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Risks and benefits of urinary catheterisation during inpatient diuretic therapy for acute congestive heart failure: A retrospective, non-inferiority, cohort study

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Title: Risks and benefits of urinary catheterisation during inpatient diuretic therapy for acute congestive heart failure: A retrospective, non-inferiority, cohort study

Running headline: urinary catheterisation in acute heart failure.

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ABSTRACT:

Objectives: Patients with acute congestive heart failure (HF) regularly undergo urinary catheterisation (UC) at hospital admission. Little evidence exists on the real benefit of using UC in patients treated by diuretics for HF. We aimed at exploring risks and clinical benefits of UC during inpatient diuretic therapy for acute congestive HF.

Design: retrospective, non-inferiority study.

Setting: Geneva University Hospitals' (HUG) Department of Medicine, a tertiary centre.

Participants and intervention: In a cohort of HF, patients catheterised within 24h of diuretic therapy (n=113) were compared with non-catheterised patients (n=346).

Primary and secondary outcome measures: The primary endpoint was the forty-eight hours weight loss after starting diuretic therapy. Secondary endpoints were the time needed to reach target weight, discontinuation of intravenous diuretics, and resolution of respiratory failure. Safety outcomes included the time to a first urinary tract infection UTI, first hospital readmission and death.

Results: Forty-eight hours weight loss was not statistically different between groups and the adjusted difference was below the non-inferiority boundary of 1kg (0.43 kg (95% CI: -0.03–0.88) in favour of UC, $p < 0.01$ for non-inferiority). UC was not associated with time to reaching target weight (adjusted HR 1.0; 95%CI: 0.7–1.5), discontinuation of intravenous diuretics (aHR 0.9; 95%CI: 0.7–1.2), or resolution of respiratory failure (aHR 1.1; 95%CI: 0.5–2.4). UC increased the risk of urinary tract infection (aHR 2.5; 95%CI: 1.5–4.2). UC was not associated with hospital readmission (aHR 1.1, 95%CI: 0.8–1.4) or one-year mortality (aHR 1.4; 95%CI: 1.0–2.1).

Conclusion: The study demonstrated that UC within 24h of initiating diuretic treatment had no impact on clinical improvement and increased risk of a urinary infection. This evidence, therefore, argues against a systematic use of UC during a diuretic therapy for HF.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first study to give an insight into the hypothetical clinically relevant benefits of UC in the context of HF.
- Using a register of prospective records and significant adjustments to potential confounding factors further strengthened our findings.
- The study's retrospective, observational approach only allowed us to hypothesise that urinary catheters were placed for HF management or to facilitate diuresis.
- Since patients are usually not weighed in emergency rooms, we focused on the weight change from days 1 to day 3. Thus, UC's impact during the first 24 h of diuretic therapy was not assessed.
- A randomised prospective design, with protocols to guide rapid diuretic adaptation, would be better able to explore the UC's real potential among HF patients. However, considering current evidence and risks, such a study may never occur.

INTRODUCTION:

Heart failure (HF) is a major, growing, worldwide public health concern, affecting 2% of the developed world's population.[1] HF results in 1.7 million consultations and over 1 million hospitalisations yearly in the USA.[2] Since acute HF is the leading cause of hospitalisations in patients ≥ 65 years old, current demography will increase hospitalisation rates and health care costs.[1, 2]

Diuretics are the mainstay treatments for volume overload.[3, 4] Randomised studies of acute congestive HF have failed to associate either low or high initial doses of diuretics, or different modes of administration (continuous vs intermittent intravenous), with clinically significant differences in outcome.[5] Nevertheless, overly aggressive or insufficient treatments can result in acute kidney injury, electrolytic imbalance, low blood pressure, prolonged hospital length of stay (LOS) or early hospital readmission.[5, 6] Assessing adequate response to diuretics, e.g. measuring diuresis, is therefore important and enables rapid treatment adjustment. This may be as or even more useful than how diuretics are initially administered.

