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REVIEW ARTICLE

Urinary markers in heart failure – types, timing and thresholds. *European Journal of Heart Failure* expert consensus document

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Several urinary markers reflect disease severity and have the potential to support the management of heart failure (HF). Collecting urine samples is easy and inexpensive, and urine sample composition can be altered not only by underlying kidney impairments (i.e. filtration barrier damage and tubular injury) but also via neurohormonal and inflammatory activation, ageing, comorbidities, other medical conditions and pharmacological interventions. For instance, urinary sodium may help to predict the response to loop diuretic therapy in acute HF, while albuminuria is used as a risk marker and therapeutic target for the progression of cardiovascular and kidney diseases in chronic HF, especially when accompanied by kidney disease. However, these markers remain underutilized in clinical practice. This review paper underscores the role of urinary markers in HF, with a specific focus on: (i) the pathophysiologic mechanisms underlying urinary marker excretion, (ii) the prognostic values of urinary markers across diverse HF phenotypes and non-cardiovascular comorbidities (i.e. chronic kidney disease and diabetes), (iii) the impact of medical therapies on urinary markers, and (iv) existing knowledge gaps that challenge their implementation in clinical practice. The recommendations are aligned with current guidelines, evidence, and expert consensus.

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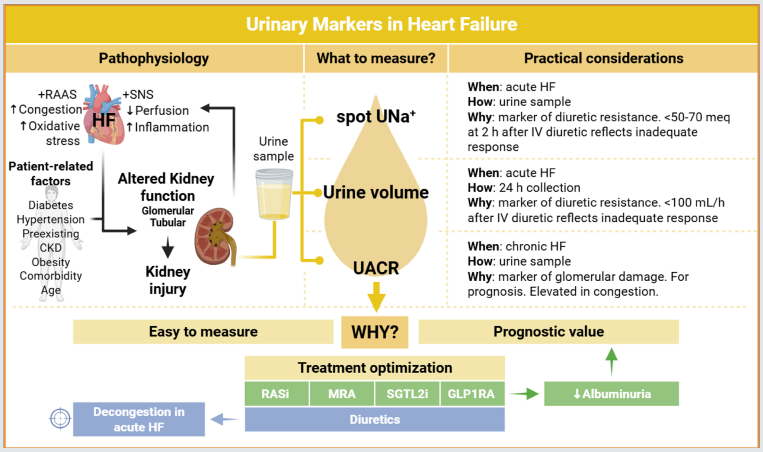
Graphical Abstract



Pathophysiologic mechanisms of heart failure (HF) (i.e. renin–angiotensin–aldosterone system [RAAS], congestion, and inflammation), together with patient-related factors such as diabetes, hypertension, and chronic kidney disease (CKD), contribute to kidney function decline and glomerular or tubular injury. These alterations can be assessed through simple urinary marker tests. In acute HF, spot urinary sodium (UNa^+) and urine volume provide important information on diuretic response, while in chronic HF, urinary albumin-to-creatinine ratio (UACR) reflects glomerular damage and is strongly associated with congestion as well as long-term CKD and/or cardiovascular disease (CVD) outcomes. Several guideline-directed therapies, including renin–angiotensin system inhibitors (RASi), mineralocorticoid receptor antagonists (MRA), sodium–glucose co-transporter 2 inhibitors (SGLT2i), and glucagon-like peptide-1 receptor agonists (GLP-1RA), support decongestion strategies by enhancing natriuresis with some agents and by reducing albuminuria. Incorporating urinary markers into routine clinical practice may therefore help improve patient care across the spectrum of HF. IV, intravenous; SNS, sympathetic nervous system.

Keywords Heart failure • Urinary markers • Chronic kidney disease • Diabetes • Prognosis

Introduction

Heart failure (HF) is a growing global health burden, driven by increasing rates of comorbidities such as hypertension and diabetes.[1,2] Chronic kidney disease (CKD), as part of a single entity with HF,[3–5] further contributes to development and progression of HF.[6–8] Once HF develops, the risks of hospitalization, mortality, and potential years of life lost are substantial, comparable to those faced by patients with cancer.[9] Therefore, improved management encompassing the entire spectrum of HF, from prevention to treatment and monitoring, is urgently needed.

Obtaining urine samples is easy and inexpensive, and urine samples may reflect the status of kidney and cardiovascular (CV) system function.[10,11] Urine volume is often monitored in patients hospitalized for acute HF to assess diuretic efficacy, while urinary markers are less frequently measured. With growing focus on kidney outcomes, incorporating urinary markers into routine care may help to improve patient care.[12,13] Furthermore, reliance solely on temporary changes in estimated glomerular filtration rate (eGFR) may misguide the assessment of kidney injury or function, especially after initiating renin–angiotensin–aldosterone system (RAAS) inhibitors, mineralocorticoid receptor antagonists (MRAs) or sodium–glucose co-transporter 2 (SGLT2) inhibitors.[14,15] A better understanding of the appropriate types, timing, and thresholds of urinary markers may help improve the lifetime management of HF.[16]

This paper from the Cardio-Renal Disease Committee of the Heart Failure Association of the European Society of Cardiology (ESC) outlines the impact of urinary markers on cardiorenal outcomes, their interaction with HF therapies, and their clinical relevance across all HF stages to support clinical use.

Current guideline recommendations for urinary markers

The 2021 ESC guidelines define 'diuretic response' for the management of diuretic therapy in acute HF: spot urinary sodium concentration >50–70 mEq/L within 2 h and/or urinary output >100–150 ml/h during the first 6 h after diuretic infusion.[17] The 2022 American Heart Association/American College of Cardiology (AHA/ACC) guidelines does not emphasize monitoring of urinary markers as objective metrics to guide diuretic therapy, but recommend the measure of urinalysis when patients are initially diagnosed with HF.[18]

Albuminuria has been traditionally assessed by dipstick, while urinary albumin-to-creatinine ratio (UACR) is a quantitative spot measure that adjusts for urine concentration and correlates well with 24-h excretion, especially in a morning sample.[19] UACR is used to define CKD in combination with eGFR (UACR ≥30 mg/g or eGFR <60 ml/min/1.73 m^2). Multiple guidelines recommend UACR and eGFR for CKD screening, especially in people with hypertension or diabetes. Once CKD is diagnosed, these should be checked at least annually, or more often if CKD progression risk is high. The 2021 ESC prevention guidelines advise albuminuria assessment in men aged >40 years and women aged >50 years or postmenopausal.[20] The 2018 ESC/European Society of Hypertension guidelines recommend UACR screening for all patients with hypertension.[21] The 2025 American Diabetes Association guidelines call for UACR and eGFR checks in type 1 diabetes ≥5 year duration and all type 2 diabetes (T2D), with 1–4 assessments per year if CKD is present.[22] Similarly, the 2024 Kidney Disease: Improving Global Outcomes guidelines recommend monitoring UACR and eGFR at least annually in CKD, with more often in patients at higher risk of CKD progression.[23]

Role of urinary biomarkers in heart failure

This document focuses on clinically useful markers and does not address those used mainly for research purposes. Various urinary biomarkers are utilized to evaluate the HF status, monitor renal and CV function, and therapeutic response.[24] Different biomarkers offer unique clinical insights; therefore, the combination of multiple markers and the trajectory of a single marker over time can yield more comprehensive clinical information than one value at a single time point.

It is essential to consider several general caveats when evaluating urinary biomarkers and their roles. First, the clinical meaning of a single biomarker can vary in relation to the population being assessed, for example, the stage of HF (A/B vs. C) and the patient's clinical status (acute HF vs. chronic HF). Moreover, some markers such as urinary sodium (UNa^+) need to be assessed under specific (or at least known) conditions to have accurate interpretation and clinical relevance. It is also important to distinguish two major types of biomarkers that reflect two distinct mechanisms: dysfunction versus injury of a specific part of the nephron. As different urinary biomarkers have varying underlying pathophysiology and result from dysfunction or injury of different parts of the nephron, they convey distinct clinical meanings (*Table 1*). Injury biomarkers typically indicate irreversible damage to specific nephron cells or segments, being linked to cellular injury and apoptosis, similar to the role of troponin in heart injury assessment. The example of a kidney injury biomarker is neutrophil gelatinase-associated lipocalin (NGAL); however, clinical usefulness of these biomarkers in HF is still limited. In contrast, biomarkers that reflect renal dysfunction (usually as a response to the pathophysiological signals in HF) have much greater clinical relevance, and include both: markers of glomerular (e.g. eGFR, cystatin C) and tubular (like UNa^+) dysfunction. As glomerular and tubular function is distinct, changes in eGFR do not necessarily reflect intrinsic tubular injury, particularly in the context of acute HF following decongestive therapy.[25] Lastly, it should be also noted that the role of urinary biomarkers is significantly limited in patients with oliguria or anuria, where assessment of kidney function is critically important.

Diuresis and natriuresis associated markers

Urinary sodium concentration

Urinary sodium and chloride excretion reflect tubular ion handling and the degree of sodium avidity (the inner force to conserve and retain sodium). Key pathophysiological factors that control sodium excretion include blood pressure and renal perfusion, haemodynamics (especially central venous pressure), inflammation, neurohormonal activity, and fluid/sodium status.[26–32] In HF, chronic exposure to diuretics additionally leads to structural and functional remodelling of the nephron, as reflected by a decreased natriuretic response to a given diuretic dose.[33,34]

Generally, UNa^+ refers to urinary sodium concentration measured in a urine sample, while natriuresis is defined as the total amount of sodium excreted at a given period. Most scientific evidence on the use of UNa^+ comes from acute HF population particularly in the emergency settings, with limited data in chronic HF and pre-HF. Natriuresis, assessed by spot UNa^+, is a key measure of diuretic response in acute HF and can be used to guide diuretic therapy,[35,36] as recommended in the latest ESC guidelines,[17] especially during the first 24 h. However, the use of UNa^+ in clinical practice remains limited,[37] possibly due to a lack of awareness or logistical issues. The cutoff values to identify adequate diuretic response have been arbitrarily proposed to be UNa^+ >70 mmol/L after 2 h.[38] A low post-diuretic UNa^+ may reflect persistent activation of sodium-retaining pathways and indicate the need for intensified diuretic therapy in most cases; thus, a cutoff value above 70 mmol/L may be appropriate.[39,40] In the Pragmatic Urinary Sodium-based algoritHm in Acute Heart Failure (PUSH-HF) trial, which included 310 patients with acute HF, a UNa^+-guided algorithm led to greater increases in diuresis and natriuresis, without impacting hospitalization stay, 180-day HF rehospitalization nor all-cause mortality.[40] In the Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure (ENACT-HF) trial, which included 401 patients with acute HF, UNa^+-guided therapy increased natriuresis, diuresis and shortened hospital stay.[41] It is also noted that the relationship between UNa^+ and urine volume is exponential (not linear), with higher UNa^+ levels associated with relatively greater urine volume.[42] Additionally, to some extent, UNa^+ is independent of eGFR since they reflect different pathophysiological processes.[43] To enhance clinical applicability, UNa^+ adjusted for urine dilution (based on urine creatinine) is proposed as a better predictor of diuretic response than unadjusted UNa^+,[44] and spot UNa^+-used formula may predict total urine and sodium output.[45]

