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1 Measures of Loop Diuretic Efficiency and Prognosis 2 in Chronic Kidney Disease

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19 Running head: Loop diuretic efficiency in chronic kidney disease.

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27 Keywords: chronic renal insufficiency; mortality; natriuresis; renal replacement therapy; sodium
28 potassium chloride symporter inhibitors; urine specimen collection

1 **Abstract**

2 Background: The evolution and prognostic impact of loop diuretic efficiency according to
3 chronic kidney disease (CKD) severity is unclear.

4 Methods: This retrospective cohort study includes 783 CKD patients on oral loop diuretic
5 therapy with a 24-hour urine collection available. Acute kidney injury and history of renal
6 replacement therapy were exclusion criteria. Patients were stratified according to Kidney
7 Disease Improving Global Outcomes (KDIGO) glomerular filtration rate class. Loop diuretic
8 efficiency was calculated as urine output, natriuresis, and chloruresis, each adjusted for loop
9 diuretic dose, and compared among strata. Risk for onset of dialysis and all-cause mortality
10 was evaluated.

11 Results: Loop diuretic efficiency metrics decreased from KDIGO class IIIB to IV in furosemide
12 users and from KDIGO class IV to V with all loop diuretics (P-value<0.05 for all comparisons).
13 The correlation between loop diuretic efficiency and creatinine clearance was moderate at best
14 (Spearman's ρ 0.298-0.436; P-value<0.001 for all correlations). During median follow-up of
15 45 months, 457 patients died (58%) and 63 received kidney transplantation (8%), while dialysis
16 was started before in 328 (42%). All loop diuretic efficiency metrics were significantly and
17 independently associated with both the risk for dialysis and all-cause mortality. In KDIGO class
18 IV/V patients, low loop diuretic efficiency (i.e., urine output adjusted for loop diuretic dose
19 $\leq 1,000$ mL) shortened median time to dialysis with 24 months and median time to all-cause
20 mortality with 23 months.

21 Conclusion: Low loop diuretic efficiency is independently associated with a shorter time to
22 dialysis initiation and a higher risk for all-cause mortality in CKD.

23

1 **Abbreviations**

2	CI	confidence interval
3	CKD	chronic kidney disease
4	CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
5	Cr	creatinine
6	GFR	glomerular filtration rate
7	HR	hazard ratio
8	KDIGO	Kidney Disease – Improving Global Outcomes
9	NKCC2	sodium-potassium-chloride cotransporter 2

10

1 **Introduction**

2 Loop diuretics are frequently used in patients with chronic kidney disease (CKD) to treat
3 or prevent volume overload. In patients with acute heart failure, loop diuretic efficiency has
4 been identified as a powerful prognostic marker, independently of underlying glomerular
5 filtration rate (GFR) or ejection fraction [1-6]. Loop diuretic efficiency is calculated as an effect
6 metric such as urine output, weight loss, net fluid balance, or natriuresis, adjusted for the loop
7 diuretic dose that is administered [6]. Irrespectively of the metric used, acute heart failure
8 patients who demonstrate lower loop diuretic efficiency have increased mortality and a higher
9 risk for hospital readmissions [1-5]. The relationship between loop diuretic efficiency and CKD
10 severity has not been thoroughly explored. Therefore, it remains unclear whether and to what
11 extent loop diuretic efficiency is a marker of prognosis in patients with stable CKD. This study
12 investigates a broad CKD population followed within a tertiary care nephrology department.
13 Presence of heart failure was neither a requirement nor an exclusion criterion for the study.
14 The evolution of 3 loop diuretic efficiency metrics (i.e., urine output, natriuresis, and
15 chloruresis) was evaluated across the severity spectrum of CKD. For each metric, the
16 correlation with loop diuretic type and dose, underlying GFR, and urine output was
17 investigated. Finally, the impact of diuretic efficiency on the risk for onset of dialysis and
18 all-cause mortality was assessed.

19

1 **Material and Methods**

2 Study design

3 This is a retrospective cohort study from a single tertiary care center (UZ Leuven, Leuven,
4 Belgium). All patients within the nephrology department who had a 24-hour urine collection
5 available between January 1992 and February 2015 were extracted through the electronic
6 medical record. As additional filter criteria, only urine collections with creatinine (Cr), sodium,
7 as well as chloride assessments were considered and only patients with a serum Cr
8 measurement available within 30 days were withheld. To prevent inclusion of patients with
9 acute kidney injury or unstable Cr values, the highest serum Cr value within this 30-day period
10 was compared to the lowest value obtained between 180 and 30 days before the date of the
11 urine collection. All patients with a >25% difference were excluded. Further exclusion criteria
12 were: (1) absence of documented daily use of loop diuretics according to prescription status in
13 the electronic medical record; (2) urine output <500 mL or >5,000 mL in order to avoid
14 unreliable collections; (3) renal replacement therapy or ultrafiltration at any time before
15 completion of the urine collection; (4) history of kidney transplantation; and (5) coding for acute
16 kidney injury in the electronic medical record at the time of the urine collection. Patients were
17 stratified according to their Kidney Disease – Improving Global Outcomes (KDIGO) class,
18 based on the estimated GFR according to the Chronic Kidney Disease Epidemiology
19 Collaboration (CKD-EPI) formula [7, 8]. Loop diuretic efficiency was compared among strata
20 and its impact on clinical outcomes evaluated. The study complies with the Declaration of
21 Helsinki and the locally appointed ethics committee has approved it. The need for written
22 informed consent was waived as this was a purely observational, retrospective study. All
23 authors had full access to the data and contributed to the writing of the manuscript. Together,
24 they take responsibility for the integrity of the data and agree to its report as written. The
25 manuscript was drafted according to the STROBE statement for observational studies.

26

1 Loop diuretic efficiency

2 Loop diuretic efficiency was assessed as urine output, natriuresis, and chloruresis,
3 each corrected for loop diuretic dose (i.e., the oral maintenance dose of the patient) [6].
4 Because of the highly unpredictable oral bioavailability of furosemide (10-100%) in comparison
5 to torsemide or bumetanide (80-100%), those patients were evaluated separately [9, 10]. Loop
6 diuretic response is expressed per 40 mg furosemide or 1 mg bumetanide equivalents
7 throughout the manuscript. Torsemide doses were converted to bumetanide equivalents with
8 a conversion factor 10:1.

