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READY: relative efficacy of loop diuretics in patients with chronic systolic heart failure—a systematic review and network meta-analysis of randomised trials

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Abstract

The majority of patients with chronic heart failure (HF) receive long-term treatment with loop diuretics. The comparative effectiveness of different loop diuretics is unknown. We searched PubMed, clinicaltrials.gov, the Cochrane Central Register of Controlled Trials and the European Union Clinical Trials Register for randomised clinical trials exploring the efficacy of the loop diuretics azosemide, bumetanide, furosemide or torasemide in patients with HF. Comparators included placebo, standard medical care or any other active treatment. The primary endpoint was all-cause mortality. Secondary endpoints included cardiovascular mortality, HF-related hospitalisation and any combined endpoint thereof. Hypokalaemia and acute renal failure were defined as additional safety endpoints. Evidence was synthesised using network meta-analysis (NMA). Thirty-four trials reporting on 2647 patients were included. The overall quality of evidence was rated as moderate. NMA demonstrated no significant differences between loop diuretics with respect to all-cause mortality, cardiovascular mortality or hypokalaemia. In contrast, torasemide ranked best in terms of HF hospitalisation, and there was a trend towards benefits with torasemide with regard to occurrence of acute renal failure. Sensitivity analyses excluding trials with a follow-up < 6 months, trials with a cross-over design and those including < 25 patients confirmed the main results. We found no significant superiority of either loop diuretic with respect to mortality and safety endpoints. However, clinicians may prefer torasemide, as it was associated with fewer HF-related hospitalisations.

Keywords Heart failure · Loop diuretics · Mortality · Prognosis · Network meta-analysis

Introduction

Guidelines recommend the use of diuretics to reduce the signs and symptoms of congestion in patients with heart failure (HF) [61]. In daily clinical practice, the majority of HF patients receive long-term treatment with a loop diuretic, since they produce symptomatic benefits more rapidly than any other drugs for HF [1, 24, 35, 55]. In addition, a Cochrane meta-analysis of 14 small trials concluded that diuretics reduce the risk of death and worsening HF [17]. The review, however, included various types of diuretics, and the evidence was based on only 15 deaths in 221 participants [17]. As data from retrospective analyses [46, 47] and observational studies [11] suggest that available loop diuretics differ in their effects on disease progression and prognosis, we performed a network meta-analysis (NMA) of all relevant randomised clinical trials to comprehensively compare the efficacy of loop diuretics in the treatment of patients with HF.

Methods

We performed the present review following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension statement for reporting systematic reviews incorporating NMAs of health care interventions [32, 49, 50, 69].

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Identification and selection of studies

We searched electronic databases (PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), European Union Clinical Trials Register) and websites (www.clinicaltrials.gov) up to 1 April 2017 using the following search terms: furosemid*, frusemid*, lasix, bumetanid*, burinex, piretanid*, azosemid*, torasemid*, torsemid*, loop diuretic*, heart failure. The PubMed search strategy is provided in the Supplemental Material (Table 1). Two reviewers independently screened citations against the following predefined selection criteria.

Study design: Prospective randomised trials with either parallel-group or cross-over design were included. There were no restrictions regarding date of publication, language or sample size.

Population: We included *s*tudies evaluating adults (≥ 18 years) with a diagnosis of chronic HF and treatment with loop diuretics for at least 4 weeks. There were no restrictions regarding sex, age, race, ejection fraction, New York Heart Association (NYHA) functional class or dose of loop diuretics. Both in-hospital and outpatients were included.

Interventions: Treatment with either azosemide, bumetanide, furosemide, piretanide or torasemide for at least 4 weeks

Comparators: Placebo, standard medical treatment or any other active treatment

Outcomes: The primary outcome was all-cause mortality. Secondary outcomes included cardiovascular mortality, HF-related hospitalisation and any combined endpoint thereof. Hypokalaemia (defined as a serum potassium concentration < 3.5 mmol/l) and acute renal failure (following the risk, injury, failure, loss of kidney function and end-stage kidney disease (RIFLE) criteria [39]) were analysed as additional safety endpoints.

Data extraction and quality assessment

All relevant articles were independently reviewed by two investigators to assess the eligibility of the article and abstract with standardised data abstraction forms, and disagreement was resolved by a third investigator. For each included study, details were extracted on study design, patient characteristics, interventions and outcomes. The quality of included trials was assessed using the Cochrane Collaboration Criteria [28].

