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Renal/Metabolic

# Co-administration of furosemide with albumin for overcoming diuretic resistance in patients with hypoalbuminemia: A meta-analysis ☆

Georgios D. Kitsios, MD PhD [a,b,*], Paolo Mascari, MD PharmD [a], Riad Ettunsi, MD MSc [a], Anthony W. Gray, MD [a]

[a] Department of Internal Medicine and Department of Pulmonary and Critical Care Medicine, Lahey Hospital and Medical Center, Burlington, MA, USA
[b] Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA, USA

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ABSTRACT

*Purpose:* To systematically review clinical studies of co-administration of albumin and loop diuretics in hypoalbuminemic patients as a strategy to overcome diuretic resistance.
*Materials and Methods:* Systematic search of electronic databases up to October 2012. We included randomized clinical trials of adults with hypoalbuminemia, comparing co-administration of loop diuretics and albumin versus loop diuretics alone. Quantitative data were synthesized with meta-analytic techniques for clinical, surrogate (urinary volume and urinary sodium excretion) and intermediate (pharmacokinetic and hemodynamic parameters) outcomes.
*Results:* Ten studies were included, of which 8 trials with crossover design were synthesized with meta-analysis. A statistically significant increase in the amount of urine volume (increment of 231 mL [95% confidence interval 135.5-326.5]) and sodium excreted (15.9 mEq [4.9-26.8]) at 8 hours were found in favor of co-administration of albumin and furosemide. These differences were no longer statistically significant at 24 hours. Meta-analyses for intermediate outcomes (ie, furosemide excretion, distribution volume etc.) did not reveal statistically significant differences.
*Conclusions:* Synthesis of a heterogeneous body of evidence shows transient effects of modest clinical significance for co-administration of albumin with furosemide in hypoalbuminemic patients. Pragmatic, large-scale randomized studies are needed to delineate the role of this strategy.


## 1. Introduction

The loop diuretic furosemide constitutes the mainstay of treatment in patients with hypervolemic conditions, such as cirrhosis, nephrotic syndrome or congestive heart failure. However, its clinical use is hampered when "furosemide resistance" is encountered, i.e. increased doses of furosemide fail to induce adequate diuretic response, and such resistance is frequently observed in patients with hypoalbuminemia [1].

Compelling experimental data demonstrate that furosemide is dependent on adequate plasma albumin concentrations for exerting its biological action [2]. More than 95% of furosemide molecules in the plasma are bound to albumin, and this albumin-bound fraction reaches the proximal tubular epithelial cells to interact with an anion transporter and finally be translocated into the tubular lumen to exert its action in the ascending limb of Henle's loop. In hypoalbuminemia, the volume of furosemide distribution is increased because the drug cannot be retained in the plasma, leading to a diminished amount of albumin-bound furosemide presented to the proximal tubules. Based on initial experiments with analbuminemic rats in which the co-administration of albumin with furosemide significantly potentiated diuretic response compared to furosemide alone [2], this co-administration of albumin and furosemide (FUR-ALB) has been proposed as a strategy to overcome diuretic resistance in hypoalbuminemic patients.

Although the clinical efficacy of FUR-ALB has not been conclusively demonstrated [3], this is a frequently employed measure in clinical practice. Albumin is not without limitations though, including high cost, periodic shortages, and even potential adverse effects, such as anaphylaxis, risk of infection or detrimental transient volume expansion in hypervolemic patients [4], and thus routine use of FUR-ALB cannot be justified without strong evidentiary support.

We aimed to draw safer conclusions and clarify misconceptions on the efficacy of co-administration of albumin with loop diuretics for overcoming diuretic resistance in patients with hypoalbuminemia, by conducting a systematic review of the literature for randomized clinical trials (RCTs) comparing this co-administration strategy versus diuretics alone.

☆ Conflicts of interest: None.

* Corresponding author. Department of Internal Medicine, Lahey Hospital and Medical Center, 41 Mall road, Burlington, MA, 01805, USA. Tel.: +1 781 744 7000.
*E-mail address:* Georgios.Kitsios@Lahey.org (G.D. Kitsios).

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## 2. Methods

### 2.1. Data sources and searches

We conducted systematic searches of the literature in Ovid Medline, Cochrane Register of Controlled Trials, PubMed, CINAHL, and SCOPUS databases from inception up to October 2012 using keywords—and MeSH terms when appropriate—relating to albumin, furosemide (and all other loop diuretics, i.e., torsemide, ethacrynic acid, bumetanide) for RCTs published in full text in English. Potentially eligible studies were retrieved in full text for further assessment of eligibility. We hand-searched reference lists of eligible studies and also retrieved and evaluated for eligibility all studies included in a previous systematic review [3]. Details of our protocol can be found in the Appendix.

