European Review for Medical and Pharmacological Sciences 2021; 25: 2971-2980

Comparison of diuretic strategies in diuretic-resistant acute heart failure: a systematic review and network meta-analysis

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Abstract. – OBJECTIVE: Up to 50% of patients hospitalized for acute heart failure (AHF) show resistance to diuretics. This condition contributes to a prolonged hospital length of stay and a higher risk of death. This review aimed to investigate whether a diuretic therapeutic approach more effective than furosemide alone exists for patients with diuretic-resistant AHF.

MATERIALS AND METHODS: We identified all randomized controlled trials (RCTs) evaluating diuretic therapy in patients with diuretic-resistant AHF. We searched Pubmed, BioMed Central, and Cochrane CENTRAL databases.

RESULTS: Six RCTs were identified, involving a total of 845 patients. The P-score ranges from 0.6663 for furosemide to 0.2294 for the tolvaptan-furosemide. We found no significant differences in efficacy for any drug comparison.

CONCLUSIONS: None of the diuretics considered in RCTs performed to date (tolvaptan, metolazone, hydrochlorothiazide, indapamide) appear to be more effective than furosemide therapy alone for the treatment of patients with diuretic-resistant AHF.

Key Words:
Acute heart failure, Furosemide, Diuretic resistance, Tolvaptan, Efficacy, Network meta-analysis.

Abbreviations

AHF: Acute Heart Failure; RCT: Randomized Controlled Trial; RoB 2: Revised Cochrane risk-of-bias tool for randomized trials; SMD: Standardized Mean Difference; 95% CI: 95% Confidence Interval.

Introduction

Acute heart failure accounts for >26 million hospitalizations per year worldwide[1-3], and a 1-year mortality rate as high as 20-30%[4], with an additive risk with each subsequent hospitalization[5].

Congestion is the most frequent clinical manifestation (70% of patients), with diuretics recommended as first-line therapy[6,7]. Amongst those, loop diuretics are the most prescribed drugs, although, despite the improvement in symptoms, at least 50% of patients fail to experience any weight loss due to reduced extracellular fluid retention, and up to 50% leave the hospital with residual congestion, leading to further readmissions and mortality[8,9].

Diuretic resistance has not an accepted unique definition, but it is commonly described as the failure to achieve effective decongestion despite an adequate dose of diuretic administered[10]. Since diuretic resistance contributes to worsening heart failure and outcome, great effort is directed towards identifying the best therapeutic strategies[11].

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The aim of this systematic literature review was to investigate whether a diuretic therapeutic approach exists that is more effective in treating patients with diuretic-resistant AHF than furosemide alone.

Materials and Methods

Data Sources and Searches

We identified all randomized controlled trials (RCTs) evaluating patients' medical therapy with diuretic-resistant AHF (i.e., the clinician-established need to add a second diuretic to initial therapy, usually a loop diuretic, to resolve a condition of acute congestive heart failure). We included studies performed in any hospital department. The following publication types were excluded: observational studies, conference abstracts, reviews, non-human studies, protocols, policy statements, and guidelines.

The electronic search strategy applied standard filters for identifying related studies. The search was performed on the Medline (PubMed), BioMed Central, Scopus, Web of Science, and Cochrane CENTRAL databases, from inception to 31st January 2020, with language restrictions.