The second key role of UNa^+ is to identify patients at high risk for HF-related events regardless of different HF severity or care setting (hospitalized or ambulatory).[30,31,36,43,46–55] The natriuretic response to loop diuretics is interpreted as sodium avidity and, consequently, may reflect disease severity associated with

Table 1 Associations of urinary markers with outcomes in heart failure

Study/First author, Year	Population	LVEF, %	eGFR, ml/min/1.73 m^2	Follow-up period	Abnormal value of urinary marker	Outcomes associated with abnormal value of urinary marker
Natriuresis and natriuresis-associated urinary markers						
Singh, 2014[46]	52 patients with acute HF	28 ± 15	55 ± 31	5 months	After initial IV furosemide, UNa^+/furosemide ratio <2 mmol/mg	Higher risk of WRF (adjusted OR 3.01, 95% CI 1.15–10.22; $p = 0.02$). Higher risk of mortality, HF hospitalization or cardiac transplantation (adjusted HR 1.62, 95% CI 1.13–2.39; $p = 0.008$). *main covariates; age, renal function, etc.
Ferreira, 2016[47]	100 patients with acute HF	41 ± 12	53 ± 17	180 days	At day 3, UNa^+ >100 mmol/L	Lower risk of CV death or HF hospitalization (HR 0.16, 95% CI 0.06–0.42; $p < 0.01$).
Doering, 2017[48]	187 patients with acute HF	53% with LVEF <45%	53 (32–72)	30 days	After IV furosemide within 24 h of the ED visits, UNa^+ <50 mmol/L	Higher risk of HF rehospitalization.
Brinkley, 2018[49]	176 patients with advanced HF in an ambulatory clinic	40 (25–55)	46 (33–57)	30 days	After IV furosemide bolus, UNa^+ <65 mmol/L and urine volume <1200 ml	UNa+ <65 mmol/L/urine volume <1200 ml was associated with a ~4-fold higher 30-day hospitalization risk vs. UNa^+ ≥65 mmol/L/urine volume ≥1200 ml.
Luk, 2018[50]	103 patients with acute HF	≈27	≈41	90 days	After an initial IV diuretic, UNa^+ ≤60 mmol/L	Higher risk of death, mechanical support, or inotrope use at discharge (HR 2.39, 95% CI 1.01–5.62; $p = 0.047$) after adjusting for baseline renal function.
Honda, 2018[31]	669 patients with acute HF	38 ± 17	39 ± 19	≈560 days	Immediately after hospitalization, UNa^+ ≤74 mmol/L	More frequent in-hospital WRF, and higher risk of death or worsening HF.
Collins, 2019[51]	61 patients with acute HF	50 (30–55)	48 (31–60)	In-hospital events	1 h after an initial IV diuretic, UNa^+ <35.4 mmol	Higher risk of worsening of HF events (100% sensitivity and 60% specificity).
Biegus, 2019[36]	111 patients with acute HF	32 ± 13	63 ± 27	1 year	NA	Low spot UNa^+ and decrease/no change in UNa^+ in the 6 and 48 h samples were associated with higher risk of 1-year mortality.
Biegus, 2021[43]	219 patients with acute HF	37 ± 14	58 ± 21	1 year	At day 1, UNa^+ <60 mmol/L.	Higher risk of mortality or mortality/HF hospitalization.
Biegus, 2021[30]	172 patients with acute HF	37 ± 14	Cr, 1.3 ± 0.5 mg/dl	1 year	NA	Higher UNa^+ after initial IV furosemide at admission, day 1 and day 2 (first morning urine samples) were associated with lower risk of mortality or HF hospitalization, while discharge UNa^+ was not.
Damman, 2020[54]	175 patients with acute HF	35 ± 16	53 ± 26	257 days	6 h after first intravenous diuretic, UNa^+ <89 mmol/L	Higher risk of mortality (HR 6.24, 95% CI 1.94–20.0, $p = 0.001$) and HF hospitalization (HR 3.62, 95% CI 1.38–9.49, $p = 0.009$). Main covariates, urinary volume.
Elias, 2021[53]	283 patients with chronic HF	76% with LVEF <40%	Cr, 1.3 ± 0.4 mg/dl	5 years	Morning UNa^+ <80 mmol/L and furosemide ≥80 mg/day	Higher risk of mortality.
Caravaca, 2021[52]	65 patients with acute HF who underwent furosemide stress test, IV furosemide bolus within the first 24 h after admission	40 ± 16	66 ± 21	6 months	At 2 h after the furosemide stress test, UNa^+ <113 mmol/L	A smaller reduction in NT-proBNP, longer hospital stay, a higher risk of in-hospital worsening HF, and death/HF rehospitalization over 6 months.
Nawrocka-Millward, 2024[62]	248 patients with acute HF	37 ± 14	Cr at 24 h, 1.3 ± 0.5 mg/dl	1 year	Admission UCl <115 mmol/L	Higher risk of combined in-hospital mortality, inotropic support, worsening HF, need for intensive cardiac care unit, and adverse CV outcomes over 1 year.
Cobo-Marcos M, 2025[55]	167 patients with ambulatory worsening HF	50 ± 15	40 (29–53)	30 days	Three hours after IV diuretics, UNa + <107 mmol/L	Higher 30-day risk of death, HF hospitalization, and outpatient IV diuretic use.
Meekers, 2025[59]	50 patients with stable HF	46 ± 11	47 (35–65)	NA	NA	Patients with successful diuretic down-titration showed increased first-void UNa^+ ($p < 0.001$), unlike those needing re-initiation ($p = 0.33$). A 10 mmol/L UNa^+ increase predicted this success (AUC = 0.85; sensitivity 79.4%, specificity 78.6%).

Table 1 (Continued)

Study/First author, Year	Population	LVEF, %	eGFR, ml/min/1.73 m^2	Follow-up period	Micro-, and macro-albuminuria	HF-related outcomes associated with albuminuria[a]
Albuminuria, urinary albumin-to-creatinine ratio						
HOPE, 2001[88]	Individuals with a history of CV disease ($n = 5545$) or diabetes and at least one CV risk factor ($n = 3498$)	NA	NA	4.5 years	Micro-albuminuria (UACR ≥2 mg/mmol): 32.6% in diabetes and 14.8% in non-diabetes	Outcome; HF hospitalization Micro-albuminuria; HR 3.08 (95% CI 2.49–3.82) *Each 0.4 mg/mmol increase in UACR increased the risk of HF hospitalization by 11%.
RENAAL, 2004[83]	1513 patients with T2D and CKD	NA	40 ± 12	3.4 years	Macro-, 100%	UACR ≥3 g/g vs. <1.5 g/g; higher risk of HF onset (= 2.70, 95% CI 1.94–3.75) *Each 50% reduction in albuminuria was associated with 18% lower risk of CV events and with 27% lower risk of HF onset.
MESA, 2008[81]	6814 participants	NA	NA	4 years	NA	Outcome; developing HF Micro-albuminuria; HR 2.73, 95% CI 1.56–4.78 Macro-albuminuria; HR 5.27, 95% CI 2.30–12.11 Main covariates; established CV risk factors
ARIC Study, 2011[82]	10 975 individuals free from HF	NA	NA	8.3 years	Micro-, 6.2% Macro-, 1.3%	Outcome; developing HF Micro-albuminuria; HR 2.49, 95% CI 1.77–3.50 Macro-albuminuria; HR 3.47, 95% CI 2.10–5.72 Main covariates; renal function and CV risk factors
PREVEND, 2013[82]	8592 individuals from a community-based, middle-aged cohort	NA	81 ± 15	11.5 years	NA	Higher albuminuria levels were associated with a higher risk of developing HFpEF, but not HFrEF.
CHS, FHS, MESA, PREVEND, 2018[80]	22 756 participants in 4 longitudinal community-based cohorts	NA	NA	12 years	NA	Outcome; developing HFpEF Higher UACR; HR 1.33, 95% CI 1.20–1.48 Outcome; developing HFrEF Higher UACR; HR 1.21, 95% CI 1.11–1.32
SPRINT substudy, 2021[86]	8913 individuals at high risk for or with CV disease, a systolic blood pressure of 130–180 mmHg but without diabetes	NA	28.4% with eGFR <60	3.2 years	Micro-, 16.3% Macro-, 2.8%	Outcome; hospitalization or emergency department visit for HF Higher risk increased stepwise from normo- to micro- to macro-albuminuria, regardless of eGFR above or below 60 ml/min/1.73 m^2.
FIDELITY (FIGARO-DKD/ FIDELIO-DKD), 2022[87]	13 026 patients with T2D and CKD (UACR 30–5000 mg/g and eGFR ≥25 ml/min/1.73 m^2)	NA	58 ± 22	3 years	Micro-, 31.5% Macro-, 66.7%	Outcome; first hospitalization for HF Higher risk increased stepwise from normo- to micro- to macro-albuminuria, regardless of eGFR above or below 60 ml/min/1.73 m^2.
SOLVD, 2000[124]	5487 patients with HF and LVEF≤35%	26 ± 6	NA	41.4 months	3.2%, proteinuria by dipstick	Outcome; HF hospitalization Proteinuria; HR 1.81, 95% CI 1.37–2.41 Outcome; mortality Proteinuria; HR 1.73, 95% CI 1.34–2.24.
CHARM program, 2009[92]	2310 patients with chronic HF	39 ± 16	76 ± 30	37.7 months	Micro-, 30% Macro-, 11%	Outcome; CV mortality or HF hospitalization Micro-albuminuria; HR 1.50, 95% CI 1.28–1.75 Macro-albuminuria; HR 1.88, 95% CI 1.53–2.33 Main covariates; treatment allocation (candesartan vs. placebo), diabetes, hypertension and NYHA class.
GISSI-HF, 2010[91]	2131 patients with chronic HF	33 ± 9	Cr, 1.2 ± 0.4	2.9 years	Micro-, 20% Macro-, 5%	Outcome; mortality Micro-albuminuria; HR 1.42, 95% CI 1.11–1.81 Macro-albuminuria; HR 1.70, 95% CI 1.16–2.50 Main covariates; diabetes, hypertension and renal function.