Between one quarter [7] and one half of patients hospitalised for HF undergoes in-dwelling urinary catheter placement.[8] Indications for UC in this population include managing hypervolemia [8, 9] or improving comfort during diuretic treatment.[10] By maximising the elimination of liquids while avoiding excessive losses, UC can have a positive impact on hospital LOS, readmission rates and even death. Although the benefits of UC remain uncertain, the risks of increased infectious and non-infectious complications are well known.[8, 11, 12] A recent retrospective study of catheterised HF

patients showed no impact on LOS and an increased risk of infection.[8] Little evidence exists on UC's impact on clinically relevant improvements such as weight loss, time to improvement of respiratory failure or time to discontinuation of intravenous therapy. The present study aimed to determine the risks and clinical benefits of UC among patients hospitalised for congestive HF.

MATERIALS AND METHODS

We conducted a retrospective, non-inferiority, cohort study using a pre-existing registry of patients admitted to Geneva University Hospitals' (HUG) Department of Medicine for acute HF.[13, 14] Patients signed an informed consent at inclusion and were followed for one year or until death. Data on weight, in-hospital diuretic use, UC and predefined outcomes were obtained from paper medical charts, electronic medical records, laboratory databases and Switzerland's national deaths registry. The institutional review board approved the study and the need for informed consent to collect retrospectively new information, was waived by the ethical committee (Comission cantonale d'éthique de la recherché (CCER)). Reporting and analyses were performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

STUDY POPULATION

All patients ≥ 18 years old and included in the HF registry between 01.01.2006 and 01.01.2010 were eligible.[13, 14] Patients were included in the registry if primarily admitted for acute decompensated HF, with or without volume overload. Patients

without available paper medical charts for the index admission or who did not receive diuretics during their first seven days of hospitalisation were excluded. We compared patients who underwent UC within 24 h of diuretic therapy initiation with those not catheterised.

OUTCOMES

The primary endpoint was the 48 h weight loss after starting diuretic therapy. Secondary endpoints were persistent excess weight at 72 h and at one week, the time needed to reach clinical improvement (reaching target weight (+/- 0.5 kg), discontinuation of intravenous diuretics, oxygen supply and continuous positive airway pressure (CPAP)), and hospital LOS.

Safety outcomes included the proportion of patients with a urinary tract infection (UTI), initial diuretic treatment failure, worsening kidney function and episodes of low blood pressure, and time to a first UTI, first hospital readmission and death. Initial treatment failure was defined as a need for increased doses of diuretics, or a switch from oral to intravenous diuretic therapy or from a bolus to a continuous intravenous diuretic therapy two days or more after the initiation of diuretics. Diuretic dose increases before that point were considered to be usual treatment adjustments.

DATA COLLECTION

Data extracted from medical charts included pre-admission diuretic use, micturition volumes during diuretic therapy, weight at discharge and, for the first seven days, daily

information on the UC, weight, diuretics administration, clinical parameters, oxygen supply and use of CPAP therapy.

Target weight was defined as the patient's weight at discharge or, when unavailable, the lowest weight during hospitalisation that did not result in increased creatinaemia or low blood pressure. We calculated excess weight by subtracting target weight from weights measured during hospitalisation. Since patients are not always weighed on admission day, 48 h weight loss was calculated between days 1 and 3 after starting diuretic therapy (day 0). When weight on day 1 or on day 3, was missing, we took double the mean daily weight loss calculated between day 0 to day 4.

Respiratory failure was defined as the need for oxygen supply or CPAP. We noted episodes of low blood pressure (systolic pressure < 100 mmHg) and the need for saline perfusion. Daily doses of torasemide were multiplied by four and doses of oral furosemide were divided by two to convert daily diuretics use into an equivalent intravenous furosemide dosage.

We obtained patients' habitual kidney function from their general practitioner.[14] Kidney function at hospital admission and during the first week was extracted from the laboratory database. When kidney function at admission was lower than its usual value, acute kidney injury (AKI) was defined using the KDIGO classification, as previously published by the same authors.[14] When kidney function decreased during hospitalisation compared to admission values, it was defined as worsening kidney function and scored according to the KDIGO classification.[14]

Comorbidity burdens were summarised using Charlson index, calculated using the CIM-10 codes from electronic medical charts.[15] HF types were stratified into intermediate or reduced left ventricular ejection fraction (LVEF < 49%), preserved LVEF (LVEF > 50%) and unknown LVEF.