### 2.2. Study selection

Two investigators determined study eligibility against a set of predefined criteria. Eligible populations included patients with hypoalbuminemia of any cause, ≥18 years old, and requiring diuresis for hypervolemia. Interventions and comparators of interest included administration of loop diuretics with and without concurrent human albumin intravenous infusion. The outcomes of interest included both surrogate outcomes (such as urinary volume excretion, urinary sodium (Na) excretion, weight loss and improvement in oxygenation) and clinical outcomes (such as mortality, rehospitalization and resolution of hypervolemic symptoms) as reported by the original studies. We also specifically examined outcomes aiming to delineate the underlying pharmacokinetic or hemodynamic mechanisms of potentiated diuresis with albumin, adjudicated as intermediate outcomes (such as furosemide excretion, furosemide volume of distribution, change in glomerular filtration rate etc.). Eligible study designs included RCTs, of either parallel or crossover design.

### 2.3. Data extraction and synthesis

From eligible studies, we extracted detailed data regarding the demographics, index and comorbid conditions of included patients, baseline laboratory values, details on study design, description of protocols regarding intervention and comparator arms, and finally, outcome data (surrogate, clinical and intermediate outcomes). Data were extracted independently by 2 investigators and disagreements were resolved through consensus.

Outcome data for categorical variables were described as odds ratios (ORs) or other relative effect sizes available with their corresponding 95% confidence intervals (CIs); adjusted estimates were recorded when available, otherwise ORs (95% CI) were calculated from raw data. Continuous outcomes were described as net differences between the 2 arms with their 95% CIs. Among studies with similar populations, interventions and outcomes, we performed quantitative synthesis of outcome data of selected continuous variables with random effects meta-analysis, when there were at least 3 unique similar studies. Based on available data and our a priori assessment of the clinical importance of specific outcomes, we performed random effects model meta-analysis [5] for the surrogate outcomes of urinary volume and Na excretion, and the intermediate pharmacokinetic and hemodynamic outcomes. Meta-analyses were possible only for crossover RCTs investigating a single-time FUR-ALB versus furosemide alone, with the outcomes measured at 2 time points (at ≤8 and at 24 hours, respectively). In crossover studies, by definition, there is only one set of baseline values for the cohort of patients, and as these cancel out, we therefore utilized the net differences between the final values obtained with each intervention (ie, incremental urinary volume or Na excreted with FUR-ALB). When such net differences were not directly reported, we calculated these values and estimated their 95% CI from the standard errors of the final values [6]. For the pharmacokinetic and hemodynamic outcomes, we conducted meta-analyses after transformation of results to standardized effect sizes (Cohen's D), given differences in estimation and reporting of these parameters by individual studies [7]. Heterogeneity among effect sizes was assessed using the $I^2$ index and Cochran's Q test. An $I^2$ index ≥50% was used to indicate medium-to-high heterogeneity [8]. To explore potential treatment-effect heterogeneity, we performed a prespecified subgroup analysis for patients with nephrotic syndrome and also conducted meta-regression analyses in which the effect sizes of individual RCTs were regressed against the doses of albumin and furosemide used in each RCT, respectively. Analyses were performed with Open Meta-analyst [9] and StatsDirect.

### 2.4. Quality assessment

We assessed the risk of bias in included RCTs by using the predefined criteria from the Cochrane's Risk of Bias tool: adequacy of randomization, allocation concealment, blinding of participants and researchers, blinding of outcome assessment, incomplete outcome data, possibility of selective reporting, and possible other sources of bias, as previously described [10]. For crossover RCTs, we also specifically evaluated the adequacy of the washout period (defined as at least 48 hours). RevMan was used for construction of the risk of bias graphs. This report was designed and prepared according to the PRISMA statement [11].

## 3. Results

### 3.1. Study selection

A flowchart of the study selection process is shown in Fig. 1. Of a total of 331 abstracts screened, 21 articles considered to be potentially eligible were evaluated in full text, and 10 articles were finally included [2,12-20].