Table 1 (Continued)

Study/First author, Year	Population	LVEF, %	eGFR, ml/min/1.73 m^2	Follow-up period	Micro-, and macro-albuminuria	HF-related outcomes associated with albuminuria[a]
CHART-2, 2012[94]	2465 patients with HF and LVEF ≥50% in Japan	65 ± 9	62 ± 24	2.5 years	29.5%, proteinuria by dipstick	Outcome; CV death Higher risk with proteinuria, regardless of eGFR above or below 60 ml/min/1.73 m^2. Main covariates; diabetes and CV diseases.
Katz, 2014[96]	144 patients with ambulatory HF and LVEF ≥50%	62 ± 7	58 ± 23	12.1 months	Micro-, 25% Macro-, 14%	Every UACR doubling was associated with greater RV remodelling (0.9 m wall thickening, worse systolic function) and higher risk of CV mortali or hospitalization (HR 1.13, 95% CI 1.05–1.31).
TOPCAT, 2018[93]	1175 patients with HF and LVEF ≥45% from TOPCAT Americas	58 ± 8	65 ± 21	3.5 years	Micro-, 35% Macro-, 13%	Outcome; CV mortality, aborted cardiac arrest, or HF hospitalization Micro-albuminuria; HR 1.47, 95% CI 1.15–1.86 Macro-albuminuria; HR 1.67, 95% CI 1.22–2.28 Covariates; diabetes, renal function and NYHA class *Each UACR reduction by 50% was associated with 10% lower risk of H hospitalization and 9% lower risk of mortality.
Shuvy, 2020[95]	4668 patients with HF in Israel	NA	68 (48–90)	2 years	Micro-, 38% Macro-, 17%	Outcome; mortality Micro-albuminuria; HR 1.18, 95% CI 1.02–1.38 Macro-albuminuria; HR 1.33, 95% CI 1.10–1.61 Main covariates; diabetes, hypertension and renal function.
Matsumoto, 2022[101]	140 patients hospitalized for acute HF	43 ± 18	52 ± 25	1 years	Micro-, 59% Macro-, 23% *Admission UACR	Outcome; HF rehospitalization Higher risk increased stepwise from normo- to micro- to macro-albuminuria collected at admission.
BIOSTAT-CHF, 2023[102]	2315 patients with worsening HF (LVEF ≤40% or BNP >400 pg/ml or NT-proBNP >2000 pg/ml)	31 ± 11	51 ± 15	21 months	Micro-, 35.4% Macro-, 10.0%	Outcome; CV death or HF hospitalization Higher risk increased stepwise from normo- to micro- to macro-albuminuria, regardless of HFrEF or HFpEF.
Ioannou, 2024[103]	1181 patients with ATTR-CA	48 ± 10	59 (47–74)	≤60 months	Micro-, 88.6% Macro-, 11.4%	Outcome; mortality Micro-albuminuria; HR 1.47, 95% CI 1.13–1.92 Macro-albuminuria; HR 1.87, 95% CI 1.15–3.05 Main covariates; diabetes and National Amyloidosis Centre disease stage *Among 330 patients without hypertension/diabetes or CKD, ≥30% UA increase was associated with higher risk of 1-year mortality (HR 1.84 95% CI 1.06–3.19; $p = 0.030$).

ATTR-CA, transthyretin cardiac amyloidosis; AUC, area under the curve; BNP, B-type natriuretic peptide; CI, confidence interval; CKD, chronic kidney disease; Cr, creatinine; CV, cardiovascular; ED, emergency department; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure and preserved ejection fraction; HFrEF, heart failure and reduced ejection fraction; HR, hazard ratio; IV, intravenous; LVEF, left ventricular ejection fraction; NA, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio; UCl, urinary chloride; UNa^+, urinary sodium; WRF, worsening renal function.

[a]Hazard ratios for HF-related events are presented for micro- and macro-albuminuria, compared to normo-albuminuria.

adverse outcomes.[32] Thus, low UNa^+ in response to diuretics is associated with poor outcomes (i.e. in-hospital complications, HF rehospitalization, and death).[31,36,43,56] Patients who fail to increase urine sodium with diuretics and require escalating diuretic dose are at high risk of outcomes.[39] Furthermore, a simple assessment of UNa^+ in acute HF provides insight into intrinsic renal sodium avidity and may help predict decongestive effectiveness, regardless of diuretic use.[57] In patients with ambulatory HF, serial UNa^+ assessments showed that declines in UNa^+ preceded HF hospitalization, while increases in UNa^+ predicted successful diuretic down-titration, potentially aiding the management of ambulatory patients with HF.[58,59]

Urinary chloride

Urinary chloride (UCl^-) is tightly linked to UNa^+, serving as a key factor of tubuloglomerular feedback regulation, modulating renin and aldosterone activity.[60] In patients hospitalized for acute HF, lower UCl^- levels on admission were significantly associated with higher blood-based markers of RAAS (i.e. plasma renin activity and serum aldosterone)[61] as well as with the risk of worsening renal function (WRF) and post-discharge adverse events.[62,63] During decongestion therapy, trajectories of UCl^- levels were strongly correlated with changes in UNa^+ at all time points from admission to hour 6. The UCl^- trajectory was influenced by the chronic use of diuretics and may serve as a predictor of diuretic response, similar to observations with UNa^+.[64]

Fractional excretion of sodium

Fractional excretion of sodium (FeNa) is a calculated variable that describes how efficiently the kidneys reabsorb/excrete sodium. It is believed that FeNa reflects the renal tubular function in response to haemodynamic, hormonal, and metabolic stimuli.[65,66] From a clinical perspective, FeNa has primarily been used for the diagnosis of acute tubular necrosis and its aetiology. A FeNa <1% suggests prerenal azotaemia and sodium retention (i.e. dehydration, renal artery stenosis, and HF). However, the use of diuretics will increase sodium excretion (by design), often pushing FeNa above 1%, even if the underlying physiology is prerenal, which significantly limits the interpretation of this biomarker in the context of acute tubular necrosis.

Fractional excretion of urea

Another measure that is derived from both urine and serum biomarkers to assess kidney function in HF, is fractional excretion of urea (FeUrea). The advantage of FeUrea is that it remains a more reliable measure of tubular function even when diuretics have been used. FeUrea serves as a surrogate for renal blood flow and tubular integrity: low FeUrea suggests effective volume depletion or low flow to the kidney, whereas high FeUrea implies intrinsic dysfunction or perhaps an overhydrated state where urea retention signals are minimal. FeUrea <35% had a 98% positive predictive value for prerenal azotaemia, significantly outperforming FeNa in this context.[65] Potentially, FeUrea in HF serves two roles: (1) diagnostic work-up of acute renal dysfunction (prerenal vs. intrinsic), especially useful when loop diuretics confound FeNa, and (2) as an index of volume status and perfusion that can help optimize congestion status during decongestion.[67,68] Notably, the interpretation of FeNa/FeUrea values should always be performed within the clinical context, rather than in isolation (*Table 2*).

Urine volume

Urine volume is a simple and clinically meaningful marker of kidney function in HF. In the acute setting, low urine volume despite adequate diuretic therapy – commonly referred to as diuretic resistance – may signal poor renal perfusion, neurohormonal activation, and progressive cardiorenal syndrome. Reduced urine volume (<100 ml/h or <500 ml/24 h) is associated with persistent fluid overload, increased central venous pressure, and a higher risk of in-hospital mortality and rehospitalization.[38,69] Conversely, an adequate or brisk diuretic response, reflected by early and sustained natriuresis and increased urine volume, is a favourable prognostic marker, indicating effective decongestion and preserved renal tubular function. Therefore, monitoring urine volume over time can aid in therapeutic decision-making and risk stratification in both acute HF and chronic HF.

Monitoring urine volume in HF is simple, non-invasive, and provides real-time feedback on the effectiveness of decongestive therapy, making it a valuable and cost-effective bedside tool. Measuring urine volume in the hour after a diuretic bolus can help identify patients with diuretic resistance and stratify potential HF risk, particularly in the acute setting. However, urine volume captures only changes in total body water, while the upstream cause of congestion is sodium accumulation rather than water retention.[70,71] Thus, it is a non-specific marker of decongestion, and its accuracy can be affected by diuretic timing and the absence of catheterization.

Albuminuria

Albuminuria is a marker of compromised glomerular integrity, permeability, and endothelial dysfunction. Increased central venous pressure, renal venous congestion and increased intraglomerular pressure allow albumin to leak into the urine, while neurohormonal activation (i.e. aldosterone) promotes kidney fibrosis and disrupts the glomerular filtration barrier.[7,72,73] Thus, an elevated UACR in HF often reflects early renal injury from a combination of volume overload, RAAS overactivation, comorbidities (i.e. diabetes, hypertension and CKD), and microvascular inflammation.[72,74,75]

Clinical practice guidelines classify UACR levels as moderately increased (micro-albuminuria: 30–300 mg/g or 3–29 mg/mmol) and severely increased (macro-albuminuria: ≥300 mg/g or ≥30 mg/mmol).[76] Even with normal eGFR, the presence of macro-albuminuria is recognized as an at high-risk population and a therapeutic target for slowing kidney disease progression in the latest guidelines. The associations between UACR levels and CV and kidney disease risk were well-documented even at levels below the micro-albuminuria threshold.[77–79] These associations also align with a risk of HF development. Greater albuminuria

Table 2 The proposed interpretation of fractional excretion of sodium and of urea

Optimal thresholds for FeNa and FeUrea	Interpretation
FeNa <1% or FeUrea <35%	A prerenal cause of AKI, such as hypovolaemia, dehydration, or HF.
FeNa 1–2% or FeUrea 35–50%	An indeterminate range.
FeNa >2% or FeUrea >50%	An intrinsic renal cause of AKI (e.g. acute tubular necrosis, toxic nephropathy)

AKI, acute kidney injury; FeNa, fractional excretion of sodium; FeUrea, fractional excretion of urea; HF, heart failure.