We extracted urinary and blood culture information from the microbiology laboratory database for each febrile episode during hospitalisation. A diagnosis of UTI was defined as bacterial growth of $10E^3$ colony-forming units in a urine sample plus the corresponding symptoms of a UTI.

Information on death was obtained from Switzerland's national deaths registry and Geneva University Hospitals' (the only public hospital in the canton) electronic databases. We reviewed charts for hospital LOS, place of discharge (home vs rehabilitation centre or care home), and all-cause and HF-related hospital readmissions within one year.

PATIENT AND PUBLIC INVOLVEMENT

Patients where not involved in the study design or conduct.

STATISTICS

For our analyses, timings (day 0) were set from the first day of diuretic use, which could differ from the hospital admission day.

Primary analysis and weight evolution

Weight loss analyses during diuretic treatment were restricted to patients with volume overload (excess weight at diuretic therapy). The primary analysis used a linear regression model, where the 48 h weight loss was the dependent variable and UC was the independent variable. The model was adjusted for age (continuous), sex (binary), Charlson index score (continuous), pre-admission diuretic dose (continuous), HF type (categorical), admission heart rate and blood pressure (continuous), respiratory failure (binary), weight excess at diuretic therapy (continuous), first diuretic dose (continuous), use of continuous intravenous diuretics (binary), AKI (categorical) and admission through the emergency room (binary). Adjustment factors were chosen based on clinical expertise. To reach non-inferiority, the upper confidence interval of a between-group difference had to be less than 1 kg (in favour of UC). The 1 kg boundary was arbitrarily chosen as a clinically relevant threshold. Unilateral T-test served to test non-inferiority.

We performed three sensitivity analyses for the main outcome. Firstly, multiple imputation method was used to replace missing values. Missing data, which were all 5% or less, were inspected to ensure that the missing at random assumption was reasonable. Imputation involved all baseline responders and utilised the variables in the adjusted models. Missing data were imputed using chained equations. Twenty imputed datasets were generated and parameter estimates were combined using Rubin's rules. The second sensitivity analysis excluded patients with urinary retention. The third matched catheterised patients 1:1 to non-catheterised patients according to sex and the closest value (< 10%) of a propensity score. The score included all the variables mentioned above except sex. A paired t-test was used to test mean differences.

We used linear regression, adjusted for confounders, to explore associations between UC and persistent weight excess at 72 h and one week. We also tested the interaction between UC and time in a mixed-effects model adjusted for the factors mentioned above. A random intercept for each patient accounted for repeated measures across days. The mean expected excess weights of patients with and without UC was calculated assuming mean values for continuous predictors and a proportion of positive categorical predictors similar to the study sample.

Clinical improvements, safety outcomes and other analyses

The unadjusted impact of UC on time-dependent outcomes was analysed using Kaplan–Meier survival analysis and an unweighted, two-sided, log-rank test to compare groups. Analysis of target weight was restricted to patients with volume overload. Analyses of intravenous diuretics, oxygen supply and CPAP were restricted to patients receiving those therapies. Multivariate Cox models were adjusted for age, sex and Charlson comorbidity index score. For target weight and the time needed to discontinue intravenous diuretics, Cox models were further adjusted for all the confounding factors in the primary analysis. The proportional hazards assumption was verified using Schoenfeld residuals and a visual inspection of the log-minus-log plots.

The association between UC and LOS was tested using a linear regression model adjusted for confounding factors and in which LOS was log-transformed to correct for skewed data. Logistic regression was used to adjust binary outcomes for confounders. Comparisons of characteristics between groups were performed using the chi-squared test or Fisher's exact test, where appropriate, for categorical variables. The Mann–Whitney test was used for continuous variables as these were

not normally distributed. Except for the primary outcomes, all analyses were two-sided, with a significance level set at 5%. All analyses were performed using STATA, version 12.0, and R statistical software, Version 4.0.0.[16]

RESULTS

Of 640 potential participants in the HF register, 174 had no available paper medical chart and 7 had had no diuretic therapy within the first 7 days, leaving a cohort of 459 patients of whom 113 underwent UC within the first 24 h (24.6%). Only four of these patients had documented urinary retention. Catheterised patients were older, more often women, more frequently experienced respiratory failure or AKI, and received higher initial diuretic doses (**Table 1**). Urinary catheters were placed for a median of 4 days (IQR: 2–8). Diuresis was recorded more often among patients with UC (58.0%) than patients without (41.2%, $p < 0.01$).