### 3.2. Descriptive characteristics

Sample sizes were generally small, ranging from 5 to 126 patients (median 11 patients) included (Table 1). Populations were heterogeneous in terms of their index disease, with 2 studies performed in patients with cirrhosis [17,19], 5 studies in patients with nephrotic syndrome [12-16], 1 study in patients with acute lung injury in an intensive care unit setting [20], 1 study in patients with chronic kidney disease [18], and 1 study in patients with various causes of hypoalbuminemia [2].

Two included RCTs were of parallel design [19,20] and the remaining 8 studies were of crossover design. Crossover and parallel RCTs had significant differences in included populations and primary aims, and thus, we evaluated their results separately. The 8 crossover studies had the mechanistic primary aim of delineating the mechanism of potentiated diuresis with albumin. Their patients were carefully selected after a roll-in period and an equilibrated state of hypervolemia was maintained in the experimental period (with intravenous or oral fluid repletion of volumes lost during diuresis) (Table E1). The 2 parallel studies were conducted in clinically decompensated patients requiring urgent diuresis.

Demonstrated resistance to diuretics was an inclusion criterion in only 1 of the 10 studies [2]. Furosemide was the single loop diuretic investigated (Table E1). The 8 crossover studies used a single time FUR-ALB, whereas the parallel studies randomized patients to titratable, sequential doses of diuretics and repeated, fixed-doses of albumin over the course of days [20] or weeks [19]. Among crossover studies, doses of furosemide ranged from 30 to 220 mg, and for albumin from 6 to 40 g (Fig. 2). The furosemide-albumin solutions were administered as a premixed solution in 3 studies.

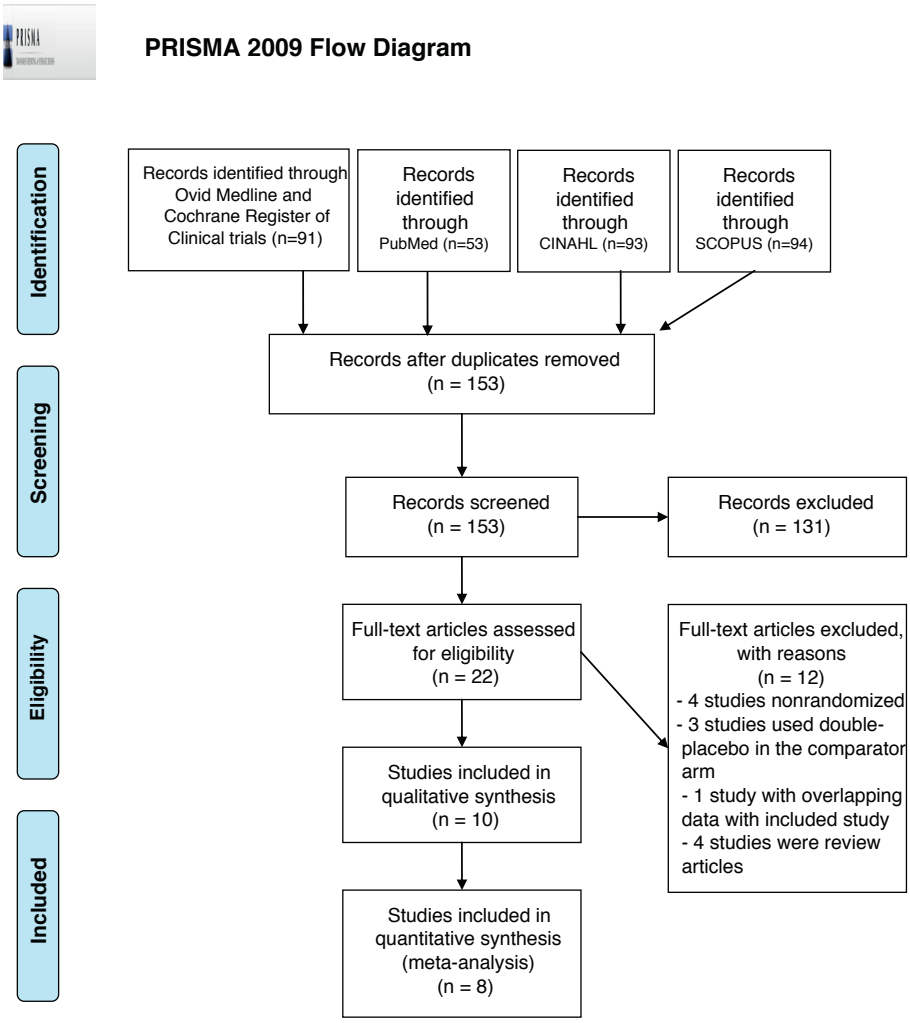


**Fig. 1.** Flowchart of study selection.

The results of individual studies for all outcomes recorded are shown in Table E2 Crossover studies examined only surrogate and intermediate outcomes.