Statistical analyses

This NMA was conducted with Stata software 15.0 (StataCorp, College Station, TX, USA) using the network family of commands [8, 29]. A random effects model was applied. The NMA was performed to obtain estimates for outcomes of primary and secondary endpoints, presented as relative risks (RR)/95% confidence intervals (CIs) for binary outcomes or weighted mean differences (WMD)/95% CI for continuous variables. The plot of a network of drugs was a visual representation of the evidence base and offered a concise description of its characteristics. It consisted of nodes representing the drugs being compared and edges representing the available direct comparisons (comparisons evaluated in at least one study) between pairs of drugs [8, 64, 65]. The quality of treatment effect estimates was rated following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [62, 67]. In order to make the rank of treatments, we used the surface under the cumulative ranking probabilities (SUCRA) [66]. To check for a publication bias, we designed a funnel plot [8]. To test the stability of the results, we performed sensitivity analyses by excluding studies with a follow-up duration < 6 months, a cross-over design, and studies including < 25 patients. All p values were two-tailed with the statistical significance set at < 0.05.

Results

Literature search

The search strategy yielded 34 eligible trials totalling 2647 patients (Fig. 1) [3, 4, 12, 18–23, 30, 31, 34, 36–38, 40–43, 45, 48, 51–54, 57, 58, 63, 70, 75, 79, 81, 83]. Agreement between reviewers was excellent ($\kappa = 0.881$, 95% CI 0.720–

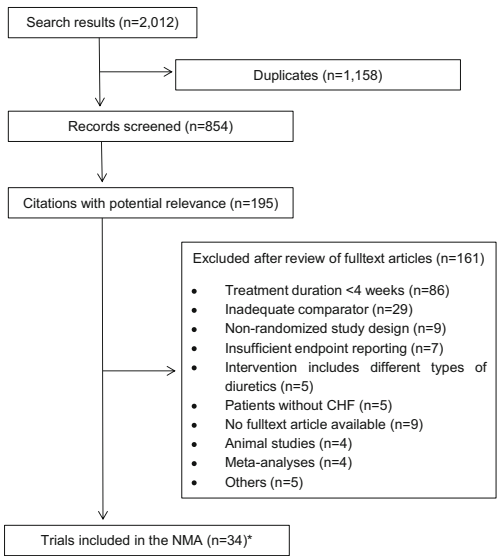

Fig. 1 Flow chart of study identification and selection. CHF, chronic heart failure; NMA, network meta-analysis. *Two records reported results from two trials. Therefore, the number of included records is n = 32, while the number of included trials is n = 34

1.000). A total of 19 trials compared two different loop diuretics, whereas 12 trials compared furosemide with other active treatments. Of these, 7 trials compared furosemide with thiazides. There was no trial exploring the use of piretanide. The corresponding network-plot detailing active treatment and endpoints reported is shown in Fig. 2.

Of the 34 trials, 26 were parallel-group trials, while 8 were designed as cross-over studies. Fourteen trials were multicentric, and 8 trials included 25 patients or less. All but two trials had a follow-up duration of less than 1 year. For study characteristics, please refer to Table 1. The inclusion and exclusion criteria varied slightly across the studies with respect to severity of HF (NYHA functional class), background HF treatment and comorbidities. For complete details, please refer to Supplemental Table 2.

Patient characteristics

Data on patient characteristics were incomplete for a number of studies. In studies providing baseline characteristics, patients were on average between 56 and 76 years old and mostly predominantly male. The mean LVEF varied between 31 and 51%. The majority of patients were in NYHA functional class II or III (Table 2). With respect to concomitant medication, 12 studies reported the fraction of patients that received any (dose of) beta-blockers or angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) (for details, see Table 3).

Risk of bias

The overall risk of bias was intermediate. With respect to the individual items of the risk of bias assessment (Supplemental Fig. 1), all studies provided adequate random sequence generation, whereas a significant number of studies had an open-label design and was thus subject to performance bias and detection bias. All-cause mortality could be retrieved for all but one trial. Few studies separately reported HF-related hospitalisation and many trials lacked information on safety endpoints. There could be seen no systematic association between type or size of the trial or the publication date and any pattern regarding missing endpoint information. The comparison adjusted funnel plot for all-cause mortality (Supplemental Fig. 2) was symmetrical, suggesting absence of small-study effects and publication bias.

Outcomes

For all endpoints and safety endpoints including the respective outcome numbers per trial arm, please refer to Supplemental Tables 3 and 4.

All-cause mortality

The NMA suggests equal efficacy of azosemide, bumetanide, furosemide and torasemide regarding the primary endpoint all-cause mortality (Fig. 3a). However, due to the small number of deaths reported in included studies ($n = 73$), this finding