9

10 Follow-up and clinical outcome

11 All patients were followed until death, kidney transplantation, or September 1, 2015,
12 whatever came first, which ensured a minimal of 6 months follow-up time for all patients. Time
13 to all-cause mortality was assessed with censoring at the time of kidney transplantation. In
14 addition, time to onset of dialysis was evaluated with censoring at the time of death or kidney
15 transplantation.

16

17 Statistical analysis

18 Continuous variables are expressed as mean \pm standard deviation if normally
19 distributed, or otherwise as median (interquartile range). Normality was assessed by the
20 Shapiro-Wilk statistic. Categorical data are expressed as percentages. The ANOVA test,
21 Kruskal-Wallis H test, and Pearson's χ^2 -test were used as indicated for comparison among
22 groups. Linear regression was used to adjust metrics of loop diuretic efficiency for differences
23 in baseline characteristics between furosemide versus bumetanide/torsemide users.
24 Spearman's ρ was used to assess correlations because of the non-normal distribution of loop
25 diuretic efficiency metrics. Cumulative, actuarial survival rates were calculated according to
26 the Kaplan-Meier method. The Cox proportional hazards model was used to calculate hazard
27 ratios (HR) with corresponding 95% confidence interval (95%CI). To allow direct comparison
28 between different metrics of loop diuretic efficiency, all HR reported throughout the manuscript

1 are presented per standard deviation change. Cox regression models were adjusted for
2 decade of inclusion (1992-1999, 2000-2009, or 2010-2015), age, gender and estimated GFR
3 by including them as covariates. Statistical significance was always set at a 2-tailed probability
4 level of <0.05. All statistics were performed using IBM® SPSS® (version 25.0) for Windows.
5

1 **Results**

2 Study population

3 A study flowchart is provided in Figure 1. From 1,075 patients followed within the
4 nephrology department with a 24-hour urinary collection and stable serum Cr, 783 were
5 withheld as the final study population. Baseline characteristics are presented in Table 1.
6 Patients had advanced kidney disease with more than half of the subjects qualifying as KDIGO
7 class IV or V. Because there were relatively few patients in KDIGO class I (n=27) and II (n=63),
8 those groups were pooled together with patients in KDIGO class IIIA for further analysis and
9 comparison. CKD causes were diverse, reflecting real-world nephrology practice. From the
10 total study population, 431 patients were treated with furosemide (55%), 346 with bumetanide
11 (44%), and 6 with torsemide (1%). The daily maintenance dose was 40 mg (40-80 mg) for
12 furosemide, 2.5 mg (1-5 mg) for bumetanide and 10 (5-20 mg) for torsemide. Furosemide
13 users were younger, with a lower prevalence of cardiovascular disease and diabetes, less
14 advanced CKD, and they more frequently had a diagnosis of glomerulonephritis, vasculitis or
15 nephrotic syndrome (Table 1).

16

17 Loop diuretic efficiency

18 Overall, patients had a urine output of $1,809 \pm 746$ mL, 24 h natriuresis of 114 mmol
19 (71-160 mmol) and 24 h chloruresis of 97 mmol (60-139 mmol). Loop diuretic efficiency was
20 significantly different across KDIGO classes of CKD, irrespectively of the metric used and with
21 both furosemide and bumetanide/torsemide (P-value<0.001 for all; Figure 2). Over CKD strata,
22 loop diuretic efficiency metrics decreased progressively from KDIGO class IIIB to class V
23 among furosemide users (P-value<0.05 for all comparisons). Among bumetanide/torsemide
24 users, only the differences from KDIGO class IV to class V were statistically significant
25 (P-value<0.001 for all). Adjusted for loop diuretic dose, urine output decreased from 1,300 mL
26 (700-2,000 mL) to 680 mL (350-1,250 mL), natriuresis from 78 mmol (36-132 mmol) to
27 38 mmol (22-81 mmol), and chloruresis from 69 mmol (38-122 mmol) to 31 mmol
28 (18-56 mmol), when patients in KDIGO class I/II/IIIA (pooled) were compared to them in

1 KDIGO class V, respectively. For all 3 metrics, loop diuretic efficiency was lower in
2 bumetanide/torsemide versus furosemide users (P-value<0.001 for all; Figure 2). After
3 adjusting for significant baseline characteristics (Table 1), this difference remained statistically
4 significant (P-value=0.002, 0.005 and 0.008 for urine output, natriuresis and chloruresis,
5 respectively).

6

7 Determinants of loop diuretic efficiency

8 Figure 3 shows the correlation strength between metrics of loop diuretic efficiency,
9 creatinine clearance, loop diuretic dose, urine output, natriuresis, and chloruresis. Because the
10 relationship between loop diuretic dose and loop diuretic efficiency is in fact logarithmic rather
11 than linear, correlations with loop diuretic efficiency calculated using the log-transformed dose
12 are provided as well.

13

14 *Creatinine clearance*

15 The correlation between creatinine clearance and loop diuretic efficiency was
16 moderately strong at best and somewhat stronger for bumetanide/torsemide (Spearman's ρ
17 0.407 to 0.436; P-value<0.001 for all) versus furosemide users (Spearman's ρ 0.298 to 0.370;
18 P-value<0.001 for all). Logarithmic transformation had no meaningful impact on this
19 relationship.

20

21 *Loop diuretic dose*

22 Loop diuretic dose was inversely correlated with loop diuretic efficiency and showed
23 the strongest correlation strength of all factors before logarithmic transformation. This was
24 similar in furosemide versus bumetanide/torsemide users (Spearman's ρ -0.703 to -0.826;
25 P-value<0.001 for all). The inverse correlation strength between loop diuretic dose and loop
26 diuretic efficiency increased over strata of more advanced CKD. From the pooled KDIGO class
27 I/II/IIIA group to the KDIGO class V group, Spearman's ρ decreased from -0.763
28 to -0.885, -0.599 to -0.759, and -0.602 to -0.729 for urine output, natriuresis, and chloruresis

1 adjusted for loop diuretic dose, respectively. After logarithmic transformation, the correlation
2 strength between loop diuretic dose and loop diuretic efficiency diminished substantially, but
3 remained statistically significant (Spearman's ρ -0.189 to -0.356; P-value<0.001 for all).