### 3.3. Evidence synthesis

#### 3.3.1. Crossover studies

*3.3.1.1. Surrogate outcomes.* The results of meta-analyses for the incremental urinary volume excretion at ≤8 hours and 24 hours are shown in Table 2 and Fig. 2 and 3. A statistically significant increase in urinary volume at ≤8 hours in favor of FUR-ALB was noted in the main analysis (net difference = 231.0 mL [95% CI 135.6-326.5]) and the nephrotic syndrome subgroup (378.4 mL [103.4-653.4]), without any statistical heterogeneity. At 24 h, there was no statistically significant difference between FUR-ALB and furosemide alone in the main analysis (Fig. 3); a statistically significant difference in favor of FUR-ALB was found in the nephrotic syndrome subgroup with a magnitude of urinary volume though similar to the one observed at ≤8 hours (420.5 mL [120.8-720.2]). Since the differences in results between ≤8 and 24 hours could reflect differences in the included studies at these 2 time-points rather than true biological differences, we conducted a sensitivity meta-analysis by including studies reporting both time points: again, no significant results at 24 hours were found (data not shown). By meta-regression analyses, no significant effects of the dose of albumin or furosemide on the urinary volumes excreted were detected ($P$ for interaction >.10).

For the outcome of urinary Na excretion, a statistically significant difference favoring co-administration was found in the main analysis with an extra 15.9 mEq of Na excreted at ≤8 hours (95% CI 4.9-26.8), without statistical heterogeneity (Table 2 and Fig. E1). No significant differences were found for the incremental urinary Na excretion at 24 hours. Meta-regression analyses did not show any statistically significant effect modification by the dose of albumin or furosemide used ($P$ for interaction >0.10).

*3.3.1.2. Intermediate outcomes.* We conducted a series of meta-analyses with the transformed effect sizes Cohen's D for several pharmacokinetic and hemodynamic parameters (Table E3). No statistically significant effects of FUR-ALB were found in pharmacokinetic parameters of furosemide (amount excreted in urine at ≤8 hours or 24 hours, area-under-the-curve concentration, volume of

**Table 1**
Descriptive characteristics of study designs and populations included

| First author, Year, Country | Study design (N of arms) | N of patients (% male) | Mean age (SD) | Index disease | Presence of edema | SBP mmHg (mean (SD) or range) | Serum albumin (mg/dl) (mean (SD) or range) | Serum Creatinine (mg/dl) (mean (SD) or range) | 24 h Urine protein at baseline (g/d) (mean (SD) or range) | Urine Na at baseline (mEq) (mean (SD) or range) |
|---|---|---|---|---|---|---|---|---|---|---|
| Phakdeekitcharoen, 2012, [18] Thailand | Crossover (2) | 24 (465) | 66.4 (12.8) | CKD with hypoalbuminemia | Y | 131.5 (6.2) | 3.0 (0.3) | 2.2 (0.8) | 0.6* (0.0-3.1) | 16.6 (15.7) |
| Ghafari, 2011, [16] Iran | Crossover (2) | 10 (NR) | NR | Nephrotic syndrome | Y | NR | NR (<3.5) | NR | NR (>3.5) | NR |
| Chalasani, 2001, [17] USA | Crossover (3) | 13 (854) | 51.2 (8.1) | Cirrhosis, requiring diuretics | NR | NR | 3.0 (0.6) | 1.0 (0.2) | (< 0.1) | 21.6 (17.7) |
| Na, 2001, [12] Korea | Crossover (2) | 7 (865) | 41.0 (23.0) | Nephrotic syndrome with primary renal disease | Y | NR | 1.7 (0.2) | 1.6 (0.8) | 12.0 (4.0) | 19.4 (7.6) |
| Fliser, 1999, [14] Germany | Crossover (2) | 9 (66) | 48.0 (4.0) | Nephrotic syndrome with primary renal disease | Y | MAP 100.0 (2.0) | NR | < 1.3, except one patient | 12.3 (1.3) | NR |
| Akcicek, 1995, [15] Turkey | Crossover (2) | 8 (NR) | NR | Nephrotic syndrome | Y | 100-140 | 1.1-2.2 | 1.2-2.4 | NR (>3.5) | 13.5 (11.5) |
| Sjostrom, 1989, [13] Sweden | Crossover (2) | 5 (80) | 48.0 (14.0) | Nephrotic syndrome | Y | NR | 2.7 (0.5) | NR | 8.8 (5.0) | NR |
| Inoue, 1987, [2] Japan | Crossover (2) | 20 (632) | 64.6 (15.1) | Hypoalbuminemia of various etiologies | NR | NR | 2.2 (0.7) | NR | NR | NR |
| Martin, 2005, [20] USA | Parallel (2) | 40 (487) | 47.7 (19.8) | ALI/ARDS with mechanical ventilation and hypoproteinemia | NR | NR | 1.7 (0.4) | 1.0 (0.6) | NR | NR |
| Gentilini, 1999, [19] Italy (a) | Parallel (2) – Protocol 1 (inpatient) | 126 (53) | 62.3 (1.3) | Cirrhosis with ascites | Y | MAP 96.1 (1.2) | 3.1 (0.8) | 1.0 (0.0) | NR | 21.6 (1.4) |
| Gentilini, 1999, [19] Italy (b) | Parallel (2) – Protocol 2 (outpatient) | 81 (NR) | NR | Cirrhosis, after successful mobilization of ascites in protocol 1 | N | NR | NR | NR | NR | NR |

