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Measures of Loop Diuretic Efficiency and Prognosis in Chronic Kidney Disease

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Running head: Loop diuretic efficiency in chronic kidney disease.

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Abstract

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

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

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

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

Abbreviations

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

Introduction

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

Material and Methods

Study design

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

Loop diuretic efficiency

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

Follow-up and clinical outcome

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

Statistical analysis

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

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

Results

Study population

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

Loop diuretic efficiency

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

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

Determinants of loop diuretic efficiency

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

Creatinine clearance

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

Loop diuretic dose

Loop diuretic dose was inversely correlated with loop diuretic efficiency and showed the strongest correlation strength of all factors before logarithmic transformation. This was similar in furosemide versus bumetanide/torsemide users (Spearman's ρ -0.703 to -0.826; P-value<0.001 for all). The inverse correlation strength between loop diuretic dose and loop diuretic efficiency increased over strata of more advanced CKD. From the pooled KDIGO class I/II/IIIA group to the KDIGO class V group, Spearman's ρ decreased from -0.763 to -0.885, -0.599 to -759, and -0.602 to -0.729 for urine output, natriuresis, and chloruresis

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

Loop diuretic efficiency and clinical outcome

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

Need for dialysis

All 3 metrics of loop diuretic efficiency were significantly associated with less frequent initiation of dialysis during follow-up after adjustments for inclusion decade, age, gender and estimated GFR (Table 2). The HR (95%CI) for urine output, natriuresis, and chloruresis 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), respectively, per standard deviation change (P-value<0.001 for all). When all 3 metrics of loop diuretic efficiency were modelled together to predict onset of dialysis, chloruresis remained significant [HR (95% CI) = 0.55 (0.40-0.74); P-value<0.001], but natriuresis (P-value=0.098) and urine output (P-value=0.203) were not.

All-cause mortality

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

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

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

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

Discussion

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

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

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

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

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

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

Clinical implications

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

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

Study limitations

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

Conclusions

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

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Statement of Ethics

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

Disclosure Statement

No conflict of interest declared.

Author contributions statement

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

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Legends for Figures

Figure 1. Study flowchart.

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

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

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

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/1.73m²)***	26 (16 – 40)	27 (15 – 47)	25 (16 – 35)
KDIGO class*			
I (eGFR ≥90 mL/min/1.73m²)	3.5%	4.2%	2.6%
II (eGFR 60-89 mL/min/1.73m²)	8.1%	10.9%	4.5%
IIIA (eGFR 45-59 mL/min/1.73m²)	9.2%	11.4%	6.5%
IIIB (eGFR 30-44 mL/min/1.73m²)	20.4%	18.5%	22.7%
IV (eGFR 15-29 mL/min/1.73m²)	37.0%	31.8%	43.5%
V (eGFR <15 mL/min/1.73m²)	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%