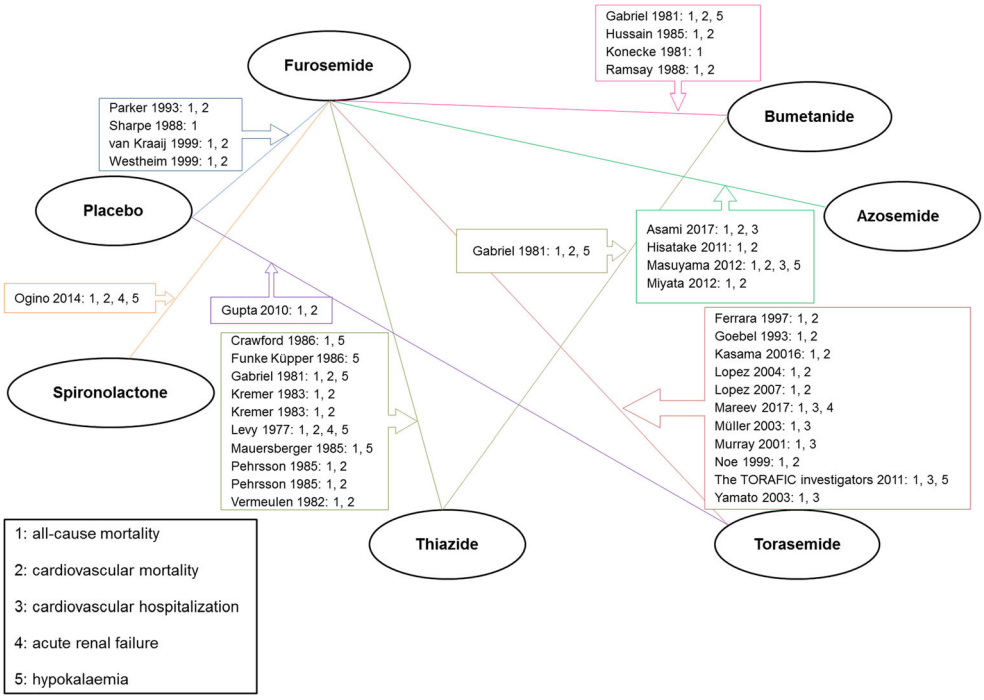

Fig. 2 Network meta-analysis scheme detailing active treatment and endpoints reported

Table 1 Baseline characteristics of included studies

Study	Publication year	Sponsor	Design	Number of centres	Number of patients	Follow-up (weeks[1])
Asami [4]	2017	Medtronic	Cross-over	1	21	27
Crawford [12]	1988	n.a.	Parallel-group	2	47	8
Ferrara [18]	1997	Menarini S.p.A., Firenze, Italy	Parallel-group	n.a.	40	4
Funke Küpper [19]	1986	n.a.	Cross-over	6	30	8
Gabriel [20]	1981	n.a.	Cross-over	1	18	13
Goebel [21]	1993	Boehringer Mannheim, Germany	Parallel-group	4	70	6
Gupta [23]	2010	Wythenshawe Heart Failure Clinic Internal Research Fund	Cross-over	1	30[2]	12
Hisatake [30]	2011	n.a.	Cross-over	1	22	26
Hussain [31]	1985	Napp Laboratories	Cross-over	1	14	8
Kasama [34]	2006	n.a.	Parallel-group	1	44	26
Konecke [36]	1981	n.a.	Parallel-group	1	42	24
Kremer [37]	1983	n.a.	Parallel-group	1	32	10
Kremer [37]	1983	n.a.	Parallel-group	1	58	10
Levy [38]	1977	n.a.	Parallel-group	1	33[3]	16
Lopez [40]	2004	n.a.	Parallel-group	1	39	35
Lopez [41]	2007	n.a.	Parallel-group	1	22	35
Mareev [42]	2017	n.a.	Parallel-group	30	470	26
Masuyama [43]	2012	Ministry of Health, Labor and Welfare, Japan; Japan Heart Foundation	Parallel-group	15	320	141
Mauersberger [45]	1985	n.a.	Cross-over	1	24	4
Miyata [48]	2012	n.a.	Parallel-group	16	98	13
Müller [51]	2003	Roche Pharmaceuticals Switzerland, Reinach, Switzerland	Parallel-group	57	39	237
Murray [52]	2001	NIHR01 DK37993, R01 AG07631, and Roche Laboratories, Nutley, New Jersey	Parallel-group	2	52	234
Noe [53]	1999	Boehringer Mannheim, Germany	Parallel-group	5	140	26
Ogino [54]	2014	Ministry of Education, Culture, Sports, Science and Technology; Tottori University, and Gout Research Foundation	Cross-over	1	16	16
Parker [57]	1993	Zambon Laboratories, Rutherford, New Jersey	Parallel-group	25	78	8
Pehrsson [58]	1985	n.a.	Parallel-group	n.a.	50	12
Pehrsson [58]	1985	n.a.	Parallel-group	n.a.	40	12
Ramsay [63]	1988	n.a.	Parallel-group	1	40	8
Sharpe [70]	1988	n.a.	Parallel-group	1	40	52
The TORAFIC investigators [22]	2011	Ferrer internacional SA, Barcelona, Spain	Parallel-group	25	155	32
van Kraaij [75]	1999	Netherlands Program for Research on Aging (NESTOR), funded by the Ministry of Education, Culture and Science and the Ministry of Health, Welfare, and Sports	Parallel-group	1	20	13
Vermeulen [79]	1982	Hoechst AG, Frankfurt, Germany	Parallel-group	1	41	6
Westheim [81]	1999	n.a.	Parallel-group	3	32	6
Yamato [83]	2003	n.a.	Parallel-group	1	50	26

[1] Per treatment arm

[2] The study included 30 patients; however, a per-protocol analyses was performed including only 28 patients

[3] The study included 33 patients; however, a per-protocol analyses was performed including only 32 patients

should be interpreted with caution. The corresponding forest plots of the pooled treatments effects are shown in Fig. 3b. SUCRA values are presented in Table 4. The graphical ranking based on the SUCRA values is shown in Fig. 3c.