NR, non-reported; NA, non-applicable; MAP, mean arterial pressure; ALI/ARDS, acute lung injury/acute respiratory distress syndrome; SD, standard deviation; CKD, chronic kidney disease.
* Median.

distribution, plasma clearance or half-life elimination) or hemodynamic parameters (change in glomerular filtration rate or effective renal plasma flow). Thus, the available data did not provide any quantitative evidence in support of specific physiologic mechanisms for the presumed effects of albumin in humans.

### 3.3.2. Parallel studies

Two parallel studies were analyzed and their interventions and findings are provided in Tables E1 and E2. In a study with patients with cirrhosis and ascites [19], incremental doses of diuretics with daily dosing of 12.5gr of albumin resulted in higher rates of treatment response (defined as weight loss >2.5 kg and/or resolution of ascites), compared to diuretics alone (odds ratio [OR] = 3.23 [1.17-8.92]). Patients receiving albumin had also shorter stays of hospitalization ($P < .05$). In a follow-up phase after discharge from the hospital and continuation of diuretics with and without weekly administration of albumin (25 g), albumin significantly reduced the odds of ascites recurrence and rehospitalization but there was no effect on mortality.

In the another study [20] with mechanically ventilated patients with acute lung injury (corresponding to mild acute respiratory distress syndrome per current criteria [21]) and hypoproteinemia, FUR-ALB showed improvement for a surrogate outcome of improvement in oxygenation ($Pao_2/Fio_2$ ratio, difference of 67 mmHg, $P < .05$). A statistically significant effect in the clinical outcome of shock-free days was observed, but no significant effects were found for the remaining clinical outcomes (time to successful extubation, ventilator-free days and 30 day mortality).

*3.3.2.1. Risk of bias assessment.* Results of the risk of bias assessment are shown in Fig. E2. In summary, crossover studies appear to be exposed to potentially high risk of bias, given almost universal lack of allocation concealment and blinding, which could affect the choice of

**Table 2**
Meta-analysis results for the outcomes of urinary volume and urinary Na excretion at 8 and 24 hours for the main analysis and the nephrotic syndrome patients subgroup

| Outcome | Main analysis | | Nephrotic syndrome subgroup | |
|---|---|---|---|---|
| | Summary Difference (95% CI), N of studies | Heterogeneity ($I^2$, $p_Q$) | Summary Difference (95% CI), N of studies | Heterogeneity ($I^2$, $p_Q$) |
| Urinary volume <8 h (mL) | **231.0** (**135.5-326.5**), **n = 6** | $I^2 = 0$, $P = .53$ | **378.4** (**103.4-653.4**), **n = 3** | $I^2 = 0$, $P = .39$ |
| Urinary volume 24 h (mL) | 267.6 (-11.8-547.1), n = 4 | $I^2 = 365$, $P = .21$ | **420.5** (**120.8-720.2**), **n = 3** | $I^2 = 0$, $P = .58$ |
| Urinary Na <8 h (mEq) | **15.9** (**4.9-26.8**), **n = 5** | $I^2 = 0$, $P = .66$ | 24.2 (-13.4-61.8), n = 3 | $I^2 = 4$, $P = .35$ |
| Urinary Na 24 h (mEq) | 23.4 (-13.0-59.9), n = 4 | $I^2 = 84$, $P = .003$ | 34.9 (-3.9-73.9), n = 3 | $I^2 = 410$, $P = .18$ |

Statistically significant results are shown in bold.
Abbreviations: CI, confidence interval; $P_Q$, p-value for heterogeneity.