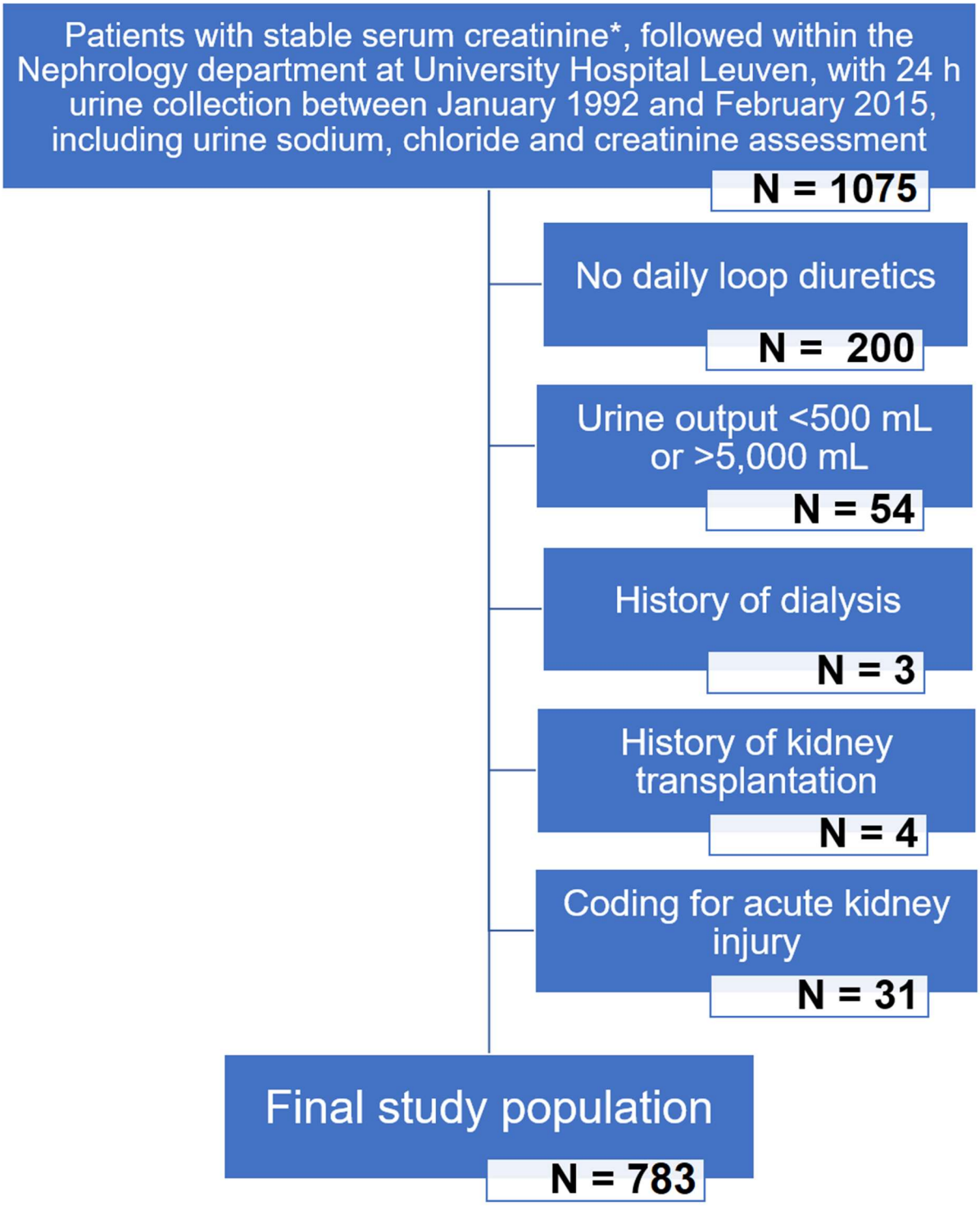
*P-value <0.001, **P-value <0.01, ***P-value <0.05 for difference between furosemide versus bumetanide/torsemide users

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

*per standard deviation change and adjusted for decade of inclusion (1992-1999, 2000-2009, or 2010-2015), age, gender and estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration formula

95%CI, 95% confidence interval; HR, hazard ratio; KDIGO, Kidney Disease – Improving Global Outcomes