4

5 Loop diuretic efficiency and clinical outcome

6 During follow-up of 45 months (19-76 months), 457 patients died (58%) and 63 were
7 transplanted (8%). Dialysis was started before death or kidney transplantation in 328 patients
8 (42%).

9

10 *Need for dialysis*

11 All 3 metrics of loop diuretic efficiency were significantly associated with less frequent
12 initiation of dialysis during follow-up after adjustments for inclusion decade, age, gender and
13 estimated GFR (Table 2). The HR (95%CI) for urine output, natriuresis, and chloruresis
14 adjusted for loop diuretic dose was 0.69 (0.59-0.80), 0.66 (0.56-0.77), and 0.63 (0.53-0.75),
15 respectively, per standard deviation change (P-value<0.001 for all). When all 3 metrics of loop
16 diuretic efficiency were modelled together to predict onset of dialysis, chloruresis remained
17 significant [HR (95% CI) = 0.55 (0.40-0.74); P-value<0.001], but natriuresis (P-value=0.098)
18 and urine output (P-value=0.203) were not.

19

20 *All-cause mortality*

21 Higher loop diuretic efficiency was also significantly associated with lower all-cause
22 mortality after adjustments for inclusion decade, age, gender and estimated GFR (Table 2).
23 The HR (95% CI) for urine output, natriuresis, and chloruresis adjusted for loop diuretic dose
24 was 0.80 (0.70-0.90), 0.86 (0.77-0.97), and 0.86 (0.76-0.97), respectively, per standard
25 deviation change (P-value<0.001, 0.014 and 0.015, respectively). The effect was mainly driven
26 by patients with advanced CKD (i.e., KDIGO class IV and V) . When all 3 metrics of loop
27 diuretic efficiency were modelled together to predict death, urine output remained significant

1 [HR (95% CI) = 0.69 (0.57-0.84); P-value<0.001], but natriuresis (P-value=0.465) and
2 chloruresis (P-value=0.919) were not.

3

4 *Incremental prognostic value of loop diuretic efficiency over glomerular filtration rate only*

5 Subsequently, the study population was divided according to loop diuretic efficiency
6 defined as high (i.e., urine output adjusted for loop diuretic dose >1,000 mL) versus low
7 (i.e., urine output adjusted for loop diuretic dose ≤1,000 mL), with this cut-off roughly
8 corresponding to the median of the population (1,037 mL) in addition to stratification according
9 to KDIGO class (I/II/III versus IV/V). Both in KDIGO class I/II/III [HR (95%CI) =
10 1.86 (1.09-3.19); P-value=0.024] and KDIGO class IV/V [HR (95%CI) = 1.83 (1.43-2.35);
11 P-value<0.001], low loop diuretic efficiency was associated with a higher risk for onset of
12 dialysis (Figure 4A). In the latter group, the median time to initiation of dialysis decreased from
13 33 to 9 months with high versus low loop diuretic efficiency. Adding loop diuretic efficiency to
14 a Cox model for all-cause mortality significantly improved risk prediction by KDIGO class alone
15 (χ^2 change 12.243; P<0.001). Median survival was 90 months in KDIGO class I/II/III patients
16 with high loop diuretic efficiency, 72 months in KDIGO class IV/V patients with high loop
17 diuretic efficiency, 66 months in KDIGO class I/II/III patients with low loop diuretic efficiency,
18 and 49 months in KDIGO class IV/V patients with low loop diuretic efficiency (P-value<0.001;
19 Figure 4B).

20

1 Discussion

2 This study provides insightful information on the occurrence of impaired loop diuretic
3 efficiency or diuretic resistance in CKD, as well as its impact on prognosis. Key findings are:
4 (1) loop diuretic efficiency decreases significantly from KDIGO class IV, while it remains
5 relatively preserved in less advanced CKD; (2) similar patterns of loop diuretic efficiency were
6 observed with furosemide versus bumetanide/torsemide; (3) the correlation between loop
7 diuretic efficiency and underlying GFR was only moderately strong at best; (4) low loop, diuretic
8 efficiency was associated with a shorter time to onset of dialysis and all-cause mortality and
9 provided improved risk stratification over KDIGO GFR class alone. Low versus high loop
10 diuretic efficiency, defined as a urine output ≤ 1000 mL versus >1000 mL per 40 mg furosemide
11 or 1 mg bumetanide, respectively, shortened time to onset of dialysis and time to all-cause
12 mortality both with approximately 2 years.

13
14 Loop diuretics block the sodium-potassium-chloride cotransporter 2 (NKCC2), located
15 at the apical membrane of tubular cells lining the thick ascending limb of Henle's loop [11]. The
16 NKCC2 normally reabsorbs approximately 25% of filtered sodium and chloride, hence loop
17 diuretics cause potent natriuresis, chloruresis, and diuresis [12, 13]. As loop diuretics are highly
18 protein-bounded ($>90\%$), they undergo minimal glomerular filtration, but instead require
19 secretion in the proximal renal tubules through organic anion transporters and the multidrug
20 resistance-associated protein 4 [14, 15]. In CKD, urate and other uremic toxins compete with
21 loop diuretic agents for proximal secretion and transport is further inhibited by metabolic
22 acidosis [16, 17]. This explains the higher dose requirements of loop diuretics in advanced
23 CKD. Nevertheless, even when low GFR is met by an appropriately higher loop diuretic dose
24 to maintain a similar fractional excretion, the absolute excretion will remain impaired because
25 of the lower filtration [18]. In this study, loop diuretic efficiency started to fall significantly from
26 KDIGO class IV, which was similar for all metrics and irrespective of the loop diuretic agent
27 used.