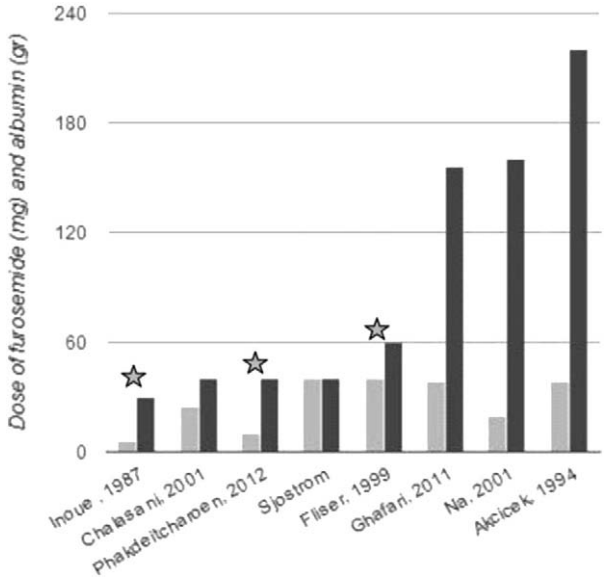


**Fig. 2.** Doses of albumin (light grey) and furosemide (dark grey) used in 8 crossover studies. Studies with statistically significant results for the outcome of urinary volume are highlighted with a grey asterisk.

treatment order and concurrent interventions. Of the two parallel studies, one was deemed of high [19] and one of low risk of bias [20].

## 4. Discussion

In this review, we quantitatively synthesized for the first time the totality of randomized evidence on FUR-ALB in patients with hypoalbuminemia. Although included studies were clinically heterogeneous (in terms of populations and interventions) and such heterogeneity may also exist in their treatment effects, we aimed to quantify the average treatment effect of FUR-ALB via random-effects model meta-analysis that accounts for such heterogeneity. By meta-analysis, FUR-ALB resulted in a statistically significant incremental volume of 231 mL of urine produced at 8 hours, but this effect was no longer significant at 24 hours, indicating that this effect was transient and a single dose of albumin did not result in different fluid balance at the end of the day. A similar pattern of results was observed for the outcome of natriuresis. Furthermore, no significant effects were found by meta-analyses for a series of intermediate outcomes for the pharmacokinetics of furosemide or hemodynamic parameters.

The clinical relevance of the detected effects of FUR-ALB remains unclear. Although we did not define any a priori categories for clinically significant amounts of diuresis and natriuresis, the magnitude of the statistically significant effects we found (increments of 231 mL of urine and 15.9 mEq of Na excreted) seems small to dictate incorporation of FUR-ALB in routine clinical practice. The generalizability of these findings is also limited, given the fact that these estimates stem from crossover studies in which the patients were maintained in stable, controlled conditions of hypervolemia to allow the crossover nature of the comparisons. Of note, in several of these studies, the patients had not received any diuretics for days prior to the experimental protocol (Table E1). Extrapolating such experimental findings to the management of real-world, clinically decompensated patients with hypervolemia and diuretic resistance is elusive. In fact, a recent observational study in failed to show any significant results in favor of albumin [22].

The doses of furosemide and albumin utilized by individual studies were remarkably variable (Fig. 2). Although our meta-regression analyses failed to demonstrate any significant effect modification by dose of furosemide used, such analyses are unfortunately underpowered when numbers of studies are small. We noted though that among studies that utilized more than 100 mg of furosemide, no significant findings were reported (Fig. 2 and Table E3). Significant effects were detected only by studies utilizing small—and indeed far from maximal—doses of furosemide. Consequently, available evidence does not provide any indication that albumin may actually enhance diuresis in patients on already maximal doses of diuretics, which is nonetheless the case when the "clinical call" of diuretic resistance is made. Any potential role for albumin may be limited in the specific case of submaximal doses of furosemide, when further furosemide uptitration is not desirable.

Furthermore, the extent of diuretic resistance may depend upon the degree of hypoalbuminemia, which in itself may act as an important effect modifier on FUR-ALB. Theoretically, it would thus be appealing to formally examine such interactions with meta-regression analyses based on the baseline serum albumin concentrations in each study. However, such analyses were not pursued: first, baseline serum albumin concentrations were not reported by all studies leading to an underpowered sample (Table 1), and second, such study-level analyses are prone to ecological bias and can lead to misleading results [23], when patient-level information is not available and informative variability is missing.