excretion is associated with a higher risk of developing HF in the communities.[80–82] In high-risk individuals (i.e. diabetes and/or CKD), the presence of micro-albuminuria is associated with a ~2-3-fold increased risk of developing HF.[83–87] Among individuals with CV disease or risk factors, even slight increases in UACR significantly heightened the risk of HF progression; each 0.4 mg/mmol rise in UACR was associated with 11% higher HF hospitalization risk.[88] Furthermore, incorporating albuminuria into HF risk models enhances the accuracy of 10-year risk prediction in individuals who were free of HF.[89,90]

For patients with chronic HF, the risk of HF-related outcomes (e.g. CV death or HF hospitalization) consistently increases stepwise from normo-albuminuria to micro-albuminuria and further to macro-albuminuria, regardless of patients with HF and a reduced ejection fraction (HFrEF) and a preserved ejection fraction (HFpEF).[91–96] Furthermore, the association between albuminuria reduction and HF-related event risk reduction was also reported.[83,93] In a sub-analysis of the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial, each UACR reduction by 50% was associated with 10% lower risk of HF hospitalization and 9% lower risk of mortality in HFpEF.[93]

Preclinical and clinical studies suggest that albuminuria is considered as a marker of congestion,[97,98] which may reflect the high prevalence of micro-albuminuria in acute HF (~70%) compared to chronic HF (~40%).[93,96,99–101] In a cohort study of 115 patients with acute HF, UACR significantly decreased from admission to day 7, paralleling decreases in circulating natriuretic peptide levels.[100] In 2315 patients with worsening HF from European countries, higher UACR levels were associated with markers of congestion, including clinical signs, echocardiographic findings, key biomarkers (i.e. natriuretic peptide, cancer antigen 125, adrenomedullin), as well as with worse prognosis.[102] Similar associations with disease severity and prognosis were also observed in transthyretin cardiac amyloidosis.[103]

Effects of guideline-directed therapies on diuretic/natriuretic markers and albuminuria

Certain foundational therapies for HF, CKD or T2D improve kidney health, i.e. increase natriuresis and reduce albuminuria and eGFR decline in the long term. RAAS inhibitors may improve diuretic efficacy,[104] while SGLT2 inhibitors add glucosuria-driven diuresis.[105,106] In the STRONG-HF trial, rapid in-hospital initiation or up-titration of HF therapies improved post-discharge prognosis,[107] which was linked with more effective decongestion, compared to usual care.[108]

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ACEIs/ARBs), SGLT2 inhibitors, and finerenone have reduced albuminuria in CKD, especially in patients with T2D, with most of the reduction observed within 4 weeks of initiation.[109–115] A 30% reduction in UACR over a 6-month period has been suggested as a surrogate marker for a 30% reduction in the risk of CKD and CV disease progression.[116,117] Although some uncertainties remain, albuminuria is expected to serve as a surrogate for HF progression.[74] Importantly, RAAS inhibitors, MRAs and SGLT2 inhibitors caused an early decrease in eGFR without kidney injury or loss of clinical benefits. This favourable effect is mirrored by a sustained albuminuria reduction, which may reflect better treatment response than eGFR alone. Key results supporting the effects of HF therapies on urinary markers are presented in *Table 3*.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Among patients at risk of HF, ACEIs/ARBs increased natriuresis and reduced albuminuria.[118,119] In patients with diabetes and hypertension who have micro- or macro-albuminuria or eGFR <60 ml/min/1.73 m^2, ACEI/ARB use is recommended.[22] Established evidence showed that, among patients with diabetes, ACEIs/ARBs reduced UACR levels, particularly in those with macro-albuminuria, and prevented the development of micro-albuminuria,[114,120,121] while albumin reduction lowered a risk of developing HF.[83,122] However, albuminuria-lowering effects of ACEIs/ARBs in HF are limited by comorbidities such as diabetes.[92,123–125]

Angiotensin receptor–neprilysin inhibitors

Angiotensin receptor–neprilysin inhibitors (ARNI) may also enhance natriuresis. In a sub-analysis of the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, which included 8399 patients with HFrEF (81% on diuretics at baseline), ARNI was associated with more frequent diuretic dose reductions and fewer dose increases compared with enalapril over 1 year.[126] The NATriuretic Response to expansion and dIUretics in huMans

Table 3 The effects of heart failure foundational therapies on urinary markers and clinical outcomes

Study/First author, Year	Population	HF stage	Trial design	Intervention	Follow-up for urinary markers	Urinary marker outcomes	Clinical outcomes
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers							
RENAAL, 2001[114]	1513 patients with CKD and type 2 diabetes (Cr ≈1.9 mg/dl, UACR ≈1250 mg/g)	Stage A/B	Double-blind, randomized, placebo-controlled trial	Losartan 50–100 mg/day vs. placebo	3.4 years	Losartan reduced UACR by 35%, while placebo increased it ($p < 0.001$ for the overall treatment effect).	Doubling serum creatinine, ESKD, or death: 16% risk reduction. First hospitalization for HF: 32% risk reduction.
BENEDICT, 2004[121]	1204 patients with type 2 diabetes and hypertension, but with normo-albuminuria (Cr ≈0.9 mg/dl, UACR ≈5 mg/g)	Stage A/B	Double-blind, randomized, placebo-controlled trial	Trandolapril plus verapamil vs. trandolapril alone vs. verapamil alone vs. placebo	3.6 years	Trandolapril decreased the incidence of micro-albuminuria, regardless of verapamil use.	
ROADMAP, 2011[120]	4447 patients with type 2 diabetes (eGFR ≈85, UACR ≈4 mg/g)	Stage A/B	Double-blind, randomized, placebo-controlled trial	Olmesartan 40 mg/day vs. Placebo	3.2 years	Micro-albuminuria development: 23% risk reduction (95% CI 6–37%).	
SOLVD, 2000[124,125]	5310 patients with chronic HF and absence of baseline proteinuria (LVEF ≈27%)	Stage C, chronic HF	Double-blind, randomized, placebo-controlled trial	Enalapril vs. placebo	2 years	Proteinuria: 62% reduction in 970 patients with diabetes but not in 4335 without diabetes.	Mortality: 16% risk reduction (95% CI 5–26%).
CHARM, 2009[92,123]	2310 North American patients with chronic HF (LVEF ≈39%, eGFR ≈75)	Stage C, chronic HF	Double-blind, randomized, placebo-controlled trial	Candesartan vs. placebo	14 months	Albuminuria: no reduction.	Mortality: no reduction over a median follow-up of 37.7 months (HR 0.90, 95% CI 0.83–1.00, $p = 0.055$).
Angiotensin receptor–neprilysin inhibitors, sacubitril/valsartan							
NATRIUM-HF, 2024[127]	216 patients with chronic HF and LVEF <40% (LVEF ≈34%, NT-proBNP ≈210 pg/ml)	Stage C, chronic HF	Non-randomized, pre-post intervention study	Before and at 2 and 3 months after sacubitril/valsartan initiation, patients underwent 3 phases: (i) rest (0 to 3 h), (ii) load (3 to 6 h, 1 L IV Ringer solution), and (iii) diuretic (6 to 9 h, furosemide given at start)	At month 3, sacubitril/valsartan-treated patients showed greater natriuresis than at baseline and greater diuresis during the load phase at months 2 and 3. Natriuresis increased significantly more than in sacubitril/valsartan-naïve patients, without a rise in urine volume.		
UK HARP-III, 2018[131]	414 patients with CKD (eGFR ≈35, UACR ≈54 mg/g, diabetes 40%)	Stage A/B	Double-blind, randomized, placebo-controlled trial	Sacubitril/valsartan 400 mg/day vs. irbesartan 300 mg/day	12 months	UACR: no difference.	
PARAMOUNT, 2015[134,135]	301 patients with chronic HF and LVEF ≥45% (LVEF ≈58%, eGFR ≈65, UACR ≈15 mg/g, NT-proBNP ≈850 pg/ml)	stage C, chronic HF	Double-blind, randomized, placebo-controlled trial	Sacubitril/valsartan 400 mg/day vs. valsartan 320 mg/day	36 weeks	UACR increased in the sacubitril/valsartan group, whereas it remained stable in the valsartan group (p between groups = 0.016).	NT-proBNP: 23% reduction at 12 weeks (95% CI 8–36%).

Table 3 (Continued)

Study/First author, Year	Population	HF stage	Trial design	Intervention	Follow-up for urinary markers	Urinary marker outcomes	Clinical outcomes
PARADIGM-HF, 2018[132,133]	1872 patients with chronic HF and LVEF ≤40% (LVEF ≈30%, eGFR ≈67, UACR ≈9 mg/g, NT-proBNP ≈110 pg/ml)	Stage C, chronic HF	Double-blind, randomized, placebo-controlled trial	Sacubitril/valsartan 400 mg/day vs. enalapril 20 mg/day	8 months	>25% increase in UACR was more common in the sacubitril/valsartan group vs. the enalapril group ($p < 0.01$).	CV death or HF hospitalization: 20% risk reduction (95% CI 13–27%) after a median follow-up of 27 months.
PARALLAX, 2021[136]	2572 patients with chronic HF and LVEF >40% (LVEF ≈56%, eGFR ≈63, UACR ≈15 mg/g, NT-proBNP ≈770 pg/ml)	Stage C, chronic HF	Double-blind, randomized, placebo-controlled trial	Sacubitril/valsartan vs. active control (i.e. enalapril and valsartan) or placebo stratified by prior use of a renin–angiotensin system inhibitor	24 weeks	Albuminuria was more often in patients treated with sacubitril/valsartan.	NT-proBNP: 16% reduction at 12 weeks (95% CI 12–20%).
Beta-blockers							
Bakris, 2005[140]	1210 patients with hypertension and type 2 diabetes	Stage A/B	Double-blind, randomized, parallel-group trial	Metoprolol tartrate vs. carvedilol	5 months	16% reduction in micro-albuminuria with carvedilol (95% CI 6–25%). Among those with normo-albuminuria, fewer developed micro-albuminuria on carvedilol vs. metoprolol ($p = 0.03$), independent of blood pressure changes.	
Mineralocorticoid receptor antagonists							
Ferreira, 2014[141]	100 patients with acute HF (LVEF ≈43%, Cr ≈1.1 mg/dl, NT-proBNP ≈2900 pg/ml)	Stage C, acute HF	Open-label, non-randomized trial with sequential 1:1 allocation	Spironolactone 50-100 mg/d vs. control	3 days	UNa^+: increase.	NT-proBNP: reduction at day 3.
ATHENA-HF, 2017[143]	360 hospitalized patients with acute HF (LVEF ≈33%, Cr ≈1.2 mg/dl, NT-proBNP ≈4100 pg/ml)	Stage C, acute HF	Double-blind and placebo (or low-dose)-controlled randomized clinical trial	High-dose spironolactone (100 mg) vs. placebo or 25 mg spironolactone (usual care) daily	96 h	Urine volume: no difference.	NT-proBNP: no reduction. Body weight: no change. Congestion relief: no difference. Diuretic dose change: no difference. Risk of 30-day mortality or HF hospitalization: no difference.
MIRAD, 2021[148]	140 patients with CKD and type 2 diabetes (eGFR ≈85, UACR ≈17 mg/g)	Stage A/B	Double-blind, randomized, placebo-controlled trial	Eplerenone 100–200 mg/day vs. placebo	26 weeks	UACR: 34% reduction (95% CI 12–51%)	
Oiwa, 2023[147]	130 patients with CKD and type 2 diabetes (eGFR ≈65, 60% with UACR ≥30 mg/g)	Stage A/B	Open-label randomized trial	Spironolactone 12.5 mg/day *vs.* Control	24 weeks	UACR: reduction	
ARTS-DN, 2015[150]	823 patients with CKD and type 2 diabetes (40% with eGFR ≤60, 37% with UACR ≥300 mg/g)	Stage A/B	Double-blind, randomized, placebo-controlled trial	Finerenone (1.25, 2.5, 5, 7.5, 10, 15 and 25 mg/day) vs. placebo	90 days	UACR reduction (vs. placebo): 21% with 7.5 mg/day, 24% with 10 mg/day, 33% with 15 mg/day, and 38% with 20 mg/day of finerenone.	
FIDELIO-DKD, 2020[109]	5734 patients with CKD and type 2 diabetes (eGFR ≈44, UACR ≈850 mg/g)	Stage A/B	Double-blind, randomized, placebo-controlled trial	Finerenone 10–20 mg/day vs. placebo	2.6 years	UACR: 31% reduction from baseline to month 4 and sustained thereafter.	Kidney composite outcomes: 18% risk reduction (95% CI 7–27%)