Secondary outcomes

Results for cardiovascular mortality and hypokalaemia mirror the main analysis for the primary outcome (all-cause mortality). When compared to furosemide, torasemide treatment significantly reduced HF-related hospitalisations by 60%. In addition, there was a non-significant trend towards benefits with torasemide in terms of acute renal failure. Detailed results are provided in Fig. 4a–d and Table 4.

Pharmacokinetics

Even though there are no significant differences in treatment between the different kinds of loop diuretics, a range of

Table 2 Baseline characteristics of patients

Study	Age (years)	Male (*n*, %)	LVEF (%)	NYHA (*n*, %)		Mean NYHA
				I/II	III/IV	
Asami [4]	72.5 ± 8.9	18 (85.7)	32.2 ± 10.0	15 (71.4)	6 (28.6)	2.2
Crawford [12]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Ferrara [18]	62.9 ± 9.3	27 (67.5)	36.1	15 (37.5)	25 (62.5)	2.6
Funke Küpper [19]	n.a.	25 (83.3)	n.a.	23 (76.7)	7 (23.3)	2.2
Gabriel [20]	71	13 (72.2)	n.a.	n.a.	n.a.	n.a.
Goebel [21]	62.6	34 (48.6)	n.a.	n.a.	n.a.	n.a.
Gupta [23][1]	59.1	25 (89.3)	n.a.	27 (96.4)	1 (3.6)	1.8
Hisatake [30]	n.a.	17 (77.3)	n.a.	15 (68.2)	7 (31.8)	2.3
Hussain [31]	62.5	7 (50.0)	n.a.	n.a.	n.a.	n.a.
Kasama [34][1]	68.0	29 (72.5)	31 ± 7	15 (37.5)	25 (62.5)	2.6
Konecke [36]	62.6	26 (61.9)	n.a.	n.a.	n.a.	n.a.
Kremer [37]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Kremer [37]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Levy [38][1]	n.a.	11 (34.4)	n.a.	26 (81.3)	6 (18.7)	2.1
Lopez [40][1]	63 ± 3	28 (87.5)	39	13 (36.1)	23 (63.9)	2.7
Lopez [41]	64	17 (77.3)	38	7 (31.8)	15 (68.2)	2.8
Mareev [42]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Masuyama [43]	71 ± 11	195 (60.9)	51	285 (89.1)	35 (10.9)	2.1
Mauersberger [45]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Miyata [48][1]	75.7	51 (52.6)	59	92 (94.8)	5 (5.2)	1.8
Müller [51][1]	74	102 (43.0)	n.a.	131 (52.3)	106 (44.7)	2.5
Murray [52]	64.1	111 (47.4)	n.a.	n.a.	n.a.	n.a.
Noe [53]	75.1	133 (95.0)	n.a.	n.a.	n.a.	2.3
Ogino [54]	63 ± 4	15 (93.8)	34.4	9 (56.3)	7 (43.7)	2.4
Parker [57]	57	64 (82.1)	n.a.	78 (100)	0 (0.0)	1.5
Pehrsson [58][1]	65	27 (57.4)	n.a.	45 (95.7)	2 (4.3)	2.0
Pehrsson [58]*	64	24 (61.5)	n.a.	39 (100)	0 (0.0)	2.0
Ramsay [63]	n.a.	9 (22.5)	n.a.	n.a.	n.a.	n.a.
Sharpe [70]	55	37 (92.5)	39	n.a.	n.a.	n.a.
The TORAFIC investigators [22]	69	90 (58.1)	n.a.	144 (92.9)	11 (7.1)	2.1
van Kraaij [75]	75 ± 1	11 (55.0)	n.a.	n.a.	n.a.	n.a.
Vermeulen [79][1]	61	n.a.	n.a.	27 (71.1)	11 (28.9)	2.1
Westheim [81]	63	29 (90.6)	n.a.	32 (100)	0 (0.0)	1.4
Yamato [83]	65	29 (58.0)	40	17 (34.0)	33 (66.0)	2.7

LVEF, left ventricular ejection fraction; *n.a.*, not available; *NYHA*, New York Heart Association functional class. [1] Baseline characteristics refer to patients who finished the study

variations of the pharmacokinetics among these medications are exists. The detailed description is shown in Table 5.