EXCESS WEIGHT UNDER DIURETIC THERAPY

At diuretic therapy initiation, 342 patients carried excess weight and were included in the primary analysis. In adjusted linear regressions, being catheterised was not associated with significantly greater 48 h weight loss than not being catheterised (0.43 Kg in favour of UC (95% CI: -0.03–0.88)). The upper confidence interval of between-group difference was bellow the non-inferiority boundary of 1 kg ($p < 0.01$ for non-inferiority).

In sensitivity analysis, the results were in line with the primary analysis. The difference in 48 h weight loss, after multiple imputation for missing values, was 0.33 kg (95% CI:

-0.1–0.76; $p < 0.01$ for non-inferiority). Excluding patients with urinary retention (n = 4) did not change the results (data not shown). In the last sensitivity analysis, 64 patients with UC were matched with 64 patients without one (none had urinary retention). The difference in weight loss was 0.29 kg (95% CI: -0.3–0.88; $p < 0.01$ for non-inferiority).

Patients with UC did not have a statistically lower persistent excess weight at 72 h: the difference was 0.27 kg (95% CI: -0.52–1.1; $p = 0.50$) in unadjusted and 0.24 kg (95% CI: -0.17–0.64; $p < 0.001$ for non-inferiority) in adjusted linear regression. At one week, the excess weight difference between patients with and without UC was -0.09 kg (95% CI: -1.0–0.8; $p = 0.84$) in unadjusted and -0.14 kg (95% CI: -0.89–0.60; $p = 0.01$ for non-inferiority) in adjusted linear regression. Similarly, there was no statistically significant interaction between UC and daily excess weight changes in the mixed-effects model ($p = 0.55$; **Figure 1**).

CLINICAL IMPROVEMENT

Time to reach target weight and time needed to discontinue CPAP were not statistically different between patients with and without UC in both unadjusted and adjusted analysis (**Figure 2, Table 2**). UC tended to be associated with a longer time to discontinuation of an intravenous diuretic or discontinuation of oxygen supply (**Figure 2**), but the associations disappeared after adjustment for confounders (**Table 2**).

The median hospital LOS was identical for patients with and without UC (12 days, IQR: 9–18). However, fewer UC patients were discharged directly home from hospital (57.3% vs 73.7%; adjusted OR 0.6 (95% CI: 0.3–0.9; $p < 0.01$)).

SAFETY OUTCOMES

The proportions of initial treatment failures, low blood pressure episodes and patients with worsening kidney function were not statistically different between groups (**Table 2**).

All-cause and HF-related readmissions were not statistically different between patients with and without UC (**Table 2** and **Figure 3**). Half the patients with UC and one third without UC were dead at one year. The difference was not statistically significant after adjustment (**Table 2**).

UC patients were at a higher risk of suffering from a UTI, and this association persisted in adjusted analyses (**Table 2** and **Figure 3**). Multiple UTIs occurred in 9 UC patients (8.0%) and in 5 patients without UC (1.2%, $p < 0.01$). Patients with a UTI had a longer hospital LOS (15 days (IQR: 10–21) vs 11 days (IQR: 8–17), $p < 0.001$) and an increased one-year mortality rate (52.5% vs 34.0%, adjusted HR 1.5; 95% CI: 1.1–2.3; $p = 0.038$).

DISCUSSION AND CONCLUSION

Among patients admitted to medical wards for acute HF, initial weight loss was not different for the strategy of abstaining from UC compared to UC placement within the first 24 h. Besides, UC had no impact on clinical improvement such as the time needed to reach target weight, discontinue intravenous diuretics or improve respiratory failure, and hospital LOS. Furthermore, UC did not prevent excessive diuresis resulting in low blood pressure episodes or worsening kidney function. However, UC was associated with a higher risk of a UTI.