28

1 Because of significant differences in their pharmacokinetic profile, furosemide and
2 bumetanide were studied separately [19]. Only a few patients received torsemide and those
3 were added to the bumetanide group as bioavailability of both agents is similar (80-100%) and
4 significantly more reliable than furosemide (10-100%) [19]. It is important to note the marked
5 differences in prescription patterns between furosemide and bumetanide/torsemide, with
6 furosemide being prescribed to younger patients with less cardiovascular comorbidity. In
7 addition, the equivalent dose prescribed for bumetanide was significantly higher, indicating
8 more severe disease. Furosemide users had higher loop diuretic efficiency in this study, even
9 after adjusting for differences in baseline characteristics, yet we cannot exclude residual
10 confounding as the furosemide versus bumetanide/torsemide groups were not randomized.
11 Importantly however, observed patterns of loop diuretic efficiency over KDIGO strata and
12 correlations with determinants were very similar with both compounds.

13

14 Remarkably, the correlation between loop diuretic efficiency and creatinine clearance
15 was only moderately strong at best in this study. This should not be surprising as electrolyte
16 homeostasis and volume regulation are mainly determined by the renal tubules in contrast to
17 clearance that is a glomerular function [12, 20]. The current results emphasize that tubular
18 function, although often overlooked in the global assessment of renal function, offers important
19 prognostic information that complements the GFR. It was somewhat surprising that urine
20 output response to loop diuretics was a more robust predictor of mortality when compared to
21 natriuretic or chloruretic response. The opposite has been observed in heart failure [21].
22 However, while volume overload clearly plays a central role in heart failure pathophysiology, it
23 is only one of the many problems in CKD, where atherosclerotic and metabolic events are at
24 least equally important. Indeed, onset of dialysis that is often provoked by difficult volume
25 control was more strongly predicted by the natriuretic and chloruretic response to loop diuretics
26 in this study. Alternatively, because patients were in a steady state, natriuresis and chloruresis
27 may primarily reflect dietary salt intake. In contrast, urine output may be uncoupled more as

1 the diuretic response (particularly when hypotonic) will quickly drive thirst leading to more fluid
2 intake.

3

4 It has been shown by others as well that the loop diuretic maintenance dose shows a
5 strong and inverse correlation with loop diuretic efficiency metrics [22]. Part of this is explained
6 by the expected logarithmic dose-response relationship of loop diuretics. Indeed, after
7 logarithmic transformation of the loop diuretic dose, the correlation with loop diuretic efficiency
8 was substantially weakened in this study, yet remained statistically significant. In other words,
9 even after accounting for the expected dose-response relationship, CKD patients on a higher
10 loop diuretic dose demonstrated a less than proportional increase in diuresis, natriuresis, and
11 choruresis, indicating tubular resistance. It is important to note that this phenomenon became
12 even stronger in patients with more advanced CKD. This might suggest that further increasing
13 loop diuretic dose in such patients may not be an efficient strategy and instead combination
14 treatment should be considered.

15

16 Clinical implications

17 Results of the current study support a more systematic assessment of tubular function
18 in CKD patients, at least in the population that needs diuretics to control volume status. Current
19 KDIGO guidelines risk stratify patients only based on GFR and albuminuria, which are basically
20 markers of glomerular function and integrity [8]. However, results of this study clearly show the
21 only modest correlation with concomitant tubular function. Nevertheless, tubular function is
22 clinically important as it is more strongly related to volume and electrolyte homeostasis, which
23 are important causes of morbidity and mortality in CKD [19]. This study provides further support
24 by showing a strong relationship of loop diuretic efficiency metrics (as a surrogate for tubular
25 function and integrity) with hard clinical outcomes. In this respect, it is important to notice that
26 urine output and electrolytes, although intrinsically coupled, may contain differential
27 information [23]. Indeed, extracellular volume status is primarily determined by sodium (and
28 chloride) rather than water homeostasis per se. This study found that chloruretic response to

1 loop diuretics was the strongest loop diuretic efficiency metric to predict time to onset of dialysis
2 (presumably due to uncontrolled volume overload). This corroborates well with observations
3 in heart failure that a sudden decrease in natriuresis because of a random trigger increases
4 the risk of hospital admission with signs or symptoms of volume overload [24]. Assessing loop
5 diuretic response might be possible through spot sampling in the outpatient nephrology or
6 cardiology clinic, yet this approach needs further study [25].

7

8 Study limitations

9 Results of this study should be interpreted in the light of some limitations. First, patients
10 with acute kidney injury or unstable serum creatinine values were excluded from this study to
11 allow focus on the impact of stable CKD on loop diuretic efficiency. Most patients with
12 cardiorenal syndrome were thus excluded, because loop diuretic efficiency may be driven by
13 other factors than CKD itself in this population. However, dedicated studies in acute heart
14 failure show a strong prognostic impact of loop diuretics in such patients as well [2, 6]. Second,
15 the proportion of patients in KDIGO class I and II was low and those patients were assessed
16 together with KDIGO class IIIA patients. However, there was no significant difference in diuretic
17 efficiency between this group and KDIGO class IIIB patients, indicating that relevant changes
18 occurred mainly in patients with more advanced CKD. Third, no information on fluid or salt
19 intake was available. As the study focused on patients with CKD and excluded patients with
20 acute kidney injury, most participants were likely in a steady state. The emphasis on sodium
21 and fluid restriction by treating physicians is likely stronger in patients with more advanced
22 CKD, which might contribute to a decreasing loop diuretic efficiency. Nevertheless, the
23 observation that loop diuretic efficiency provided incremental prognostic information over GFR
24 alone was robust. Finally, no information on the use of non-loop diuretics or medication
25 compliance/adherence was available in this study. However, if anything this would be expected
26 to decrease the signal-to-noise ratio.

27

28 Conclusions

1 In a real-world CKD population, loop diuretic efficiency decreased from KDIGO class
2 IV. Its correlation with creatinine clearance was only moderately strong, indicating a reflection
3 of tubular rather than glomerular function. Urine output adjusted for loop diuretic dose was
4 most robustly associated with mortality independent of inclusion period, age, gender and
5 estimated GFR, while natriuresis and especially chloruresis predicted better the time to onset
6 of dialysis. Loop diuretic efficiency metrics improved risk stratification based on GFR alone in
7 CKD.

8

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3

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7

8 **Statement of Ethics**

9 This research complies with internationally accepted standards for research practice and
10 reporting in line with the COPE guidelines.