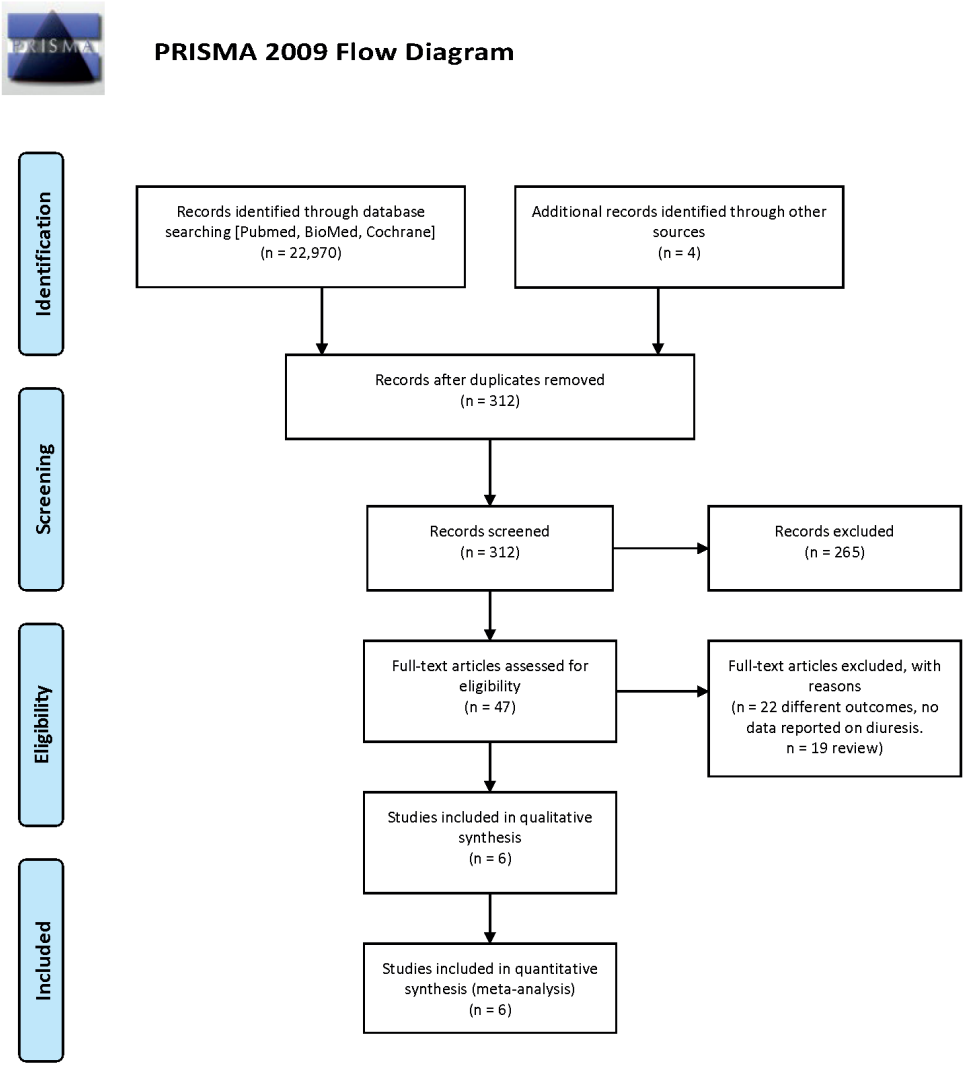

Figure 1. PRISMA 2009 Flow-diagram for the search and selection process of articles. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi: 10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org.

The meta-analysis was conducted according to the PRISMA guidelines[12]. Our search strategy's specific details can be seen in the Online Data Supplement appended to this paper **(Supplementary Material S1)**. The protocol for this systematic review was registered on PROSPERO (registration number CRD42020168905).

Data Extraction and Quality Assessment

Two independent couples of reviewers (DO/NF and FM/DP) identified all relevant titles and abstracts. Full-text copies of all potentially relevant studies were then obtained for detailed evaluation by each pair of reviewers, and the data from each study were independently extracted using a standardized abstraction module. One pair of reviewers (FM/DP) evaluated the data in the absence of author and journal names, institutional affiliations, and publication date. The data extracted from the documents were checked by an additional reviewer (LV) for accuracy. Each study was assessed for methodological quality using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2). We examined each article for information on the sampling method, the presence of a control group, the comparability of the control group (if included), and methods used to obtain the results.