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

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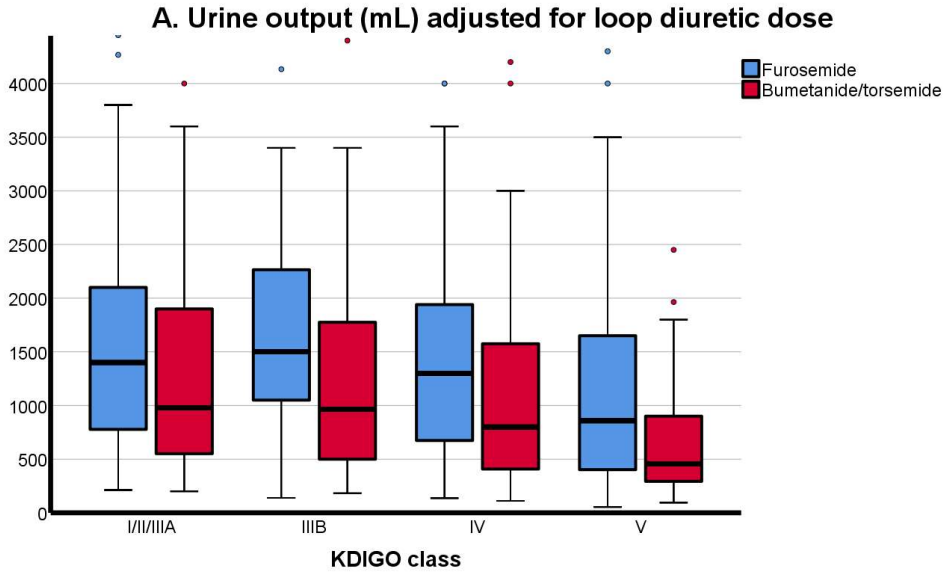
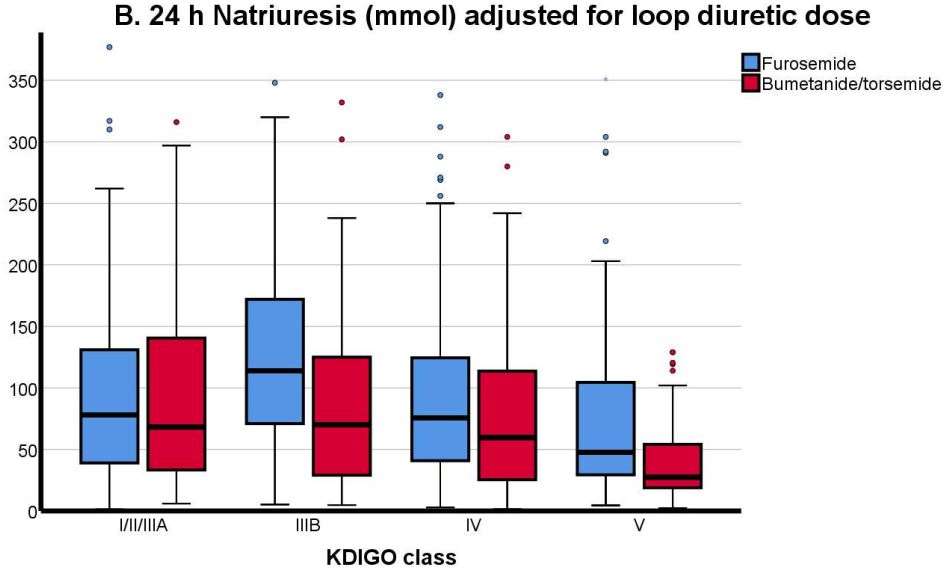
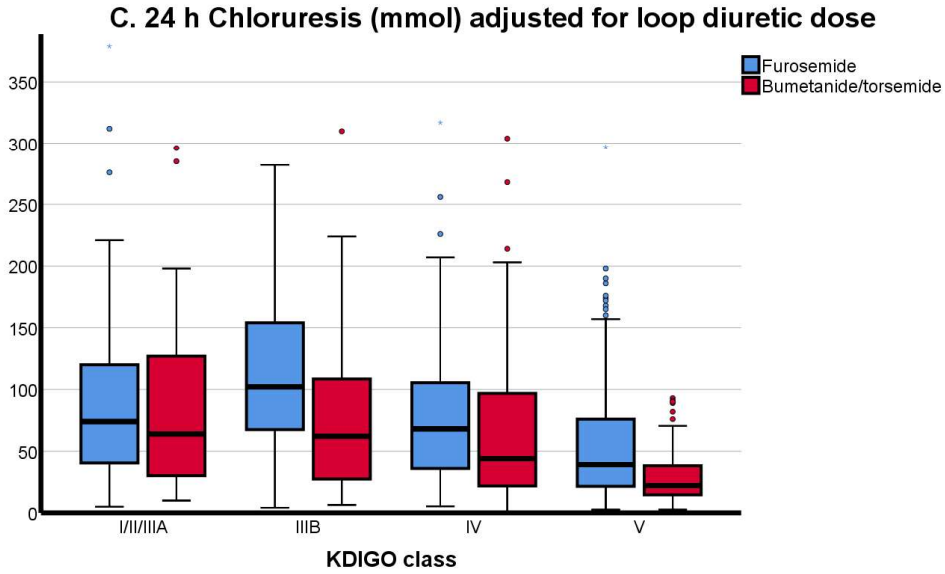