Table 3 (Continued)

Study/First author, Year	Population	HF stage	Trial design	Intervention	Follow-up for urinary markers	Urinary marker outcomes	Clinical outcomes
FIGARO-DKD, 2021[110]	7437 patients with CKD and type 2 diabetes (eGFR ≈68, UACR ≈310 mg/g)	Stage A/B	Double-blind, randomized, placebo-controlled trial	Finerenone 10–20 mg/day vs. placebo	3.4 years	UACR: 32% reduction from baseline to month 4 and sustained thereafter.	CV composite outcomes: 13% risk reduction (95% CI 2–24%)
CONFIDENCE, 2025[156]	800 patients with CKD and type 2 diabetes (eGFR ≈54, UACR ≈580 mg/g)	Stage A/B	Double-blind, randomized trial	Finerenone 10–20 mg/day + empagliflozin 10 mg/day vs. finerenone 10–20 mg/day vs. empagliflozin 10 mg/day	180 days	UACR: 29% reduction (finerenone/empagliflozin vs. finerenone) 32% reduction (finerenone/empagliflozin vs. empagliflozin).	Blood pressure: doubled with combination (finerenone/empagliflozin) vs. alone.
ARTS-HF, 2013[152]	392 patients with HFrEF and moderate CKD (LVEF ≤40%, eGFR ≈47, UACR ≈20 mg/g, NT-proBNP ≈1400 pg/ml)	Stage C, chronic HF	Double-blind, randomized, placebo-controlled trial and open-label spironolactone comparator arms	Finerenone (2.5, 5, or 10 mg q.d., or 5 mg twice daily) was compared with placebo and open-label spironolactone (25 or 50 mg/day)	1 month	UACR: reduction in all finerenone dose groups and in spironolactone group, whereas increase in placebo group.	NT-proBNP: reduction in all finerenone dose groups and in spironolactone group, whereas a small increase in placebo group.
TOPCAT Americas, 2018[93,155]	1175 patients with chronic HF and LVEF ≥45% (LVEF ≈58%, eGFR ≈65, 50% with UACR ≥30 mg/g, NT-proBNP ≈900 pg/ml)	Stage C, chronic HF	Double-blind, randomized, placebo-controlled trial	Spironolactone 25–50 mg/day vs. control	1 year	UACR: 39% reduction in overall patients and 76% reduction among those with macro-albuminuria.	CV death, aborted cardiac arrest or HF hospitalization: 18% risk reduction over a median follow-up of 3.3 years in TOPCAT Americas (95% CI 2–31%).
FINEARTS-HF, 2025[153,154]	5797 patients with chronic HF and LVEF ≥40% (LVEF ≈52%, 50% with eGFR ≥60, 50% with UACR ≈60 mg/g, NT-proBNP ≈1100 pg/ml)	Stage C, chronic HF	Double-blind, randomized, placebo-controlled trial	Finerenone 40 mg/day vs. placebo	2.6 years	UACR: 30% reduction from baseline to month 6 and sustained thereafter. New-onset of micro-albuminuria: 24% reduction. New-onset of macro-albuminuria: 38% reduction.	CV death, first or recurrent HF hospitalization or urgent visit for HF: 16% risk reduction over a median follow-up of 32 months (95% CI 5–26%)
Sodium–glucose co-transporter 2 inhibitors							
Mordi, 2020[168]	23 patients with diabetes and stable HF (70% with LVEF <45%, 75% with eGFR ≥60, NT-proBNP ≈2400 pg/ml)	Stage C, chronic HF	Double-blind, randomized, placebo-controlled crossover trial	Empagliflozin 25 mg/day vs. placebo	6 weeks with a 2-week washout period	Urine volume: increase on day 3 and after 6 weeks. Fractional sodium or 24-h urinary sodium excretion: no increase.	NT-proBNP: no change. Body weight: decrease at week 6.
Griffin, 2020[158]	20 patients with diabetes and HF (LVEF ≈43%, eGFR ≈70, NT-proBNP ≈400 pg/ml)	Stage C, chronic HF	Double-blind, randomized, placebo-controlled crossover trial	Empagliflozin 10 mg/day vs. Placebo	Each for 14 days	Urine volume: increase. Fractional and total sodium excretion: increase. Urinary KIM-1: decrease.	NT-proBNP: no change. Body weight: decrease. Blood volume: decrease. Plasma volume: decrease.

Table 3 (Continued)

Study/First author, Year	Population	HF stage	Trial design	Intervention	Follow-up for urinary markers	Urinary marker outcomes	Clinical outcomes
EMPA-RESPONSE-AHF, 2020[163]	79 patients with ADHF (LVEF ≈36%, eGFR ≈55, NT-proBNP ≈5200 pg/ml)	Stage C, acute HF	Double-blind, randomized, placebo-controlled trial	Empagliflozin 10 mg/day vs. Placebo	30 days	Urine volume; increase. Fractional sodium or 24-h urinary sodium excretion: no change.	Dyspnoea score: no change. Diuretic response: no change. Length of hospital stay: no change. Body weight: no change. NT-proBNP on day 4: no change.
Tamaki, 2021[166]	59 patients with type 2 diabetes, within 96 h of ADHF (LVEF ≈44%, eGFR ≈38, NT-proBNP ≈3200 pg/ml)	Stage C, acute HF	Open-label randomized trial	Empagliflozin 10 mg/day vs. other diabetic therapy	7 days	Urine volume: increase. 24-h urinary sodium excretion: increase.	Body weight: no change. NT-proBNP: reduction. WRF: no difference.
EMPAG-HF, 2022[164]	60 patients with ADHF, within 12 h of admission (LVEF ≈45%, eGFR ≈38, NT-proBNP ≈3200 pg/ml)	Stage C, acute HF	Double-blind, randomized, placebo-controlled trial	Empagliflozin 25 mg/day vs. placebo	5 days	Urine volume: increase. Fractional sodium excretion or total urinary sodium excretion: no change.	Body weight: no change. NT-proBNP: reduction.
Kolwelter, 2023[169]	74 patients with stable HF (LVEF ≈40%, eGFR ≈74, NT-proBNP ≈450 pg/ml)	Stage C, chronic HF	Double-blind, randomized, placebo controlled parallel-group trial	Empagliflozin 10 mg/day vs. placebo	3 months	Urine volume: increase. 24-h urinary sodium excretion: no change.	Body weight: decrease. NT-proBNP: no change.
DAPA-RESIST, 2023[167]	61 hospitalized patients with fluid retention resistant to loop diuretics (LVEF ≈40%, eGFR ≈41, NT-proBNP ≈4000 pg/ml)	Stage C, acute HF	Open-label, randomized, parallel group trial	Dapagliflozin 10 mg/day vs. metolazone 5–10 mg daily	3 days	Urine volume: no change. UNa^+: increase.	Cumulative furosemide dose: decrease. Body weight: no change. Pulmonary congestion (lung ultrasound): no change. Fluid volume: no change.
DICTATE-AHF, 2024[165]	240 patients with hypervolaemic acute HF within 24 h of hospital presentation (LVEF ≈40%, eGFR ≈53, NT-proBNP ≈2600 pg/ml)	Stage C, acute HF	Open-label, randomized, parallel group trial	Dapagliflozin 10 mg/day vs. control	5 days	Urine volume: increase. 24-h urinary sodium excretion: increase.	Cumulative weight change/cumulative loop diuretic dose: no change.
EMPA-REG OUTCOME, 2017[178]	4304 patients with type 2 diabetes and at high CV risk (eGFR ≈74, 40% with UACR ≥30 mg/g)	Stage A/B	Double-blind, randomized, placebo-controlled trial	Empagliflozin 10 or 25 mg/day vs. placebo	164 weeks	UACR: 29% reduction (95% CI 10–44%) in macro-albuminuria. 22% reduction (95% CI 11–32%) in micro-albuminuria. 1% reduction (95% CI −10% to 8%) in normo-albuminuria. Progression to macro-albuminuria: 38% reduction.	CV death, non-fatal MI, or non-fatal stroke: 14% reduction (95% CI 1–26%). HF hospitalization: 35% reduction (95% CI 15–50%).