Qualitative Analysis

A narrative synthesis approach was used to explore each study's characteristics and the variations between the studies. We collected demographic data, information about the study's design and planning objectives, and information about the diuretic drugs and control groups compared. As an indication of therapeutic efficacy, the urine volume produced in the first 24 hours was considered. We did not consider a cut-off value of urine volume, but instead considered the comparison in terms of absolute quantities of urine produced in the post-treatment period. We adopted this outcome because the subjective assessment of dyspnea improvement is prone to methodological bias, whereas measurement of the volume of urine produced is a pragmatic outcome. Unlike the urinary sodium concentration, many of the studies involved reported the total amount of urine produced[8]. Furthermore, all biomarkers (creatinine, B-type natriuretic peptide, etc.) explored to date to verify the efficacy of diuretics have failed to demonstrate a linear correlation with achieving decongestion[13].

Statistical Analysis

A default fixed-effect model or random-effects model was used if a high degree of inconsistency/heterogeneity was detected through Cochran's Q value. The I^2 was used to measure the percentage of variation across studies due to heterogeneity rather than chance. When I^2 results between 50 and 90%, the heterogeneity is assumed as substantial, while I^2 is 75-100%, the heterogeneity is considerable. Results were illustrated using forest plots. A funnel plot and Egger's test for asymmetry were planned to evaluate potential publication bias. The standardized mean difference (SMD) and 95% confidence interval (95% CI) were calculated according to the intention-to-treat principle. Tau^2 defined the between-study variance. The difference in the estimates of the treatment effect between the treatment groups for each hypothesis was tested using a two-sided z test. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using the R environment (version. 3.6.1. The R Foundation for Statistical Computing; Vienna, Austria) with the 'netmeta' and 'metacont' packages[14,15].

Results

Characteristics of the Included Studies

Diuretic resistance was considered as the persistence of congestion (orthopnea, edema, pulmonary rales, elevated jugular venous pulse, or congestion on chest radiograph) despite the diuretic administration. Cox et al[16] defined "diuretic-resistance" as the production of less than 2 L of urine in 12 hours, despite a furosemide dosage greater than 240 mg/die.

Six studies fulfilled the specified criteria involving 845 patients[16-21] (Figure 1). Four studies were double-blind RCTs, and 2 were open-label RCTs. All but 2 studies were multicenter studies.

Five out of the 6 studies investigated tolvaptan; 2 studied metolazone, 1 hydrochlorothiazide, and 1 indapamide. In 3 studies, one or more arms evaluated an incremental dose of furosemide. Only 2 of the 6 randomized trials considered a placebo-arm. All but 2 of the studies considered two intervention arms only; 1 considered three, and 1 investigated four intervention arms (Figure 2). The observation time to define diuretic-resistant varied from 6 to 48 hours (Table I).

Table I. Characteristics of the included studies and definition of "diuretic-resistance". AHF: acute heart failure; HF: heart failure; n.s.: not specified.

Study	Population	Sample Size	Definition	Initial Treatment	Dose considered	Time
Udelson et al[17]	Patients admitted with diagnosis of HF (NYHA > II)	83	Congestion signs despite daily diuretic therapy	n. s.	n. s.	48 h
Matsue et al[19]	AHF patients with renal dysfunction	217	Congestion signs despite daily diuretic therapy	Furosemide	n. s.	6 h
Felker et al[18]	Patients with AHF	257	Congestion signs despite daily oral diuretic therapy	Furosemide	40 mg	24 h
Inomata et al[20]	HF patients with fluid retention	81	Congestion signs despite daily diuretic therapy	Furosemide or equivalents	≥ 40 mg	n. s.
Cox et al[16]	Hospitalized patients with hypervolemic AHF	60	Total urine output of <2 l in the 12 h prior to enrollment	Furosemide or equivalents	> 240 mg	12 h
Salahudin et al[21]	Patients admitted with diagnosis of refractory HF (NYHA > III)	150	Congestion signs despite intravenous diuretic therapy	Furosemide	40 mg x 3	12 h

Diuretic Efficacy

In all the studies considered, except for Udelson et al[17], where the diuretic is not specified, the patients showed a diuretic resistance after treatment with a loop diuretic or furosemide at equivalent dosage. The amount of urine produced per 24 hours ranges from 6,464 mL in the tolvaptan group compared to the furosemide group in the study by Matsue et al[19], to 79 mL in the furosemide group compared to tolvaptan in the study by Inomata et al[20] **(Supplementary Material S2).**

Analyzing the individual studies, the standardized mean difference (SMD) in drug efficacy was not statistically significant for any of the direct comparisons: by evaluating the SMD values for each comparison, all confidence intervals cross the zero value **(Supplementary Material S3)**. Evaluating the P-score, the values range from 0.6663 for furosemide to 0.2294 for the tolvaptan-furosemide **(Supplementary Material S4)**. The results for all the individual treatment comparisons (both direct and indirect), applying a fixed-effects model, are shown in **Supplementary Material S5**.