A. Urine output (mL) adjusted for loop diuretic dose
Furosemide
Bumetanide/torsemide
4000
3500
3000
2500
2000
1500
1000
500
0
I/II/IIIA
IIIB
IV
V
KDIGO class


B. 24 h Natriuresis (mmol) adjusted for loop diuretic dose
Furosemide
Bumetanide/torsemide
350
300
250
200
150
100
50
0
I/II/IIIA
IIIB
IV
V
KDIGO class

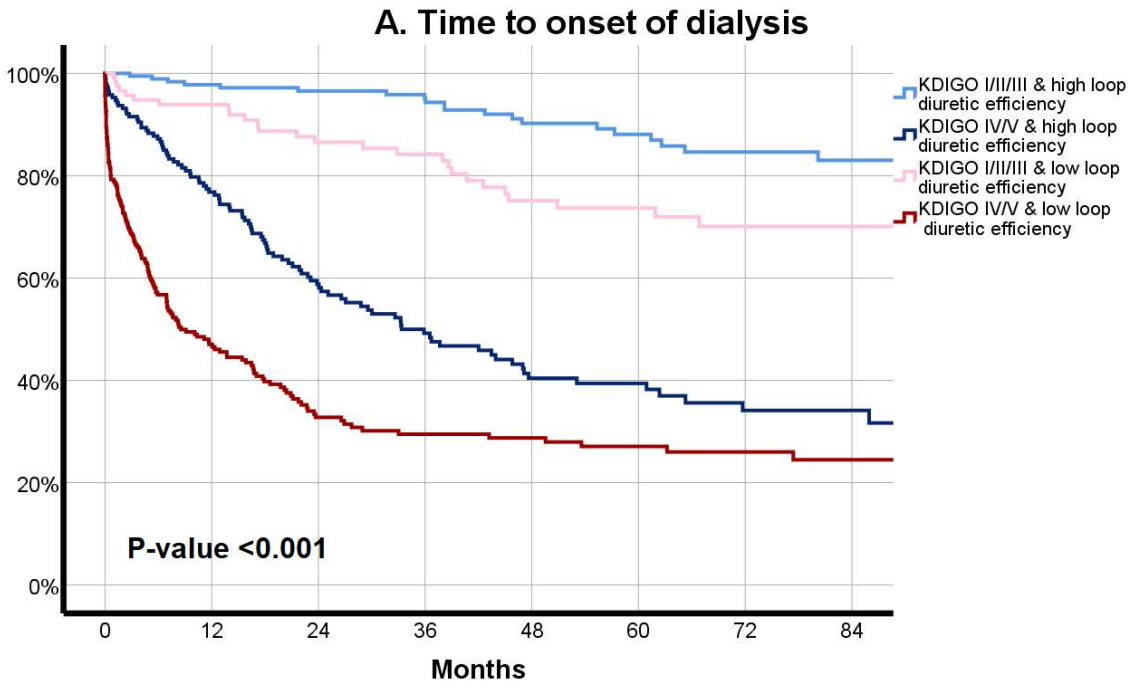

C. 24 h Chloruresis (mmol) adjusted for loop diuretic dose
Furosemide
Bumetanide/torsemide
350
300
250
200
150
100
50
0
I/II/IIIA
IIIB
IV
V
KDIGO class