Subgroup meta-analyses for patients with nephrotic syndrome demonstrated statistically significant increases in urinary volume at both time points, with an absolute magnitude larger than the main analysis (i.e. an incremental volume of 421 mL by 24 hours). No significant effects on natriuresis were found. Prior physiological hypotheses stated that albumin could be counterproductive in such patients, given that pathologic albuminuria would result in excessive albumin in the renal tubules capturing the unbound and biologically active furosemide [17]. Our meta-analysis results support the presence of a beneficial biologic effect of albumin on increasing the volume diuresed with furosemide, compared to furosemide alone. The authors of a primary study that detected a significant effect of similar magnitude to our meta-analytic summary conceded that such effects are modest, of limited clinical significance, and that increasing the dose of diuretics would be a more sensible first step instead of administering albumin [17]. Nonetheless, results from both our meta-analysis and from the component studies suggest that a biological effect of at least modest clinical significance is present in the subgroup of patients with nephrotic syndrome, and thus future studies should primarily focus on this patient population.

Our meta-analyses for pharmacokinetic and hemodynamic outcomes raise further questions about the mechanisms mediating the effects of albumin. The ubiquitous absence of statistical significance in all outcomes examined was unexpected and leaves unanswered questions about which mechanisms operate in humans. Although the seminal study by Inoue et al. [2] demonstrated a convincing increase in furosemide excretion in analbuminemic rats and concurrently confirmed that in humans, subsequent studies failed to show such an effect [12-14,17] and the cumulative evidence does not support any detectable change in the pharmacokinetics of furosemide. On the other hand, other studies supported hemodynamic changes mediating the benefits of albumin, via increases in the glomerular filtration rate and the effective renal plasma flow [14,16]; however, by meta-analysis, no significant effects were found. Thus, the pathophysiologic mechanisms of diuresis enhancement with albumin remain elusive, and any clinical use of albumin on the basis of pathophysiologic rationale seems unjustified.

The evidence supporting FUR-ALB on clinical outcomes comes mainly from 2 parallel RCTs. A large scale study in patients with cirrhosis [19] showed strong effects of FUR-ALB in ascites resolution and rehospitalizations but its internal validity is questionable, since such effects were derived only from a subgroup of responders from the initial randomized sample, and its applicability is limited, given a cumbersome protocol requiring repeated albumin infusions. The other parallel study in an intensive care unit setting showed