Finally, over-all Q value was 2.57 (degree of freedom = 3; p-value = 0.462), Q value within designs was 0.12 (d.f. = 1; p-value = 0.730) and between designs was 2.99 (d.f.= 2; p-value = 0.224). I^2 was 0% (95% CI 0.0%; 82.2%), so no random-effects model was required. The net heat plot shows no inconsistency about any direct evidence in the whole network **(Supplementary Material S6)**. The summary forest plot substantially demonstrated no differences between treatment efficacy (Figure 3).

Detection of Systematic Errors

Most of the trials included were at low risk of bias (Table II). Randomization seemed to be adequate and correctly complied in all studies. However, regarding the two open-label studies, it was not possible to affirm the absence of bias (even unintentional bias) related to the experimenters' discretion. Only one study considered relief from dyspnea as the primary outcome of diuretic therapy through a 7-point Likert scale[18]. This outcome could be subject to bias due to difficult

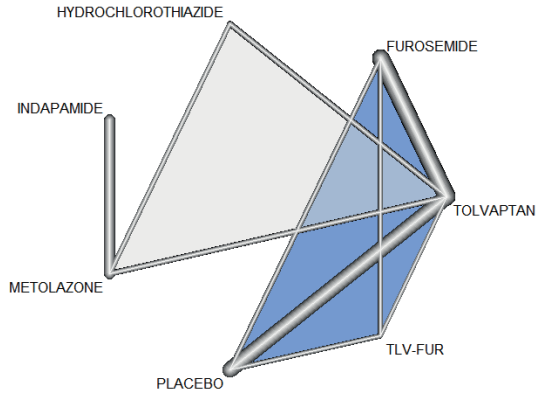

Figure 2. A plot of the diuretics network. The thickness of the edges is proportional to the precision (the inverse of the variance) of each direct comparison. The blue trapeze represents the multi-arm trial. TLV-FUR: tolvaptan + furosemide.

objectivity. The Egger's test, used to quantify the funnel plot's asymmetry (Figure 4), was statistically significant, confirming asymmetry (p-value = 0.037). Specifically, some arms of the study by Udelson et al[17] were affected by the small sample size.

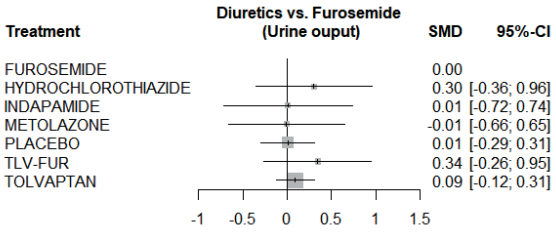

Figure 3. Forest plot displaying the in-network comparisons with furosemide. TLV-FUR: tolvaptan + furosemide; SMD: standard mean difference; 95% CI: 95% confidence interval.

Discussion

In our analysis, no differences were found between the different diuretic strategies for the treatment of diuretic-resistant AHF. Additionally, we did not detect any significant difference between any of the diuretics tested in the individual studies and patients receiving placebo. Therefore, there is no evidence that any therapeutic strategy among those studied in the literature is particularly effective. Loop diuretics play a crucial role in