Table 3 (Continued)

Study/First author, Year	Population	HF stage	Trial design	Intervention	Follow-up for urinary markers	Urinary marker outcomes	Clinical outcomes
CREDENCE, 2019[111]	4401 patients with CKD and type 2 diabetes (eGFR ≈56, UACR ≈927 mg/g)	Stage A/B	Double-blind, randomized, placebo-controlled trial	Canagliflozin 100 mg/day vs. placebo	2.62 years	UACR: 31% reduction (95% CI 26–35%)	ESKD, serum creatinine doubling or renal/CV death: 30% reduction (95% CI 18–41%). HF hospitalization: 39% reduction (95% CI 20–53%).
DAPA-CKD, 2020[112]	4304 patients with CKD (eGFR ≈43, UACR ≈950 mg/g, diabetes 68%)	Stage A/B	Double-blind, randomized, placebo-controlled trial	Dapagliflozin 10 mg/day *vs.* Placebo		UACR: 29% reduction (95% CI 26–35%). UACR reduction was greater in T2D than non-diabetes (p for interaction <0.001).	ESKD, eGFR decline >50% or renal/CV death: 39% reduction (95% CI 28–49%). CV death or HF hospitalization: 29% reduction (95% CI 8–45%).
EMPA-KIDNEY, 2023[113]	6609 patients with CKD (eGFR ≈37, UACR ≈330 mg/g, diabetes 46%)	Stage A/B	Double-blind, randomized, placebo-controlled trial	Empagliflozin 10 mg/day vs. placebo	2.0 years	UACR: 19% reduction (95% CI 15–23%).	CKD progression or CV death: 28% reduction (95% CI 18–36%).
EMPEROR-program (EMPEROR-Reduced and Preserved), 2022[180–182]	9673 patients with stable HF (LVEF ≈44%, eGFR ≈58, UACR ≈110 mg/g, NT-proBNP ≈1310 pg/ml)	Stage C, chronic HF	Patient level meta-analysis of double-blind, randomized, placebo-controlled trial	Empagliflozin 10 mg/day vs. placebo	EMPEROR-Reduced, 16 months EMPEROR-Preserved, 26.2 months	New macro-albuminuria: 19% reduction (95% CI 6–30%). Remission to sustained normo- or micro-albuminuria: 31% increase (95% CI 7–59%). UACR: 19% reduction in diabetes, 12% reduction in macro-albuminuria no change in overall population.	CV death or HF hospitalization EMPEROR-Reduced: 25% reduction (95% CI 24–35%). EMPEROR-Preserved: 21% reduction (95% CI 10–31%).
Glucagon-like peptide-1 receptor agonists							
LEADER, 2016[185]	9340 patients with high CV risk and type 2 diabetes (BMI ≈33 kg/m^2, 24% with eGFR ≤60, 12% with UACR ≥30 mg/g)	Stage A/B	Double-blind, randomized, placebo-controlled trial	Liraglutide 1.8 mg/day vs. placebo	3.8 years	In a pooled analysis of LEADER and SUTAIN-6 UACR reduction (vs. placebo): 24% (20–27%) from baseline to year 2.	CV death, non-fatal MI and non-fatal stroke: HR 0.87, 95% CI 0.78–0.97.
SUSTAIN-6, 2016[186]	3297 patients with type 2 diabetes (BMI ≈33 kg/m^2, 70% with eGFR ≤60)	Stage A/B	Double-blind, randomized, placebo-controlled trial	Semaglutide 0.5 or 1.0 mg/week vs. placebo	2.1 years		CV death, non-fatal MI and non-fatal stroke: HR 0.74, 95% CI 0.58–0.95.
SELECT, 2023[187,188]	17 604 obese patients without diabetes (BMI ≈33 kg/m^2, 11% with eGFR <60, 14% with UACR ≥30 mg/g)	Stage A/B	Double-blind, randomized, placebo-controlled trial	Semaglutide 2.4 mg/week vs. placebo	40 months	UACR reduction (vs. placebo): 10.7% (9.2%–13.2%) from baseline to week 104.	CV death, non-fatal MI and non-fatal stroke: HR 0.80, 95% CI 0.72–0.90.

Table 3 (Continued)

Study/First author, Year	Population	HF stage	Trial design	Intervention	Follow-up for urinary markers	Urinary marker outcomes	Clinical outcomes
FLOW, 2024[189]	3533 patients with CKD and type 2 diabetes (BMI ≈ 32 kg/m^2, eGFR ≈47, UACR ≈570)	Stage A/B	Double-blind, randomized, placebo-controlled trial	Semaglutide 1.0 mg/week vs. placebo	3.4 years	UACR reduction (vs. placebo): 32% (25–38%) from baseline to week 104.	ESKD, >50% decrease in eGFR or kidney/CV-related death: HR 0.76, 95% CI 0.66–0.88).
SUMMIT, 2025[192,193]	731 patients with HFpEF and obesity (BMI ≈ 38 kg/m^2, LVEF ≈60%, eGFR ≈64, NT-proBNP ≈200 pg/ml)	Stage C, chronic HF	Double-blind, randomized, placebo-controlled trial	Tirzepatide up to 15 mg/week vs. placebo	104 weeks	UACR reduction (vs. placebo): 25% (13–36%) from baseline to week 24, 15% (−0.1% to 28%) from baseline to week 52.	CV death or worsening HF event: HR 0.62, 95% CI 0.41–0.95.
Diuretics							
DOSE, 2011[195]	308 patients with ADHF (LVEF ≈35%, Cr ≈1.5 mg/dl, NT-proBNP ≈7400 pg/ml)	Stage C, acute HF	Double-blind, randomized and controlled trial	Either a low-dose or high-dose strategy and to administration of furosemide either by IV bolus every 12 h or by continuous IV infusion	72 h	Urine volume: Greater in high-dose vs. low-dose strategy No change between continuous and bolus infusion groups.	Symptomatic congestion: greater relief in high-dose vs. low-dose strategy. Body weight: greater reduction in high-dose vs. low-dose strategy. NTproBNP: greater reduction in high-dose vs. low-dose strategy WRF: more often in high-dose vs. low-dose strategy
CLOROTIC, 2023[197]	230 patients with ADHF who required furosemide 80–240 mg/day (LVEF ≈56%, eGFR ≈43, NT-proBNP ≈4500 pg/ml)	Stage C, acute HF	Double-blind, randomized, placebo-controlled trial	Hydrochlorothiazide vs. placebo	5 days	24 h urine volume: 27% increase. 96 h natriuresis: increase.	72 h body weight: reduction. Patient-reported dyspnoea: no difference.
DIURESIS-CHF, 2019[202]	34 patients with acute HF at high risk for loop diuretic resistance (LVEF ≈43%, eGFR ≈31, NT-proBNP ≈7850 pg/ml)	Stage C, acute HF	Single-blind, randomized and controlled trial	Acetazolamide 250-500 mg/day and low-dose loop diuretics vs. monotherapy with high-dose loop diuretics	72 h	24 h natriuresis: no difference. 24-h natriuresis corrected for loop diuretic dose: increase.	WRF (>0.3 mg/dl Cr): increase. 72-h NT-proBNP: no reduction. Peak neurohumoral activation: no change. Mortality or HF hospitalization: no difference.
ADVOR, 2023[39,203]	462 patients with ADHF (LVEF ≈43%, eGFR ≈48, NT-proBNP ≈6000 pg/ml)	Stage C, acute HF	Double-blind, randomized, placebo-controlled trial	Acetazolamide vs. placebo	72 h	UNa^+: increase. Total natriuresis: increase.	Successful decongestion (no signs of volume overload by day 3 without therapy escalation): 46% increase (95% CI 17–82%).
ECLIPSE, 2008[206]	181 patients with advanced HF (LVEF ≈24%, Cr <3.0 mg/dl)	Stage C/D, chronic HF	Double-blind, randomized, placebo-controlled trial	Tolvaptan at a single oral dose (15, 30 or 60 mg) vs. placebo	12 h	Urine volume: increase. Urinary osmolality: decrease.	Catheter-assessed intracardiac pressure (i.e. pulmonary capillary wedge pressure): decrease.

Table 3 (Continued)

Study/First author, Year	Population	HF stage	Trial design	Intervention	Follow-up for urinary markers	Urinary marker outcomes	Clinical outcomes
TACTICS-HF, 2017[205]	257 patients with ADHF (LVEF ≈33%, Cr≈1.5 mg/dl, NT-proBNP ≈10 200 pg/ml)	Stage C, acute HF	Double-blind, randomized, placebo-controlled trial	Tolvaptan 30 mg vs. placebo	72 h	48-h fluid loss: increase. 72-h fluid loss: no difference.	Dyspnoea relief at 8 h: no change. Dyspnoea relief at 24 h: no change. Need for rescue therapy: no change. In-hospital outcomes: no change. Post-discharge outcomes: no change. Body weight: decrease. WRF: more often.
CLICK, 2021[201]	160 patients with stage 4 CKD and uncontrolled hypertension (eGFR ≈23, UACR ≈840 mg/g, NT-proBNP ≈590 pg/ml, diabetes 75.6%)	Stage A/B	Double-blind, randomized, placebo-controlled trial	Chlorthalidone vs. placebo	12 weeks	UACR: 50% reduction (95% CI 37–60%).	24 h systolic blood pressure: 10.5 mmHg reduction.
Vasodilators							
ASCEND-HF, 2013[207,208]	4881 patients with ADHF (LVEF ≈30%, eGFR ≈60, NT-proBNP ≈4500 pg/ml)	Stage C, acute HF	Double-blind, randomized, placebo-controlled trial	Nesiritide vs. placebo	24 h	24-h urine volume: no difference.	Dyspnoea at 6 h: improved. Dyspnoea at 24 h: improved. Death or HF rehospitalization: no difference. WRF: no difference.
ROSE, 2013[209]	360 patients with acute HF and renal dysfunction (eGFR 15–60 ml/min/1.73 m^2) (LVEF ≈33%, eGFR ≈43, NT-proBNP ≈5100 pg/ml)	Stage C, acute HF	Double-blind, randomized, placebo-controlled trial	Patients were first randomized 1:1 to dopamine or nesiritide groups. Within each, they were further randomized in a double-blind 2:1 ratio to low-dose dopamine or placebo, and low-dose nesiritide or placebo, respectively	72 h	72-h cumulative urine volume: no difference.	Symptom relief: no difference. NT-proBNP: no change. WRF: no difference. Hypotension: no difference.
LASCAR-AHF, 2025[210]	247 patients with ADHF (LVEF ≈30%, eGFR ≈60, NT-proBNP ≈4500 pg/ml)	Stage C, acute HF	Open-label, randomized controlled trial	Carperitide vs. control	72 h	72-h cumulative urine volume: no difference.	Death or HF hospitalization at 2 years: no difference. Dyspnoea: no difference. BNP: no reduction.