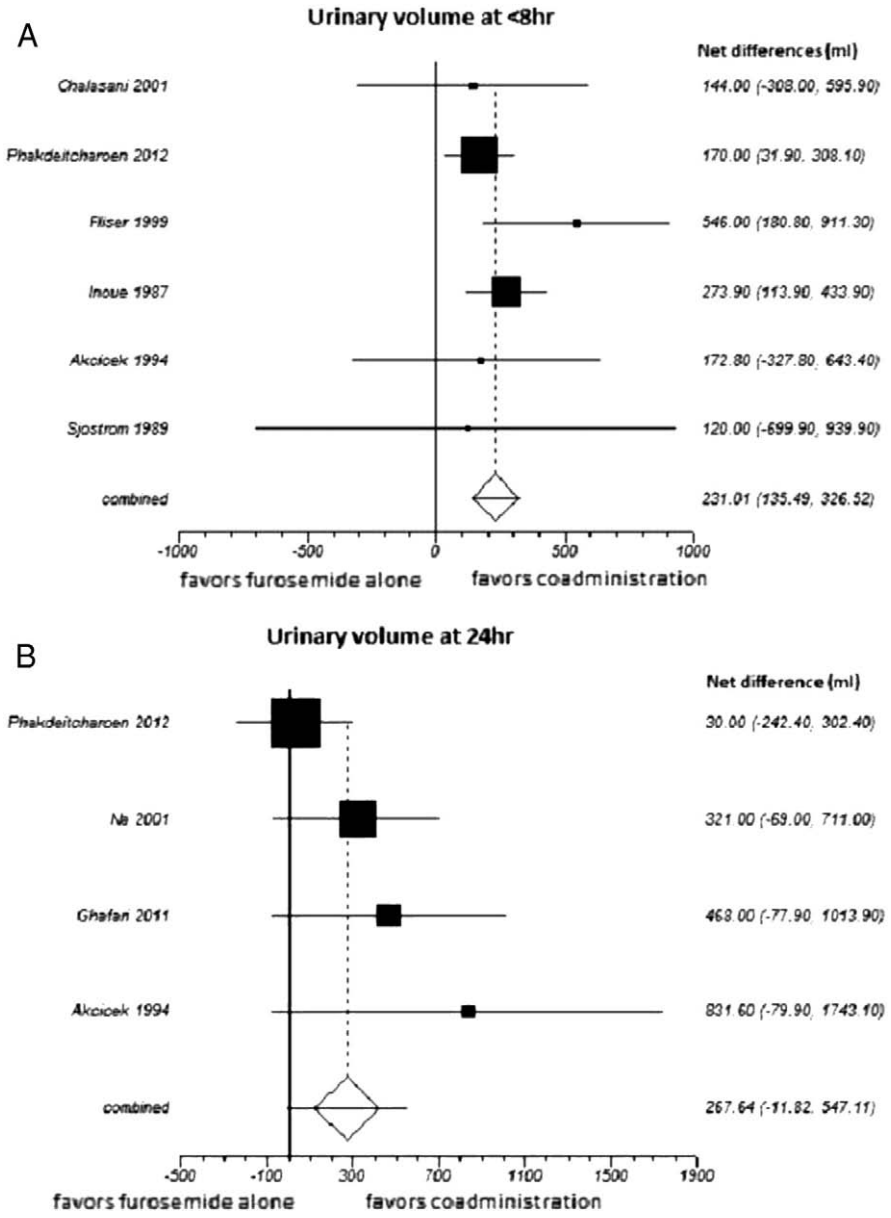


**Fig. 3.** Forest plots for the meta-analysis of the outcomes of Urinary volume at <8 hours (plot A) and at 24 hours (plot B).

promising results for an oxygenation surrogate outcome, but no significant effects on clinical endpoints such as mortality or critical care length of stay [20]. The authors considered that the beneficial in oxygenation effects of albumin could not be totally accounted by diuretic-induced changes in fluid balances, and thus, specific biochemical attributes of albumin may be at play. Thus, any benefit of albumin in such patients remains to be replicated.

Limitations of our review inevitably reflect limitations of included studies, and any type of quantitative evidence synthesis cannot overcome drawbacks of the component building blocks of evidence. Numbers of included studies were small, and thus, regression based techniques for the detection and explanation of statistical heterogeneity were underpowered. Additionally, remarkable variability in interventions and populations studied can also make interpretation of meta-analytic summaries counterintuitive. We aimed to estimate an average treatment effect of FUR-ALB under a random-effects model that allows for a distribution of effects across studies and thus, summaries estimated here, although may not apply to individual patients, should be still viewed as best estimates produced by available evidence. Our review did not consider observational studies that can inform on the pragmatic effectiveness of interventions [24]. We focused on RCTs only because the efficacy of the FUR-ALB intervention has not been established and we aimed to draw inferences from evidence free from confounding bias. Most papers were published before the widespread endorsement of guidelines for publication of RCTs [25], and so, major deficiencies in reporting in several studies limited a robust evaluation for their risk of bias. Finally, no study explored the effects of other loop diuretics, and no inferences on the effects of albumin across the class of loop diuretics can be drawn. Experimental data on bumetanide for example have shown that despite its high protein binding (~97%), bumetanide urine excretion is not dependent on serum albumin concentrations (possibly due to high globulin binding) [26] and thus albumin-bumetanide interactions may not be biologically plausible [27].

In summary, the cumulative evidence analyzed here does not provide any justification for routine adoption of FUR-ALB to overcome diuretic resistance in hypoalbuminemic patients. Statistically significant diuretic and natriuretic effects were transient, and of limited clinical significance and generalizability. On pathophysiological grounds, our meta-analyses highlighted the fact that the presumed

mechanisms of albumin diuresis enhancement remain undefined. Based on these findings, future research should be directed towards answering the critical clinical question at hand, that is, whether albumin can offer any benefit in patients on submaximal doses of diuretics as opposed to diuretic dose maximization or consideration of an alternative loop diuretic (ie, bumetanide). Pragmatic, large-scale RCTs in this setting seem both feasible (given the commonality of this condition) and ethically justified (since no clinical benefit of albumin has been demonstrated). Until more high-quality randomized evidence becomes available, utilizing albumin infusions cannot be considered as a best evidence-based practice.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcrc.2013.10.004.

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