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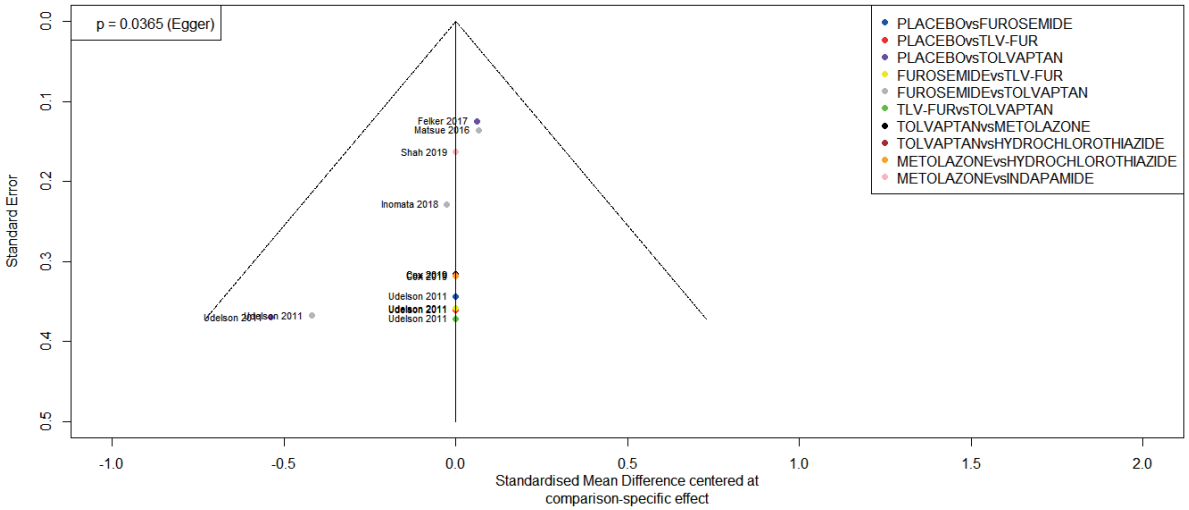

Figure 4. Comparison-adjusted funnel plot assessing the publication bias of the network studies. Small sample studies are placed in the bottom of the funnel; the large sample studies are in the up. Deviation from the center could represent a source of publication bias.

Table II. Methodological quality assessment using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2).

Study ID	Randomization	Design	Sample Size	Experimental	Main Comparator	Arms	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Udelson et al[17]	double-blind	Multicentric	83	Tolvaptan	Placebo	4	+	+	+	+	+	+
Matsue et al[19]	open label	Multicentric	217	Tolvaptan	Furosemide	2	+	?	+	+	?	?
Felker et al[18]	double-blind	Multicentric	257	Tolvaptan	Placebo	2	+	+	+	?	+	?
Inomata et al[20]	open label	Multicentric	81	Tolvaptan	Furosemide	2	+	?	+	+	+	?
Cox et al[16]	double-blind	Monocentric	60	Chlorothiazide	Metolazone	3	+	+	+	+	+	+
Salahudin et al[21]	double-blind	Monocentric	150	Indapamide	Metolazone	2	+	+	+	+	+	+

the treatment of AHF. Although no evidence exists to define the first-choice diuretic and dosage, furosemide is the most used for patients admitted with AHF[8,22,23]. A reasonable response to diuretics should result in approximately 3-4 L of urine per 40 mg of furosemide[24] or an output greater than 1400 mL of urine[25]. Diuretic resistance has been described in 20% to 50% of patients hospitalized for AHF[26], and residual congestion at the time of discharge is recognized as negative prognostic factor in terms of mortality and re-hospitalization[11,13,27,28]. The main underlying mechanisms of diuretic resistance in AHF, resides in the renal tubule defect and consequent activation of

the vasoactive neuro-hormonal systems[9,29-31]. The prolonged or continuous use of loop diuretics may cause a diuretic "braking" through distal compensatory sodium reabsorption. This progressive loss of efficacy is probably linked to the characteristic "ceiling effect", due to the progressive loss of sodium, which sometimes exceeds the corresponding elimination of water and determines a form of diuretic resistance in heart failure patients[32].