11

12 **Disclosure Statement**

13 No conflict of interest declared.

14

15 **Author contributions statement**

16 Research idea and study design: FHV; data acquisition: FHV, BB; data analysis/interpretation:
17 all authors; statistical analysis: FHV; supervision or mentorship: BB. Each author contributed
18 important intellectual content during manuscript drafting or revision, accepts personal
19 accountability for the author's own contributions, and agrees to ensure that questions
20 pertaining to the accuracy or integrity of any portion of the work are appropriately investigated
21 and resolved.

22

1 **References**

- 2 1. Valente MA, Voors AA, Damman K, Van Veldhuisen DJ, Massie BM, O'Connor CM et al.
3 Diuretic response in acute heart failure: clinical characteristics and prognostic significance. *Eur*
4 *Heart J.* 2014;35(19):1284-93. doi:10.1093/eurheartj/ehu065.
- 5 2. Testani JM, Brisco MA, Turner JM, Spatz ES, Bellumkonda L, Parikh CR et al. Loop diuretic
6 efficiency: a metric of diuretic responsiveness with prognostic importance in acute
7 decompensated heart failure. *Circ Heart Fail.* 2014;7(2):261-70.
8 doi:10.1161/CIRCHEARTFAILURE.113.000895.
- 9 3. Singh D, Shrestha K, Testani JM, Verbrugge FH, Dupont M, Mullens W et al. Insufficient
10 natriuretic response to continuous intravenous furosemide is associated with poor long-term
11 outcomes in acute decompensated heart failure. *J Card Fail.* 2014;20(6):392-9.
12 doi:10.1016/j.cardfail.2014.03.006.
- 13 4. ter Maaten JM, Dunning AM, Valente MA, Damman K, Ezekowitz JA, Califf RM et al. Diuretic
14 response in acute heart failure-an analysis from ASCEND-HF. *Am Heart J.* 2015;170(2):313-
15 21. doi:10.1016/j.ahj.2015.05.003.
- 16 5. Verbrugge FH, Dupont M, Bertrand PB, Nijst P, Penders J, Dens J et al. Determinants and
17 impact of the natriuretic response to diuretic therapy in heart failure with reduced ejection
18 fraction and volume overload. *Acta Cardiol.* 2015;70(3):265-73.
19 doi:10.2143/AC.70.3.3080630.
- 20 6. Verbrugge FH. Editor's Choice-Diuretic resistance in acute heart failure. *Eur Heart J Acute*
21 *Cardiovasc Care.* 2018;7(4):379-89. doi:10.1177/2048872618768488.
- 22 7. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI et al. A new
23 equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-12.
24 doi:150/9/604 [pii].
- 25 8. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K et al. The definition,
26 classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference
27 report. *Kidney Int.* 2011;80(1):17-28. doi:10.1038/ki.2010.483.

- 1 9. McCrindle JL, Li Kam Wa TC, Barron W, Prescott LF. Effect of food on the absorption of
2 furosemide and bumetanide in man. *Br J Clin Pharmacol*. 1996;42(6):743-6.
- 3 10. Shankar SS, Brater DC. Loop diuretics: from the Na-K-2Cl transporter to clinical use. *Am*
4 *J Physiol Renal Physiol*. 2003;284(1):F11-21. doi:10.1152/ajprenal.00119.2002.
- 5 11. Somasekharan S, Tanis J, Forbush B. Loop diuretic and ion-binding residues revealed by
6 scanning mutagenesis of transmembrane helix 3 (TM3) of Na-K-Cl cotransporter (NKCC1). *J*
7 *Biol Chem*. 2012;287(21):17308-17. doi:10.1074/jbc.M112.356014.
- 8 12. Verbrugge FH, Dupont M, Steels P, Grieten L, Swennen Q, Tang WH et al. The kidney in
9 congestive heart failure: 'are natriuresis, sodium, and diuretics really the good, the bad and the
10 ugly?'. *Eur J Heart Fail*. 2014;16(2):133-42. doi:10.1002/ejhf.35.
- 11 13. Ellison DH, Felker GM. Diuretic Treatment in Heart Failure. *N Engl J Med*.
12 2017;377(20):1964-75. doi:10.1056/NEJMra1703100.
- 13 14. Wilcox CS. New insights into diuretic use in patients with chronic renal disease. *J Am Soc*
14 *Nephrol*. 2002;13(3):798-805.
- 15 15. Hasegawa M, Kusuhara H, Adachi M, Schuetz JD, Takeuchi K, Sugiyama Y. Multidrug
16 resistance-associated protein 4 is involved in the urinary excretion of hydrochlorothiazide and
17 furosemide. *J Am Soc Nephrol*. 2007;18(1):37-45. doi:10.1681/ASN.2005090966.
- 18 16. Loon NR, Wilcox CS. Mild metabolic alkalosis impairs the natriuretic response to
19 bumetanide in normal human subjects. *Clin Sci (Lond)*. 1998;94(3):287-92.
- 20 17. Uwai Y, Saito H, Hashimoto Y, Inui KI. Interaction and transport of thiazide diuretics, loop
21 diuretics, and acetazolamide via rat renal organic anion transporter rOAT1. *J Pharmacol Exp*
22 *Ther*. 2000;295(1):261-5.
- 23 18. Ellison DH. Clinical Pharmacology in Diuretic Use. *Clin J Am Soc Nephrol*.
24 2019;14(8):1248-57. doi:10.2215/CJN.09630818.
- 25 19. Verbrugge FH, Mullens W, Tang WH. Management of Cardio-Renal Syndrome and
26 Diuretic Resistance. *Curr Treat Options Cardiovasc Med*. 2016;18(2):11. doi:10.1007/s11936-
27 015-0436-4.