There are few appropriate indications for UC,[11] and 7% to 50% of UCs are done outside these indications.[17, 18] Rates of UC subsequent to HF vary greatly and could be very high. In one study, more than half of haemodynamically stable patients underwent UC.[8] The rationale for UC in HF is weak yet somehow based on beliefs that it facilitates urine elimination and increases comfort by decreasing toilet visits. However, there is good evidence that UC does not increase the comfort of patients undergoing diuretic therapy, even at high dosages.[10] Most guidelines on UC good practice do not list HF as a standard indication.[19] Through their *Choosing Wisely* campaigns, Swiss and American authorities recommend avoiding in-dwelling UC for urine output monitoring in stable patients who can void or for patient or staff convenience.[20, 21] Indication lists, authorities' recommendations and financial penalties have reduced the overall inappropriate use of UC.[11] An American study showed that the proportion of UC among HF patients decreased by 8% between 2009 and 2014.[7]

Catheter-associated UTIs (CAUTIs) are the second most common infections associated with patients hospitalised for HF after *Clostridium*-related infections.[22] Previous reports among HF patients found associations between CAUTI and increased risks of discharge to a skilled care facility, longer hospital LOS, higher total hospital costs and in-hospital mortality.[8, 22] Condom catheters are a better option when diuresis affects older patients with a disability: they lead to fewer complications,[23] are more comfortable and are less painful than UC.[10]

The present study is the first to give an insight into the hypothetical clinically relevant benefits of UC in the context of HF. Using a register of prospective records and significant adjustments to potential confounding factors (some collected retrospectively) further strengthened our findings. However, the study has limitations. Firstly, the study's retrospective, observational approach only allowed us to hypothesise that urinary catheters were placed for HF management or to facilitate diuresis. To minimise these issues, we only selected UCs which occurred in the first 24 h of diuretic therapy. Secondly, since patients are usually not weighed in emergency rooms, we focused on the weight change from days 1 to day 3. Thus, UC's impact during the first 24 h of diuretic therapy was not assessed. A randomised prospective design, with protocols to guide rapid diuretic adaptation, would be better able to explore the UC's real potential among HF patients. However, considering current evidence and risks, such a study may never occur. It is of note that records of the amount of urine passed were only available for half of the patients, with or without UC. Thus, checking for adequate diuresis after treatment with diuretics might be a simpler, safer recommendation than UC for improved HF management. Finally, some medical charts

could not be retrieved, but their unavailability was random and unrelated to their UC status or outcomes. Thus, there is little risk that unavailable charts biased the results.

UC within 24 h of diuretic therapy initiation had no proven impact on the clinically relevant outcomes of time to reach target weight, time to resolve respiratory failure and hospital LOS. The lack of benefits and the increased risk of a UTI preclude systematic UC for the management of HF.

DATA AVAILABILITY

The database, variable explanation, and Stata do-file (in Word format) are available at request to gregor.john@h-ne.ch.

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AUTHORS STATMENT

G.J.: planned the study (protocol), performed the analyses and wrote the manuscript.

S.C.: planned the study (protocol) and reviewed and approved the final manuscript.

D.C.: planned the study (protocol) and reviewed and approved the final manuscript.

N.G.: planned the study (protocol) and reviewed and approved the final manuscript.

J.S.: planned the study (protocol), performed the analyses, and reviewed and approved the final manuscript.

M.A.: collected the data and reviewed and approved the final manuscript.

G.B.: collected the data and reviewed and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

ABBREVIATIONS

AKI: acute kidney injury

CI: confidence interval

CPAP: continuous positive airway pressure HF: heart failure

HR: hazard ratio

HUG: Geneva University Hospitals

KDIGO: Kidney Disease: Improving Global Outcomes

LVEF: left ventricular ejection fraction

OR: odds ratioUC: urinary catheterisation

UTI: urinary tract infection

Figure 1: Predicted excess weight for patients with (black line) and without (green line) urinary catheterisation (UC). Mean expected excess weights and their confidence intervals were calculated using an adjusted mixed-effects model assuming mean values for continuous predictors and a proportion of positive categorical predictors similar to the study sample. UC had no statistical effect on excess weight evolution over time (*p* for interaction = 0.55).

Figure 2: Time to reach clinical improvement for patients with urinary catheterisation (black line) and controls (green line): (A) time to reach target weight; (B) time to discontinuation of intravenous diuretics; (C) time to discontinuation of continuous positive airway pressure therapy; and (D) time to discontinuation of oxygen supply.