ADHF, acute decompensated heart failure; BNP, B-type natriuretic peptide; CI, confidence interval; CKD, chronic kidney disease; Cr, creatinine; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; HR, hazard ratio; KIM-1, kidney injury molecule-1; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; UACR, urinary albumin-to-creatinine ratio; UNa^+, urinary sodium; WRF, worsening renal function.

with Heart Failure (NATRIUM-HF) trial showed increased UNa^+ and urine volume at 2–3 months after ARNI initiation compared to baseline.[127] The natriuretic and diuretic effect of ARNI may mirror its clinical benefits in worsening HF, regardless of left ventricular ejection fraction (LVEF).[128–130]

The effect of ARNI on albuminuria excretion may differ between HF and non-HF populations. In the United Kingdom Heart and Renal Protection-III (UK HARP-III) trial, which included 414 patients with CKD (eGFR 20–60 ml/min/1.73 m^2), ARNI did not alter UACR levels over 12 months compared with irbesartan.[131] In contrast, among trials with available albuminuria data, ARNI consistently increased UACR levels in patients with HF, compared with comparators, including enalapril in HFrEF from the PARADIGM-HF trial, valsartan in HFpEF from the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) trial, and control (i.e. enalapril, valsartan, or placebo) in HFpEF from the Prospective Comparison of ARNI vs Comorbidity-Associated Conventional Therapy on Quality of Life and Exercise Capacity (PARALLAX) trial, despite robust CV benefits, particularly in HFrEF, and potential renal risk reduction.[132–138] These intriguing findings may reflect ARNI-induced afferent vasorelaxation and efferent vasoconstriction, which together increase intracapillary hydraulic pressure and albumin ultrafiltration, partly via natriuretic peptides.[139]

Beta-blockers

The impact of beta-blockers on urinary markers has been scarcely reported. In patients with diabetes, their effects on blood pressure, sympathetic tone, and vascular inflammation may influence podocyte integrity and endothelial function, potentially altering albuminuria.[140]

Mineralocorticoid receptor antagonists

Although preclinical studies support the natriuretic effects of MRAs, clinical data in HF remain limited.[141,142] In the Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) trial, which included 360 patients with acute HF, spironolactone 100 mg/day did not increase urine volume, reduce natriuretic peptides, nor improve congestion over 72 h in acute HF, compared to placebo or spironolactone 25 mg/day.[143] However, given the slow onset of spironolactone (>24 h), eplerenone, with its shorter half-life and faster onset, may be more suitable for acute HF.[4] In the Early Initiation of Eplerenone Treatment in Patients with Acute Heart Failure (EARLIER) trial, which included 300 patients with acute HF, eplerenone versus placebo reduced diuretic requirements, lowered natriuretic peptide, and improved echocardiographic measures of cardiac filling pressures despite lacking urinary data.[144,145]

Mineralocorticoid receptor antagonists, both steroidal and non-steroidal, consistently reduced albuminuria in patients with CKD.[146–150] In particular, finerenone lowered UACR levels compared with placebo in 5734 patients with T2D and advanced CKD in the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial,[109] and also in 7437 patients with a broader eGFR range (up to 90 ml/min/1.73 m^2) and moderate albuminuria (≈310 mg/g) in the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial.[110] Using these data, 30% UACR reduction with finerenone was associated with a lower risk of kidney outcomes by 64% and CV outcomes by 26%.[151] Similarly, steroidal or non-steroidal MRAs reduced albuminuria in HF. In the MinerAlocorticoid Receptor antagonist Tolerability Study-Heart Failure (ARTS-HF) trial, spironolactone or finerenone lowered UACR levels over 1 month in patients with HFrEF and CKD.[152] In the TOPCAT Americas and Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure (FINEARTS-HF) trials, spironolactone and finerenone reduced UACR levels compared with placebo, findings that may align with their potential benefits in HFpEF and HF with mildly reduced ejection fraction.[93,153–155] It should be noted that, in TOPCAT Americas, reducing UACR by 50% was independently associated with reduced risk of all-cause mortality and HF hospitalization.[93]

Furthermore, a combination of finerenone and empagliflozin reduced UACR levels by approximately 30% greater than either drug alone in T2D and CKD.[156] Whether MRAs/SGLT2 inhibitors may further reduce albuminuria in HF and help prevent HF progression warrants further investigation.[157]

Sodium–glucose co-transporter 2 inhibitors

Sodium–glucose co-transporter 2 inhibitors block glucose reabsorption and simultaneously modulate tubular sodium reabsorption through their structural coupling with sodium–hydrogen exchanger isoform (NHE3).[158] Given the varied pharmacokinetics of SGLT2 inhibitors across HF severity, evidence was conflicting on whether their natriuretic or glycosuric effects increased diuresis in acute HF.[159–169] In the Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure (EMPA-RESPONSE-AHF) and Empagliflozin in Acute Decompensated Heart Failure (EMPAG-HF) trials, empagliflozin 10 mg and 25 mg, respectively, increased urine volume over 4–5 days compared to placebo without affecting UNa^+,[162–164] while another trial showed empagliflozin 10 mg/day versus control increased UNa^+ at 24 h.[166] However, despite the various natriuretic effects and the attenuated diuretic response observed over time,[170] the EMPagliflozin 10 mg compared with placebo, initiated in patients hospitalized for acUte heart faiLure who have been StabilisEd (EMPULSE) trial showed that patients treated with empagliflozin experienced greater congestion relief and clinical benefit compared to those with placebo in acute HF.[171,172] In-hospital initiation of SGLT2 inhibitor may reduce the early risk of CV death in patients with acute HF.[173]

Sodium–glucose co-transporter inhibitors reduce albuminuria and slow progression from micro- to macro-albuminuria in patients with T2D and/or CKD,[111,113,174–178] likely due to reduced intraglomerular hyperfiltration and tubular inflammation.[179] In the EMPAREG-OUTCOME trial, which included 4304 patients with T2D and high CV risk, empagliflozin reduced UACR

levels compared to placebo.[178] Albuminuria-lowering effects of SGLT2 inhibitors were also confirmed in landmark CKD trials: canagliflozin in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE; 4401 patients with T2D and CKD),[111] dapagliflozin in the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD; 4304 patients with CKD),[112] and empagliflozin in the Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY; 6609 patients with CKD).[113] However, their effects on albuminuria reduction in HF remain insufficiently studied. In the EMPEROR-program, empagliflozin versus placebo consistently reduced the risk of HF-related events and new-onset macro-albuminuria, and increased remission to normo- or micro-albuminuria irrespective of LVEF, whereas UACR reduction was limited to patients with concomitant diabetes or baseline macro-albuminuria.[180–182]

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 (GLP1) receptor agonists reduced albuminuria particularly in patients with diabetes, by inhibiting renal oxidative stress, fibrosis and apoptosis.[183,184] Among patients with coexisting diabetes and/or obesity, GLP1 receptor agonists are associated with significant UACR reductions compared to placebo, regardless of comorbid CKD.[185–190] However, despite the potential albuminuria reduction effects in patients at risk of HF (i.e. diabetes, obesity and CKD), whether this drug reduced future HF events remained unclear, particularly in HFrEF.[185,191] Nonetheless, among obese patients with HFpEF (LVEF >50%), in the SUMMIT trial, tirzepatide versus placebo reduced the risk of CV death or worsening HF events over 104 weeks, while lowering circulating natriuretic peptide levels, increasing eGFR, and decreasing UACR levels over 52 weeks.[192,193]

Diuretic therapy, vasodilators, and extracorporeal ultrafiltration

Loop diuretics, which inhibit NaCl reabsorption in the ascending limb of the Henle loop, have steep dose–response curves, with minimal natriuretic effect below a threshold dose.[66] Their efficacy may be limited by enhancing distal NaCl reabsorption with chronic use, known as 'braking phenomenon'[33] as well as gut oedema, hypoperfusion, and hypoalbuminaemia which reduce oral absorption and tubular binding.[194] In the Diuretic Optimization Strategies Evaluation (DOSE) trial, high-dose intravenous furosemide improved diuresis and symptom relief but increased the risk of WRF despite no overall efficacy difference among dose strategies or modes of administration (i.e. continuous infusion or bolus) in acute HF.[195]

As other diuretic agents, thiazides block NaCl reabsorption in the distal tubule and increase natriuresis even in cases with loop diuretic resistance via 'sequential nephron blockage'.[196] The classical perspective was recently supported by the results of the Combination of Loop With Thiazide-type Diuretics in Patients With Decompensated Heart Failure (CLOROTIC) trial, in which adding hydrochlorothiazide versus placebo increased 24-h diuresis and natriuresis despite no impact on clinical outcomes in acute HF.[197] Thiazide or thiazide-like diuretics also reduce albuminuria excretion in CKD due to reduced intraglomerular pressure.[198–201] Furthermore, acetazolamide, a carbonic anhydrase inhibitor, blocks proximal tubular sodium reabsorption. In the Diamox/Aldactone to Increase the Urinary Excretion of Sodium: an Investigational Study in Congestive Heart Failure (DIURESIS-CHF) trial, acetazolamide plus bumetanide versus high-dose loop diuretics increased 24-h natriuresis corrected for loop diuretic dose.[202] In the Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial, acetazolamide versus placebo increased natriuresis (>30%), urine volume (>500 ml) over 2 days and achieved successful decongestion.[39,203] Tolvaptan, a vasopressin-2 receptor antagonist, acts on collecting duct, inhibiting water reabsorption without altering UNa^+. Tolvaptan substantially increased urine volume, weight loss, and had short-term favourable effects on the degrees of congestion in acute HF, despite their neutral effects on CV outcomes.[204–206]

Vasodilators may stabilize haemodynamics and accelerate congestion relief in patients with acute HF, treatment with vasodilators failed to augment diuresis, natriuresis or diuretic efficacy.[207–210]

Furthermore, after ultrafiltration, UNa^+ generally decreases since ultrafiltration mechanically removes excess plasma volume and solutes (i.e. sodium), often extracting more sodium than diuretic interventions, which causes RAAS activation and enhances tubular sodium reabsorption.[211,212] While ultrafiltration may achieve efficient decongestion and reduce the risk of rehospitalization, whether it reduces mortality risk remains uncertain.[213–215]

Other urinary markers

Several other urinary markers were assessed for their diagnostic and prognostic values in patients with HF; however, they are not commonly measured in clinical practice. For example, urinary kidney injury molecule-1 (KIM-1) was approved for assessing drug-related toxic side effects in clinical trials, but not for routine clinical use.[216] Measuring urinary NGAL may incur excessive medical expenses, limited insurance coverage and inconsistent reimbursement across healthcare systems. Other urinary markers (i.e. NGAL, KIM-1, N-acetyl-β-D-glucosaminidase [NAG], β-2-microglobulin, N-terminal pro-B-type natriuretic peptide [NT-proBNP] and proteomics) are discussed in online supplementary material.

