dopamine, dopexamine plus norepinephrine, norepinephrine, norepinephrine plus terlipressin, phenylephrine, terlipressin, vasopressin.	Dopamine appeared worse than norepinephrine for survival, cardiac events, and hemodynamic endpoints.

Table 5 Bibliometric indexes and social usage of recent network meta-analyses on acute heart failure

First author	Web of Science citations	Scopus citations	Google Scholar citations	Tweets	Social comments
Belletti	3	5	8	10	1
Gibbison	5	5	9	150	8
Khan	0	0	0	0	0
Lee	4	7	8	1	0
Zhou	10	10	22	7	2

Measured on December 19, 2017

Conclusion and Future Directions

Notwithstanding that recent network meta-analyses on acute heart failure may begin to offer guidance for comparative effectiveness and improved clinical decision-making, further synthesizing efforts are needed to provide a more comprehensive and updated synthesis of the multitude of clinical alternatives for physicians caring for patients with acute heart failure.

Compliance with Ethical Standards

Conflicts of Interest Prof. Biondi-Zoccai has consulted for Abbott Vascular and Bayer.

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