Sensitivity analyses

Sensitivity analysis of estimated summary effects with regard to all-cause mortality excluding studies with less than 25 patients per treatment arm, studies with cross-over design and those with less than 6 months of follow-up confirmed the base case analysis (results not shown).

Discussion

Diuretics are a mainstay of treatment both in chronic and in acute HF. Although controlled trials have demonstrated the ability of diuretics to decrease physical signs of fluid retention

Table 3 Medication characteristics of included studies

Study	Active treatment	Dose (mg/d)*	Comparator no. 1	Dose (mg/d)*	Comparator no. 2	Dose (mg/d)*	Beta-blockers (*n*, %)	ACE inhibitors/ ARBs (*n*, %)
Asami [4]	Azosemide	n.a.	Furosemide	n.a.			81	n.a.
Crawford [12]	Furosemide (+ amiloride)	40 (+ 5)–1-20 (+ 15)	Cyclopenthiazide (+ potassium chloride)	0.5 (+ 1200)–1.-5 (+ 3600)			n.a.	n.a.
Ferrara [18]	Torasemide	10	Furosemide	25			n.a.	n.a.
Funke Küpper [19]	Furosemide (+ triamterene)	48 (+ 60)	Hydrochlorothiazide (+triamterene)	30 (+ 60)			n.a.	n.a.
Gabriel [20]	Bendrofluazide	5	Bumetanide	1	Furosemide	40	n.a.	n.a.
Goebel [21]	Torasemide	n.a.	Furosemide	n.a.			n.a.	n.a.
Gupta [23][1]	Torasemide	5	Placebo	5			96	100
Hisatake [30]	Azosemide	30–60	Furosemide	20–40			45	91
Hussain [31]	Bumetanide	1.07 ± 0.26	Furosemide	42.9 ± 10.3			n.a.	n.a.
Kasama [34][1]	Torasemide	6.8 ± 1.9	Furosemide	33 ± 9.8			n.a.	100
Konecke [36]	Bumetanide	n.a.	Furosemide	n.a.			n.a.	n.a.
Kremer [37]	Furosemide (+ potassium chloride)	40 (+ 750)	Hydrochlorothiazide (+ amiloride)	50 (+ 5)			n.a.	n.a.
Kremer [37]	Furosemide (+ potassium chloride)	80 (+ 1500)	Hydrochlorothiazide (+ amiloride)	100 (+ 10)			n.a.	n.a.
Levy [38][1]	Furosemide	40–80	Spironolactone (+hydrochlorothiazide)	50 (+ 50)–100 (+ 100)			n.a.	n.a.
Lopez [40][1]	Torasemide	10.6 ± 0.9	Furosemide	32.2 ± 3.2			n.a.	n.a.
Lopez [41]	Torasemide	10.9 ± 0.6	Furosemide	34.5 ± 3.8			100	100
Mareev [42]	Torasemide	20	Furosemide	80			n.a.	n.a.
Masuyama [43]	Azosemide	30–120	Furosemide	20–80			51.9	70.6
Mauersberger [45]	Furosemide (+spironolactone)	40 (+ 100)	Butizide (+ spironolactone)	10 (+ 100)			n.a.	n.a.
Miyata [48][1]	Azosemide	39.9 ± 25.3	Furosemide	26.3 ± 10.5			18.6	97.9
Müller [51][1]	Torasemide	11.4 ± 11.8	Furosemide	40.0 ± 21.8			n.a.	n.a.
Murray [52]	Torasemide	72 ± 76	Furosemide	136 ± 122			20.5	78.7
Noe [53]	Torasemide	59	Furosemide	133			n.a.	n.a.
Ogino [54]	Spironolactone	25	Furosemide	20			50	100
Parker [57]	Furosemide	40	Placebo	n.a.			0	0
Pehrsson [58][1]	Furosemide (slow release)	60	Bendroflumethiazide	2.5			n.a.	n.a.
Pehrsson [58][1]	Furosemide (slow release)	30	Bendroflumethiazide	2.5			n.a.	n.a.
Ramsay [63]	Bumetanide	1–3 (1.1)	Furosemide	40–120 (70)			n.a.	n.a.
Sharpe [70]	Furosemide	40–80	Placebo	n.a.			n.a.	n.a.
The TORAFIC investigators [22]	Torasemide	10.9 ± 3.1	Furosemide	43.7 ± 11.7			43.2	48.4
van Kraaij [75]	Placebo (furosemide withdrawal)	n.a.	Furosemide	29 ± 11			10	25
Vermeulen [79][1]	Furosemide (slow release)	60	Hydrochlorothiazide	50			n.a.	n.a.
Westheim [81]	Furosemide	40	Placebo	n.a.			n.a.	n.a.
Yamato [83]	Torasemide	6.2 ± 2.0	Furosemide	32 ± 9.8			56	100

n.a., not available. [1] Depending on the information provided in the respective study, doses are presented as mean ± SD, dose range or fixed dose

and improve cardiac function in patients with congestive HF [9, 71, 82], there has been scant evidence regarding their long-term effects on disease progression and prognosis. On the one hand, a number of retrospective analyses reported that the use of diuretics was associated with increased mortality and hospitalisations [2, 13, 14, 16, 25, 59, 68]. The authors postulated that prescription of loop diuretics identifies patients with more advanced features of HF and congestion, which may account for their worse prognosis [59]. On the other hand, a Cochrane review of 14 prospective trials including 221