- 1 20. Ter Maaten JM, Rao VS, Hanberg JS, Perry Wilson F, Bellumkonda L, Assefa M et al.
2 Renal tubular resistance is the primary driver for loop diuretic resistance in acute heart failure.
3 Eur J Heart Fail. 2017;19(8):1014-22. doi:10.1002/ejhf.757.
- 4 21. Hodson DZ, Griffin M, Mahoney D, Raghavendra P, Ahmad T, Turner J et al. Natriuretic
5 Response Is Highly Variable and Associated With 6-Month Survival: Insights From the ROSE-
6 AHF Trial. JACC Heart Fail. 2019;7(5):383-91. doi:10.1016/j.jchf.2019.01.007.
- 7 22. Brinkley DM, Jr., Burpee LJ, Chaudhry SP, Smallwood JA, Lindenfeld J, Lakdawala NK et
8 al. Spot Urine Sodium as Triage for Effective Diuretic Infusion in an Ambulatory Heart Failure
9 Unit. J Card Fail. 2018;24(6):349-54. doi:10.1016/j.cardfail.2018.01.009.
- 10 23. Verbrugge FH, Nijst P, Dupont M, Penders J, Tang WH, Mullens W. Urinary composition
11 during decongestive treatment in heart failure with reduced ejection fraction. Circ Heart Fail.
12 2014;7(5):766-72. doi:10.1161/CIRCHEARTFAILURE.114.001377.
- 13 24. Martens P, Dupont M, Verbrugge FH, Damman K, Degryse N, Nijst P et al. Urinary Sodium
14 Profiling in Chronic Heart Failure to Detect Development of Acute Decompensated Heart
15 Failure. JACC Heart Fail. 2019;7(5):404-14. doi:10.1016/j.jchf.2019.02.011.
- 16 25. Verbrugge FH, Martens P, Boonen L, Nijst P, Verhaert D, Noyens P et al. Loop diuretic
17 down-titration in stable chronic heart failure is often achievable, especially when urinary
18 chloride concentration is low. Acta Cardiol. 2018;73(4):335-41.
19 doi:10.1080/00015385.2017.1385152.
- 20

1 **Legends for Figures**

2 Figure 1. Study flowchart.

3

4 Figure 2. Loop diuretic efficiency as (A) urine output, (B) natriuresis, and (C) chloruresis
5 adjusted for loop diuretic dose, according to Kidney Disease – Improving Global Outcomes
6 (KDIGO) class and type of loop diuretic used.

7

8 Figure 3. Correlation heatmap (Spearman's ρ) for metrics of loop diuretic efficiency with
9 creatinine (Cr) clearance, loop diuretic dose, urine output, natriuresis, and chloruresis
10 according to type of loop diuretic used (All P-values <0.001).

11

12 Figure 4. Time to (A) onset of dialysis and (B) all-cause mortality according to Kidney Disease
13 – Improving Global Outcomes (KDIGO) class (I/II/III versus IV/V) and loop diuretic efficiency
14 (high or urine output adjusted for loop diuretic dose >1,000 mL versus low or urine output
15 adjusted for loop diuretic dose \leq 1,000 mL). Patients were censored at the time of kidney
16 transplantation for both analyses and in case of mortality for the initiation of dialysis analysis.

17

1 Tables

Table 1. Baseline characteristics of the study population

	Total population	Furosemide users	Bumetanide or torsemide users
	N = 783	N = 431	N = 352
Age (years)*	68 ± 14	66 ± 14	71 ± 12
Men/Women	58%/42%	58%/42%	58%/42%
Renal diagnosis**			
Diabetic nephropathy	166 (21%)	79 (18%)	87 (25%)
Hypertensive nephropathy	43 (6%)	19 (4%)	24 (7%)
Minimal change disease/nephrotic syndrome	35 (5%)	29 (7%)	6 (2%)
Glomerulonephritis/vasculitis	120 (15%)	76 (18%)	44 (12%)
Interstitial nephritis	19 (2%)	10 (2%)	9 (2%)
Polycystic kidney disease	30 (4%)	19 (4%)	11 (3%)
Amyloidosis/Myeloma	25 (3%)	15 (4%)	10 (3%)
Other/Unknown/Unclassified	345 (44%)	184 (43%)	161 (46%)
Weight (kg)	76 ± 16	76 ± 16	76 ± 16
Blood pressure (mmHg)			
Systolic***	146 ± 26	148 ± 26	143 ± 26
Diastolic*	78 ± 14	81 ± 14	75 ± 12
Cardiovascular disease*	58%	49%	68%
Hypertension	56%	58%	54%
Diabetes**	36%	32%	41%
Hemoglobin (g/dL)	11.7 ± 2.0	11.6 ± 2.1	11.7 ± 1.9
Serum sodium (mmol/L)**	139 ± 4	139 ± 4	140 ± 4
Serum urea (mg/dL)**	110 ± 56	104 ± 57	118 ± 54
eGFR (mL/min/1.73m ²)***	26 (16 – 40)	27 (15 – 47)	25 (16 – 35)
KDIGO class*			
I (eGFR ≥90 mL/min/1.73m ²)	3.5%	4.2%	2.6%
II (eGFR 60-89 mL/min/1.73m ²)	8.1%	10.9%	4.5%
IIIA (eGFR 45-59 mL/min/1.73m ²)	9.2%	11.4%	6.5%
IIIB (eGFR 30-44 mL/min/1.73m ²)	20.4%	18.5%	22.7%
IV (eGFR 15-29 mL/min/1.73m ²)	37.0%	31.8%	43.5%
V (eGFR <15 mL/min/1.73m ²)	21.8%	23.2%	20.2%
Medication use			
Angiotensin-converting enzyme inhibitors	42%	43%	41%
Angiotensin receptor blockers	18%	18%	18%
Mineralocorticoid receptor antagonists**	7%	5%	10%

*P-value <0.001, **P-value <0.01, ***P-value <0.05 for difference between furosemide versus bumetanide/torsemide users

eGFR, estimated glomerular filtration rate according to the Chronic Kidney Disease Collaboration formula; KDIGO, Kidney Disease

–Improving Global Outcomes.