Various diuretic strategies have been explored in the literature to overcome diuretic-resistance. In individual comparison studies, these new diuretics showed clinical superiority over furosemide alone or placebo. Udelson et al[17] demonstrated more consistent weight loss and urine production in the tolvaptan group than placebo, but not compared with furosemide alone. However, the authors used a single 80 mg dose of furosemide – the same as used in all randomization arms; therefore, it is unknown whether further effects can be observed increasing the dosage of furosemide. Although the literature data are controversial, high daily intravenous doses of furosemide (2.5 times the total daily oral dosage) effectively improve diuresis[33]. Matsue et al[19] demonstrated the decongestion efficacy of tolvaptan, allowing a furosemide down-titration. However, it should be noted that this study was not blinded; thus, bias cannot be excluded, and no conclusion regarding tolvaptan superiority over furosemide could be drawn.

Conversely, Felker et al[18] detected significantly more weight and fluid loss in the group treated with tolvaptan and furosemide compared with the group treated with furosemide alone. Inomata et al[20] obtained the same results in patients with renal dysfunction. Cox et al[16], comparing hydrochlorothiazide, metolazone and tolvaptan in AHF patients with diuretic-resistance, did not find greater efficacy in any of the three drugs compared to each other[16]. Likewise, Salahudin et al[21] found no significant difference between indapamide and metolazone.

In our analysis, no single significant differences were found for both: the effect of one drug *vs.* another and between any of the diuretics tested in the individual studies and placebo.

Therefore, there is no evidence that any therapeutic strategy among those studied in the literature is particularly effective.

However, other drug strategies exist besides those compared, such as ethacrynic acid and nesiritide. Ethacrynic acid is a phenoxyacetic acid derivative belonging to the family of loop diuretics that includes furosemide[34]. However, no comparative study exists in the literature addressing ethacrynic acid and furosemide, leaving the field open to the opinions and suggestions of the individual clinicians. Nesiritide, on the other hand, is a recombinant formulation of type-B natriuretic peptide, and it acts through the counter-regulation of the renin-angiotensin-aldosterone system. If the pathophysiological rationale underlying the clinical administration of nesiritide was robust, a randomized, double-blind, placebo-controlled trial – ASCEND-HF – failed to show any statistically significant difference in mortality or re-hospitalization rates. However, nesiritide associated with furosemide has never been tested in a clinical trial in patients with diuretic-resistance[35].

Given the abovementioned risks related to residual congestion in patients with heart failure, especially in terms of re-hospitalization, the decline in cardiac and renal function, and, ultimately, mortality, some mechanical removal strategies of the intravascular volume have been tested. Ultrafiltration (or aquaferesis) has been implemented in some trials to investigate whether the mechanical removal of intravascular volume (and, because of the absorption mechanism, interstitial fluid) presents a valid option[36]. However, all the studies conducted so far comparing ultrafiltration with diuretic therapy have failed to demonstrate any substantial advantages. So, whether ultrafiltration constitutes a particularly useful solution to diuretic-resistance remains to be determined[37,38].

In conclusion, there is no one more effective therapeutic drug to decongest patients with AHF than furosemide. Furthermore, some therapeutic strategies require further study, either because they were not studied adequately or because they have not been explored at all (i.e., ethacrynic acid, other drug combinations, higher drug doses, and so on).

Limitations

Despite the absence of inconsistencies in the pooling data analysis, we cannot exclude some heterogeneity due to the individual studies' different designs. For example, the dosage of the drugs used is variable (although it is around the standard dosages) for each study considered. Furthermore, we considered the total volume of urine produced in 24 hours as the diuretic-resistance criterion, rather than a cut-off value. This for two reasons: first of all, because there is no shared univocal value in literature; and, secondly, because the absolute comparison between the different

diuretics considered can benefit from this choice, rather than a predetermined value that may not reflect the patient's clinical needs. However, even this somewhat arbitrary choice could reduce the reliability of the result.

Conclusions

In short, there is no evidence supporting the efficacy of additional diuretic therapies than furosemide alone in treating acute heart failure patients with diuretic-resistance.

Sources of Funding
The Authors declare that they have no conflict of interests.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Ethical approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Human subjects/informed consent
Not applicable.

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