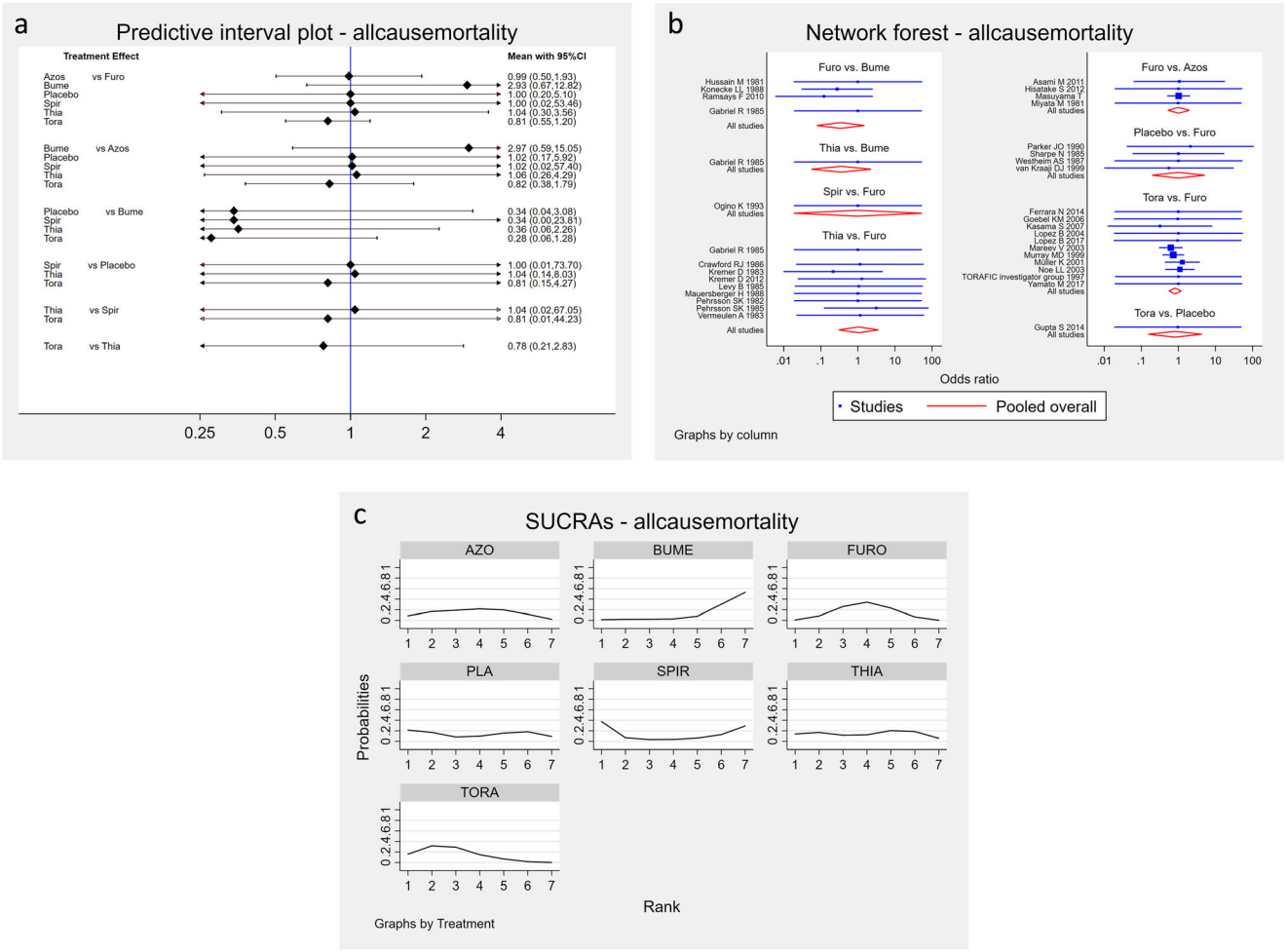

Fig. 3 **a** Network meta-analysis all-cause mortality. Azos, azosemide; Bume, bumetanide; CI, confidence interval; Furo, furosemide; Spir, spironolactone; Thia, thiazide; Tora, torasemide. **b** Forest plots of the pooled treatments effects (all-cause mortality). Azos, azosemide; Bume, bumetanide; Furo, furosemide; Spir, spironolactone; Thia, thiazide; Tora, torasemide. **c** Graphical ranking of diuretics based on SUCRA values (all-cause mortality). AZO, azosemide; BUME, bumetanide; FURO, furosemide; PLA, placebo; SPIR, spironolactone; SUCRA, surface under the cumulative ranking curve; THIA, thiazide; TORA, torasemide