Table 2. Loop diuretic efficiency and clinical outcome

	Initiation of dialysis		All-cause mortality	
	HR (95%CI)*	P-value	HR (95%CI)*	P-value
Urine output/ loop diuretic dose	0.69 (0.59 – 0.80)	<0.001	0.80 (0.70 – 0.90)	<0.001
KDIGO I/II/IIIA	0.88 (0.57 – 1.35)	0.556	0.71 (0.52 – 0.97)	0.033
KDIGO IIIB	0.66 (0.43 – 1.02)	0.063	0.89 (0.72 – 1.10)	0.273
KDIGO IV	0.78 (0.62 – 0.98)	0.032	0.74 (0.61 – 0.91)	0.004
KDIGO V	0.56 (0.42 – 0.74)	<0.001	0.74 (0.53 – 1.02)	0.069
Natriuresis/ loop diuretic dose	0.66 (0.56 – 0.77)	<0.001	0.86 (0.77 – 0.97)	0.014
KDIGO I/II/IIIA	0.78 (0.45 – 1.35)	0.376	0.82 (0.61 – 1.10)	0.182
KDIGO IIIB	0.58 (0.35 – 0.95)	0.029	0.99 (0.84 – 1.16)	0.900
KDIGO IV	0.80 (0.64 – 1.01)	0.060	0.77 (0.63 – 0.95)	0.013
KDIGO V	0.55 (0.40 – 0.74)	<0.001	0.73 (0.51 – 1.06)	0.101
Chloruresis/ loop diuretic dose	0.63 (0.53 – 0.75)	<0.001	0.86 (0.76 – 0.97)	0.015
KDIGO I/II/IIIA	0.84 (0.51 – 1.38)	0.500	0.90 (0.69 – 1.17)	0.421
KDIGO IIIB	0.67 (0.42 – 1.06)	0.088	0.98 (0.85 – 1.12)	0.717
KDIGO IV	0.70 (0.53 – 0.91)	0.009	0.70 (0.56 – 0.89)	0.003
KDIGO V	0.54 (0.39 – 0.77)	<0.001	0.64 (0.42 – 0.98)	0.038

- 1 *per standard deviation change and adjusted for decade of inclusion (1992-1999, 2000-2009, or 2010-2015), age,
- 2 gender and estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration
- 3 formula
- 4 95%CI, 95% confidence interval; HR, hazard ratio; KDIGO, Kidney Disease – Improving Global Outcomes
- 5

Patients with stable serum creatinine*, followed within the Nephrology department at University Hospital Leuven, with 24 h urine collection between January 1992 and February 2015, including urine sodium, chloride and creatinine assessment

N = 1075

No daily loop diuretics

N = 200

Urine output <500 mL
or >5,000 mL

N = 54

History of dialysis

N = 3

History of kidney
transplantation

N = 4

Coding for acute kidney
injury

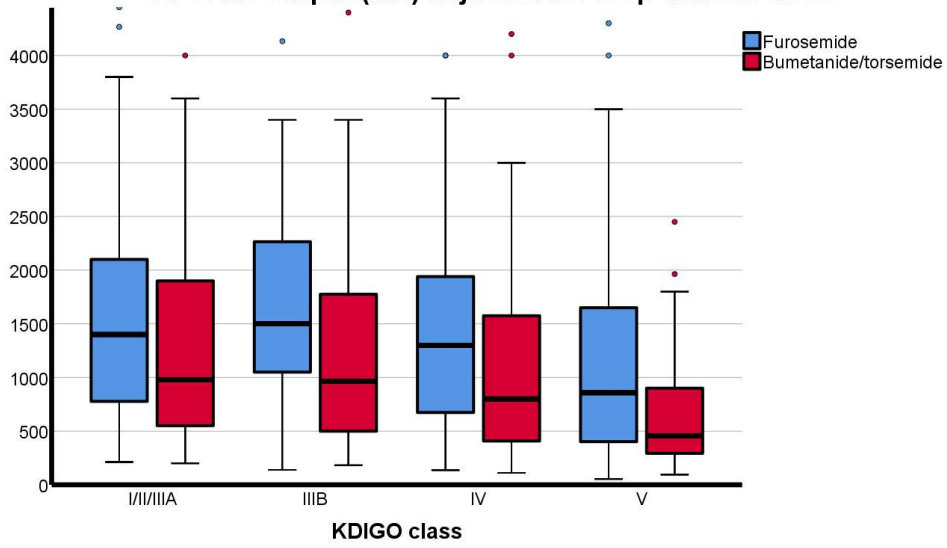
N = 31

Final study population

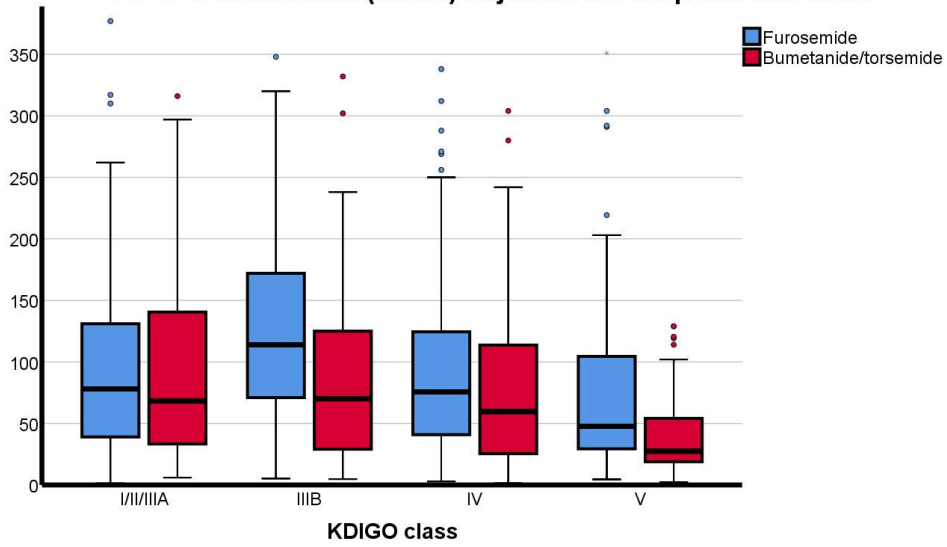
N = 783

*Difference between highest serum creatinine within 30 days of the urine collection and lowest serum creatinine 180 to 30 days before $\leq 25\%$