Urinary markers between heart failure with reduced and preserved ejection fraction

Given that distinct pathophysiology, risk factor profiles, and treatment responses of HFrEF and HFpEF,[217,218] urinary biomarker compositions may differ between these two phenotypes. Patients with HFpEF are more likely to present with albuminuria and

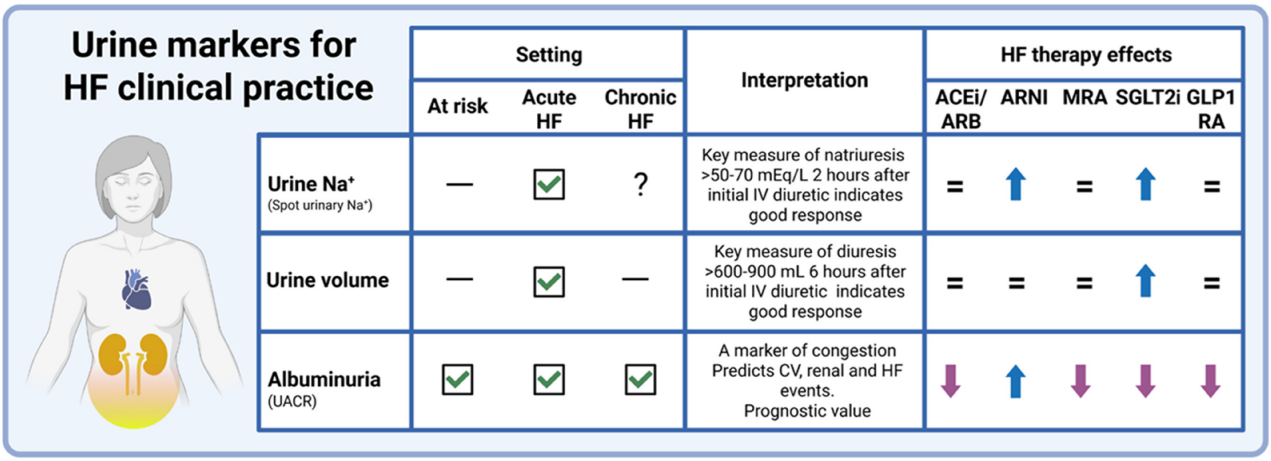


Figure 1 Practical guidance of urinary markers across heart failure (HF) stages. Across HF stages, urinary sodium (Na^+), urine volume and albuminuria provide important clinical insights. Urinary Na^+ and volume are particularly relevant in acute HF, as they help guide diuretic therapy and achieve adequate decongestion. Albuminuria is a surrogate marker for cardiovascular (CV) and HF risk stratification, especially in patients with diabetes and/or chronic kidney disease (CKD), and may also serve as a congestion marker in acute HF. Beyond diuretics, which increase both diuresis and natriuresis (except for vaptans), angiotensin receptor–neprilysin inhibitors (ARNIs) and sodium–glucose co-transporter 2 inhibitors (SGLT2i) increase diuresis, whereas SGLT2i may also increase natriuresis. Most guideline-directed medical therapies lower albuminuria, with the exception of ARNIs, which modestly increase it despite their robust cardiorenal benefits. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; GLP1 RA, glucagon-like peptide-1 receptor agonist; IV, intravenous; MRA, mineralocorticoid receptor antagonists; UACR, urinary albumin-to-creatinine ratio.

show greater severity of albuminuria, compared to those with HFrEF.[102,219] This finding is likely attributable to HFpEF-specific pathophysiology, including systemic endothelial dysfunction and microvascular rarefaction as well as relatively high prevalence of comorbidity burdens such as diabetes and CKD.[220–222] Additionally, beyond glomerular leakage, intrinsic tubular injury or dysfunction may contribute more prominently to kidney impairment in HFpEF than in HFrEF, as suggested by higher levels of tubular injury markers such as urinary NGAL, KIM-1, and NAG.[75,219] However, it remains unclear whether these differences in urinary markers translate into distinct prognostic implications between HFpEF and HFrEF, or whether they represent modifiable therapeutic targets.

Current challenging and practical approach

In clinical practice, natriuresis and albuminuria are not routinely measured. In a global survey on the management of acute HF, spot UNa^+ was infrequently or never measured by ≥85% of physicians, although UNa^+ and urine volume are more commonly measured in academic centres than in non-academic centres.[37] Albuminuria screening rates are globally suboptimal, even among individuals at risk of developing CKD and/or HF.[223–225] To mitigate the existing knowledge gaps that challenge their implementation in clinical practice, we present a summary of clinical information on urinary biomarkers across different stages of HF (*Figure 1*).

At risk of heart failure

In patients with hypertension and diabetes, annual UACR measurement is recommended. If macro-albuminuria persists for ≥3 months or eGFR falls below 60 ml/min/1.73 m^2, a diagnosis of CKD is made. Treatment should include initiation of an ACEI/ARB and an SGLT2 inhibitor, and finerenone is also recommended in patients with T2D and CKD to mitigate potential risk of developing HF. UACR can be re-assessed at least 4 weeks after treatment initiation to identify responders to these treatments. Subsequently, UACR measurements can be monitored one to four times per year, depending on their risk of progression.

Stage C, acute heart failure

In patients hospitalized for acute HF with volume overload, UNa^+ and urine volume should be measured 2 h after initiating intravenous diuretics; if UNa^+ is <70 mmol/L or urine volume is <150 ml/h, the diuretic treatment should be intensified. When diuretic therapy should be optimized on the first day, and once an adequate response is achieved, the same dose should be repeated every 12 h until decongestion is achieved. If 24-h urine volume remains <3 L and congestion persists, further escalation of diuretic doses should be considered. Additional strategies include ultrafiltration, inotropes in cases with low-output states, or combination diuretic therapy (acetazolamide or oral thiazide) in cases with poor diuretic response.

Urinary albumin-to-creatinine ratio can be also monitored during HF hospitalization. During decongestion therapy, UACR typically decreases from admission to the compensated stage, reflecting renal decongestion.

Stage C, chronic heart failure

Patients with chronic HF should be treated with RAAS inhibitors and SGLT2 inhibitors, and steroidal MRAs (i.e. spironolactone and eplerenone) for HFrEF and finerenone for HFpEF. Alongside beta-blockers (for HFrEF), these therapies should be initiated and up-titrated within 6 weeks following acute HF hospitalization if tolerated. UACR should be rechecked 4 weeks after initiation, and can be also interpreted in the context of congestion status, optimized with HF treatments (e.g. diuretics), and closely monitored over time. Additionally, UNa^+ is also monitored to identify patients with high risk of HF-related events.

Future directions

Dedicated trials for urinary markers are essential to implement into clinical practice. For UNa^+ monitoring, several ongoing trials will further evaluate the usefulness of protocolized diuretic therapy in patients with acute HF. The Urine Chemistry Guided Acute Heart Failure Treatment (ESCALATE; NCT04481919) trial is focusing on diuretic titration until decongestion,[226] whereas the Diuretic Treatment in Acute Heart Failure With Volume Overload Guided by Serial Spot Urine Sodium Assessment (DECONGEST; NCT05411991) trial is assessing combination therapy with acetazolamide and chlorthalidone, using a hierarchical composite outcome (i.e. mortality, morbidity and natriuretic peptide change).[227] The use of point-of-care sensor for UNa^+ may facilitate nurse-led diuretic titration or ambulatory diuretic down-titration, thereby enhancing clinical adoption.[59,228] However, as examples of natriuretic peptide-guided management,[229,230] whether natriuresis-guided therapy is weighed over usual care in terms of hard clinical outcomes remains unclear.[40] Furthermore, as albuminuria changes over 6 weeks are considered surrogate endpoints of CKD progression, within the framework of the heart–kidney continuum, it remains unclear whether direct reduction of albuminuria translates into improved HF outcomes, namely, successful decongestion in acute HF and reductions in worsening HF events and CV death in chronic HF.[83,93] Other urinary markers (e.g. NGAL, KIM-1 and NAG) may help clarify the pathophysiology of HF and identify patient subgroups at heightened risk of adverse outcomes. Their clinical adoption, however, awaits robust validation across diverse populations, regulatory approval, and clear demonstration of cost-effectiveness.

Conclusions

Urinary markers, particularly natriuresis and albuminuria, show promise throughout the entire journey of HF from prevention to treatment and monitoring, with natriuresis being used for acute HF management and albuminuria benefiting both prevention and monitoring of chronic HF (especially comorbid CKD). Ongoing trials are expected to clarify the clinical benefits of urinary markers, which may improve routine care for HF. Further evidence from clinical trials and real-world experience, based on guideline-directed management, could promote the broader adoption of these markers in clinical practice.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: M.K. has received speaker fees from Boehringer Ingelheim, Eli-Lilly, Bayer, Daiichi-Sankyo, AstraZeneca, Novartis, and Ono, Kowa and Mochida pharmaceutical company. B.B. has received consultancy fees from Abbott, Abiomed, American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardurion, Cytokinetics, Daiichi Sankyo, Johnson & Johnson, Lantheus, Liva Nova, Merck, Regeneron, Renovacor, Respicardia/Zoll, Roche, Sanofi Aventis, and Vifor. P.L.M. has served on advisory boards and/or received speaker fees from Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Novartis, Novo Nordisk, Pharmacosmos, Roche, Sanofi, US2.ai, and Vifor. G.B. has received personal fees from Abbott, AstraZeneca, and Boehringer Ingelheim. J.D. has received speaker fees from AstraZeneca, Bayer, Boehringer Ingelheim, and Novartis and travel grants from AstraZeneca, Bayer and Daiichi Sankyo. P.P. has received consultancy fees on advisory boards, and received speaker honoraria from Boehringer Ingelheim, AstraZeneca, Vifor Pharma, Servier, Novartis, Merck, Moderna, Bayer, MSD, Abbott Vascular, Novo Nordisk, Pharmacosmos, Reprieve, WhiteSwell, and Relaxera. M.M. has received consulting honoraria from Bayer, Boehringer Ingelheim, Medtronic, Novo Nordisk, and Roche Diagnostics. J.B. has received honoraria from Bayer, Boehringer Ingelheim, and AstraZeneca for lectures, and from Alleviant Medical, Reprieve Cardiovascular, and WhiteSwell for participation in clinical trial advisory boards. All other authors have nothing to disclose.

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