Table 4 SUCRA values of endpoints

Endpoint	SUCRA azosemide	SUCRA bumetanide	SUCRA furosemide	SUCRA placebo	SUCRA spironolactone	SUCRA thiazide	SUCRA torasemide
All-cause mortality	0.54	0.14	0.51	0.55	0.52	0.53	0.71
CV mortality	0.69	0.17	0.45	0.52	0.51	0.46	0.69
HF hospitalisation	0.56	n.a	0.02	n.a.	n.a.	n.a.	0.93
Hypokalaemia	0.24	0.89	0.61	n.a.	0.54	0.42	0.31
Acute renal failure	n.a.	n.a.	0.29	n.a.	0.40	0.51	0.80

CV, cardiovascular; *HF*, heart failure; *n.a.*, not available; *SUCRA*, surface under the cumulative ranking curve

patients showed prognostic benefits from diuretic treatment [17]. The review, however, comprised various types of diuretics including spironolactone. As the main action of spironolactone is blockade of the mineralocorticoid receptor, prognostic benefits may result from aldosterone antagonism rather than from diuresis [60].

In the present NMA, none of the loop diuretics azosemide, bumetanide, furosemide or torasemide was superior to placebo with respect to all-cause or cardiovascular mortality. In addition, our analyses demonstrate equal efficacy of different loop diuretics with respect to mortality and safety endpoints. This contrasts to preclinical and clinical data which suggest beneficial pharmacological and disease-specific effects with long-acting loop diuretics such as torasemide as compared to short-acting furosemide [6, 7, 26, 27, 30, 34, 40, 44, 72, 73, 76–78, 80, 83]. In brief, there is evidence that torasemide reduces aldosterone production, myocardial fibrosis, sympathetic activation and ventricular remodelling [27, 30, 34, 44, 72, 73, 76, 80, 83]. A meta-analysis performed by Di Nicolantonio et al. reported a 14% reduction in all-cause mortality with torasemide compared to furosemide [15]. However, the meta-analysis included only 2 trials totalling 471 patients. In contrast, the comparison of furosemide against torasemide in the present NMA includes 11 trials totalling 1501 patients, and results were confirmed in sensitivity analyses. Our results are further supported by a meta-analysis published by Bikdeli et al. that showed no significant improvements in NYHA functional class or mortality with torasemide versus furosemide [5].

Then again, we found that torasemide was superior to furosemide in terms of HF-related hospitalisations. It is unclear why this benefit did not translate into improved survival with torasemide. Ideally, an adequately powered randomised controlled trial would investigate the prognostic effects of different loop diuretics. However, considering the required sample size and its associated costs, such a trial may never be done.

The use of diuretics in the management of chronic HF may be limited by hypokalaemia, which may predispose patients to serious arrhythmias. In addition, excessive use of diuretics can decrease blood pressure and severely impair renal function [10, 56]. Studies in rats suggest that torasemide produces less kaliuresis as compared to furosemide secondary to its anti-aldosteronic effects [74]. In the present NMA, however, no