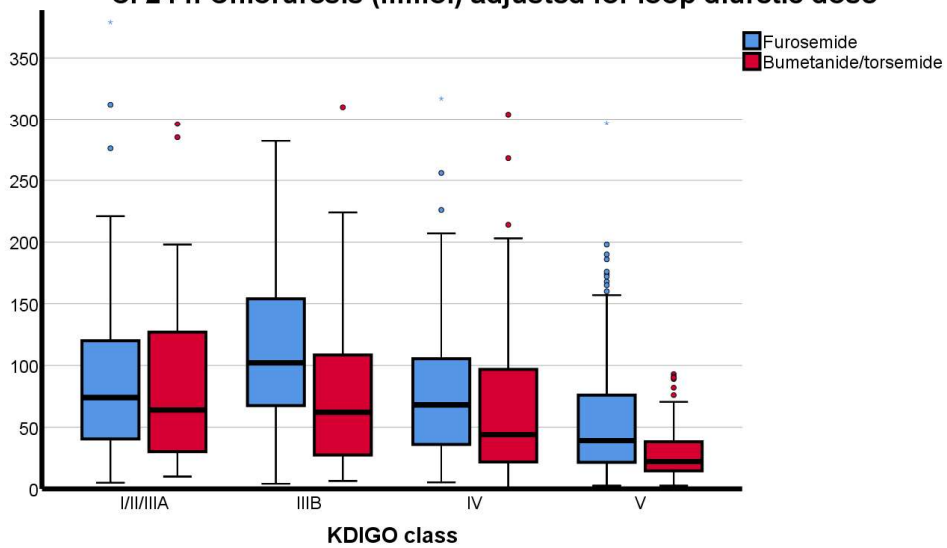
A. Urine output (mL) adjusted for loop diuretic dose



B. 24 h Natriuresis (mmol) adjusted for loop diuretic dose



C. 24 h Chloruresis (mmol) adjusted for loop diuretic dose

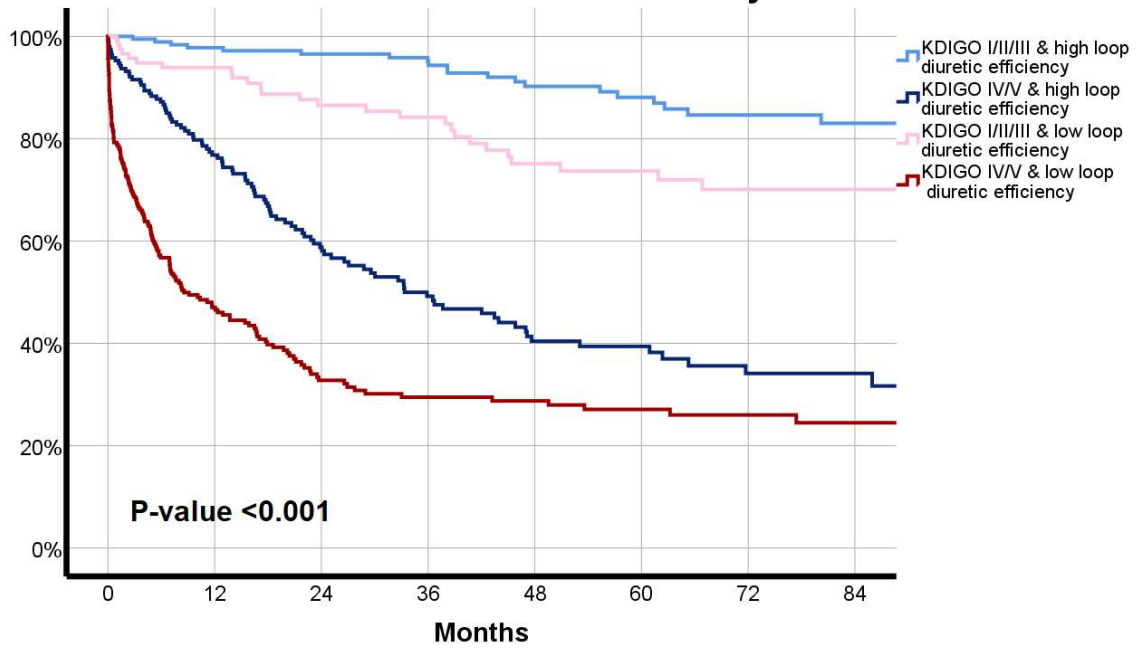


Furosemide	Urine output/ loop diuretic dose*	Natriuresis/ loop diuretic dose*	Chloruresis/ loop diuretic dose*
Cr clearance	$\rho = 0.370$	$\rho = 0.298$	$\rho = 0.358$
	* $\rho = 0.308$	* $\rho = 0.180$	* $\rho = 0.246$
Loop diuretic dose	$\rho = -0.821$	$\rho = -0.703$	$\rho = -0.703$
	* $\rho = -0.321$	* $\rho = -0.198$	* $\rho = -0.189$
Urine output	$\rho = 0.477$	$\rho = 0.379$	$\rho = 0.376$
	* $\rho = 0.910$	* $\rho = 0.620$	* $\rho = 0.606$
Natriuresis	$\rho = 0.292$	$\rho = 0.626$	$\rho = 0.589$
	* $\rho = 0.589$	* $\rho = 0.962$	* $\rho = 0.908$
Chloruresis	$\rho = 0.280$	$\rho = 0.583$	$\rho = 0.632$
	* $\rho = 0.569$	* $\rho = 0.904$	* $\rho = 0.966$

Bumetanide/torseamide	Urine output/ loop diuretic dose*	Natriuresis/ loop diuretic dose*	Chloruresis/ loop diuretic dose*
Cr clearance	$\rho = 0.436$	$\rho = 0.407$	$\rho = 0.428$
	* $\rho = 0.538$	* $\rho = 0.436$	* $\rho = 0.447$
Loop diuretic dose	$\rho = -0.826$	$\rho = -0.760$	$\rho = -0.734$
	* $\rho = -0.356$	* $\rho = -0.320$	* $\rho = -0.282$
Urine output	$\rho = 0.481$	$\rho = 0.423$	$\rho = 0.422$
	* $\rho = 0.918$	* $\rho = 0.669$	* $\rho = 0.634$
Natriuresis	$\rho = 0.390$	$\rho = 0.613$	$\rho = 0.601$
	* $\rho = 0.662$	* $\rho = 0.950$	* $\rho = 0.891$
Chloruresis	$\rho = 0.343$	$\rho = 0.547$	$\rho = 0.619$
	* $\rho = 0.614$	* $\rho = 0.867$	* $\rho = 0.954$

*Correlations with loop diuretic efficiency calculated as urine output, natriuresis, and chloruresis divided by the log-transformed loop diuretic dose

A. Time to onset of dialysis



B. Time to all-cause mortality