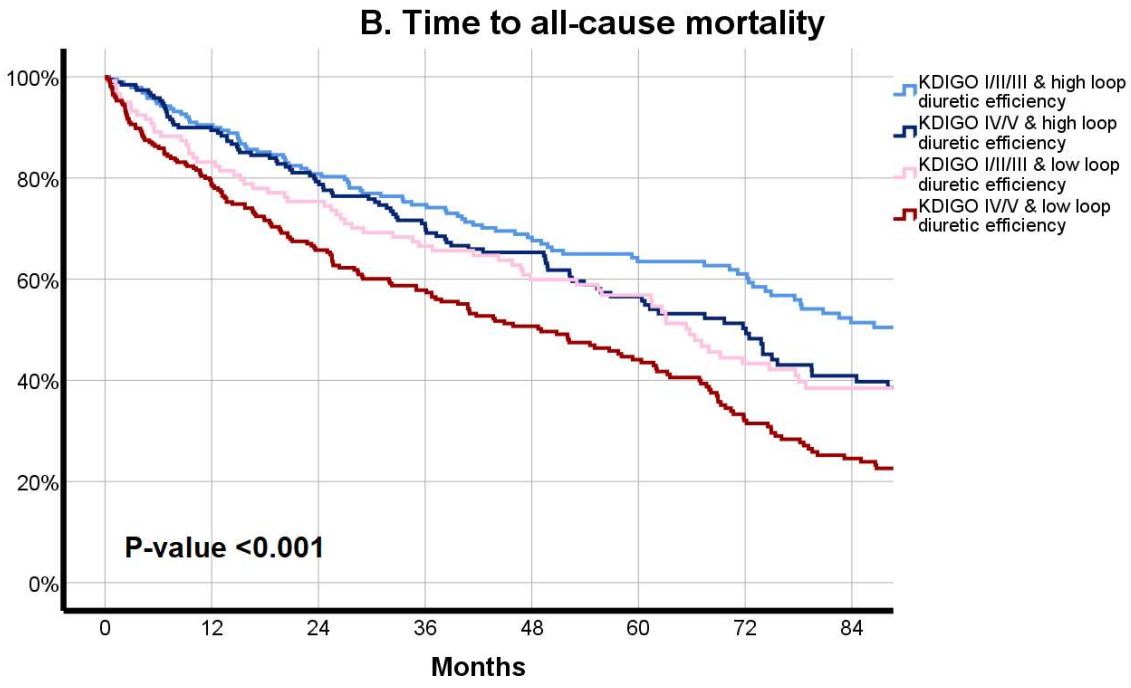
1

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

Bumetanide/torsemide	Urine output/ loop diuretic dose*	Natriuresis/ loop diuretic dose*	Chloruresis/ loop diuretic dose*
Cr clearance	ρ = 0.436	ρ = 0.407	ρ = 0.428
	*ρ = 0.538	*ρ = 0.436	*ρ = 0.447
Loop diuretic dose	ρ = -0.826	ρ = -0.760	ρ = -0.734
	*ρ = -0.356	*ρ = -0.320	*ρ = -0.282
Urine output	ρ = 0.481	ρ = 0.423	ρ = 0.422
	*ρ = 0.918	*ρ = 0.669	*ρ = 0.634
Natriuresis	ρ = 0.390	ρ = 0.613	ρ = 0.601
	*ρ = 0.662	*ρ = 0.950	*ρ = 0.891
Chloruresis	ρ = 0.343	ρ = 0.547	ρ = 0.619
	*ρ = 0.614	*ρ = 0.867	*ρ = 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
100%
80%
60%
40%
20%
0%
0
12
24
36
48
60
72
84
Months
P-value <0.001
KDIGO I/II/III & high loop diuretic efficiency
KDIGO IV/V & high loop diuretic efficiency
KDIGO I/II/III & low loop diuretic efficiency
KDIGO IV/V & low loop diuretic efficiency


B. Time to all-cause mortality
100%
80%
60%
40%
20%
0%
0
12
24
36
48
60
72
84
Months
P-value <0.001
KDIGO I/II/III & high loop diuretic efficiency
KDIGO IV/V & high loop diuretic efficiency
KDIGO I/II/III & low loop diuretic efficiency
KDIGO IV/V & low loop diuretic efficiency

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