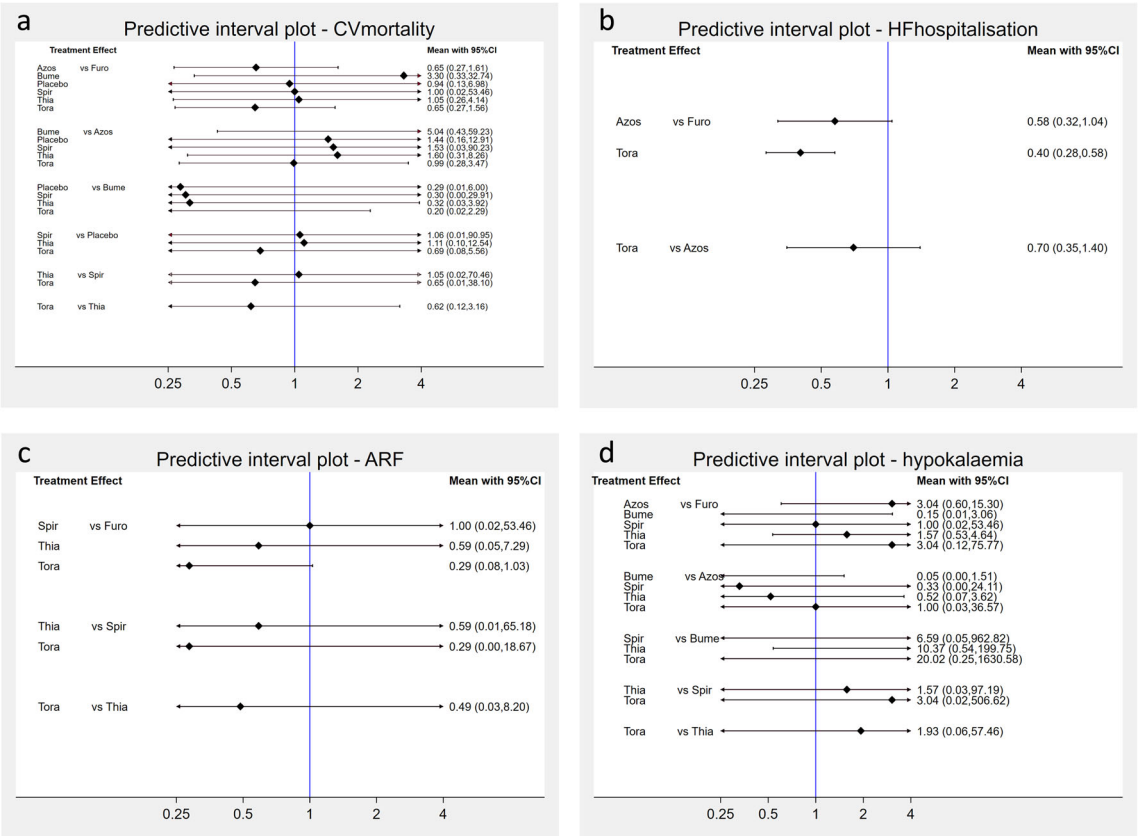

Fig. 4 Network meta-analyses of secondary and safety endpoints. **a** Cardiovascular mortality. **b** HF-related hospitalisation. **c** Acute renal failure. **d** Hypokalaemia. ARF, acute renal failure; Azos, azosemide; Bume, bumetanide; CI, confidence interval; Furo, furosemide; Spir, spironolactone; Thia, thiazide; Tora, torasemide

Table 5 Pharmacokinetics of the different loop diuretics

Pharmacokinetics	Furosemide	Torasemide	Bumetanide	Azosemide	Piretanide
Absorbed	70%	80%	80%	20–30%	80–90%
Bioavailability	60%	80%	90%	20%	80–90%
Half-life	1 h	3–4 h	60 to 90 min	2–3 h	1–2 h
Protein binding	98%	> 98%	97%	95%	90%
Volume of distribution	0.1 l/kg	< 0.15 l/kg	0.1 l/kg	0.262 l/kg	0.12 l/kg
Excretion	> 65% renal	Hepatic	Renal	Renal	Renal
Start of effect (oral)	30–60 min	30–60 min	30 min	60 min	60 min
Duration of effect	4 h	12 h	4–6 h	9 h	4–6 h
Metabolising	30% hepatic	75% hepatic	20% hepatic	> 50% hepatic	10–20% hepatic
Solubility	Hydrophilic	Lipophilic	Hydrophobic	Hydrophilic	Hydrophobic
oral LD50 (rat)	> 2.6 mg/kg	5 mg/kg	6 mg/kg	Not available	5.6 mg/kg
oral TDLO	6.25 mg/kg	5 mg/kg	6 mg/kg	Not available	Not available

All data refer to oral use of medication

differences in the occurrence of hypokalaemia were noted between different loop diuretics. In contrast, we found a trend towards benefits with torasemide with regard to renal function. As the number of studies included in this safety analysis was limited, results have to be interpreted with caution.

The present study is in accordance with the ISPOR-AMCP-NPC Good Practice Task Force consensus criteria regarding credibility and relevance to guide and inform decision makers in health care [33]. Given that loop diuretics do not affect long-term prognosis in patients with HF, different agents may be used interchangeably. In light of the slight benefits of torasemide regarding HF-related hospitalisation and worsening of renal function, however, the present analysis favours the use of torasemide over azosemide, bumetanide and furosemide.

Limitations

Several important potential study limitations should be considered. First, many trials included in our meta-analysis were open-label studies, and 8 trials were designed as cross-over studies. Second, most trials included a relatively small number of patients, with 3 studies contributing to approximately 67% of mortality events [42, 43, 52]. Third, the mean follow-up duration of included studies was only 22 weeks, which may limit mortality analyses. Fourth, as only few studies reported occurrence of acute renal failure, our NMA may be underpowered to detect significant differences between loop diuretics in their effects on renal function. Finally, as in most NMAs comparing several therapeutic agents, various dosages of individual agents were used. Then again, the present NMA includes all available evidence regarding the long-term use of loop diuretics in patients with HF, and main results were confirmed in sensitivity analyses.

Conclusion

In the present NMA, we found comparable results with respect to all-cause mortality, cardiovascular mortality and hypokalaemia for the long-term use of different loop diuretics. However, torasemide was superior in terms of HF-related hospitalisations, and there was a trend towards fewer renal complications with the use of torasemide. Regarding the risk-benefit ratio of different loop diuretics, clinicians may prefer torasemide over other loop diuretics in the long-term treatment of patients with HF.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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