Figure 3: Time to reach unfavourable outcomes for patients with urinary catheterisation (black line) and controls (green line): (A) time to first urinary tract infection; (B) time to first all-cause hospital readmission; (C) time to first heart failure-related readmission; and (D) time to death.

Table 1: Characteristics of participants with and without urinary catheterisation (UC). Only UC within 24 h of diuretic therapy initiation was considered. Values are numbers (percentage) unless otherwise stated.

Characteristic	**Cohort (N = 459)**	**With UC (N = 113)**	**Without UC N = 346)**	***P* value**
Age (y), median (IQR)	81 (73–86)	83.5 (76–89)	80 (71–85)	< 0.001
Male	248 (55.2%)	52 (47.3%)	196 (57.8%)	0.053
Admitted through ER	398 (86.7%)	97 (85.8%)	301 (87.0%)	0.754
Night-time admission (19h00–07h00)	169 (36.8%)	37 (32.7%)	132 (38.1%)	0.301
Current smoker	79 (18.0%)	18 (17.3%)	61 (18.1%)	0.844*
High blood pressure	331 (73.7%)	83 (73.7%)	248 (73.2%)	0.709
Diabetes	135 (30.1%)	34 (30.9%)	101 (29.8%)	0.812
Myocardial infarct	27 (6.1%)	6 (5.5%)	21 (6.3%)	0.762*
Stroke	52 (11.8%)	18 (16.1%)	34 (10.2%)	0.076*
Peripheral vascular disease	76 (17.2%)	23 (21.1%)	53 (15.9%)	0.242*
Dementia	30 (6.8%)	9 (8.3%)	21 (6.3%)	0.482*
COPD	66 (14.7%)	16 (14.5%)	50 (14.7%)	0.958*
Oncological disease	32 (7.2%)	8 (7.3%)	24 (7.2%)	0.963*
Liver disease	24 (5.4%)	7 (6.4%)	17 (5.1%)	0.598*
CKD II III IV V	 174 (38.7%) 154 (34.4%) 22 (4.9%) 2 (0.5%)	 39 (35.4%) 40 (36.4%) 6 (5.5%) 0	 135 (39.2%) 114 (33.6%) 16 (4.7%) 2 (0.6%)	0.380
Charlson comorbidity index, median (IQR)	3 (1–4)	3 (2–4)	3 (1–4)	0.115
Pre-admission medication				
ACE/ARB	290 (64.6%)	65 (59.1%)	225 (66.4%)	0.165
Beta-blocker	204 (45.4%)	49 (44.5%)	155 (45.7%)	0.829
Aldosterone inhibitor	62 (13.8%)	14 (12.7%)	48 (14.2%)	0.753*
Diuretics	239 (52.1%)	66 (58.4%)	173 (50.0%)	0.120
Admission characteristics				
Heart rate (beat/min), median (IQR)	81 (70–94)	82.5 (70–91)	80 (69.5–95)	0.785
Mean blood pressure (mmHg), median (IQR)	90 (80–100)	88.3 (78.3–100)	90 (80.3–100)	0.162
AKI I II III	 143 (31.5%) 24 (5.3%) 5 (1.1%)	 46 (41.8%) 9 (8.2%) 3 (2.7%)	 97 (28.6%) 15 (4.4%) 2 (0.6%)	0.002*
Respiratory failure: - Needs oxygen supply - CPAP	371 (80.8%) 365 (79.5%) 75 (16.3%)	105 (92.9%) 104 (92.0%) 27 (23.9%)	266 (76.9%) 261 (75.4%) 48 (13.9%)	< 0.001*
Volume overload - Target weight (kg), median (IQR)	342 (74.5%) 69.2 (58.1–80.8)	86 (76.1%) 70 (58–81.4)	256 (74.0%) 68.7 (58.6–80.5)	0.654
Intravenous therapy	431 (93.9%)	108 (95.6%)	323 (93.4%)	0.391*
Continuous intravenous diuretic therapy	42 (9.2%)	15 (13.4%)	27 (7.8%)	0.076*
Initial diuretic doses (mg), median (IQR)	40 (30–80)	60 (40–90)	40 (20–60)	< 0.001

* Fischer test

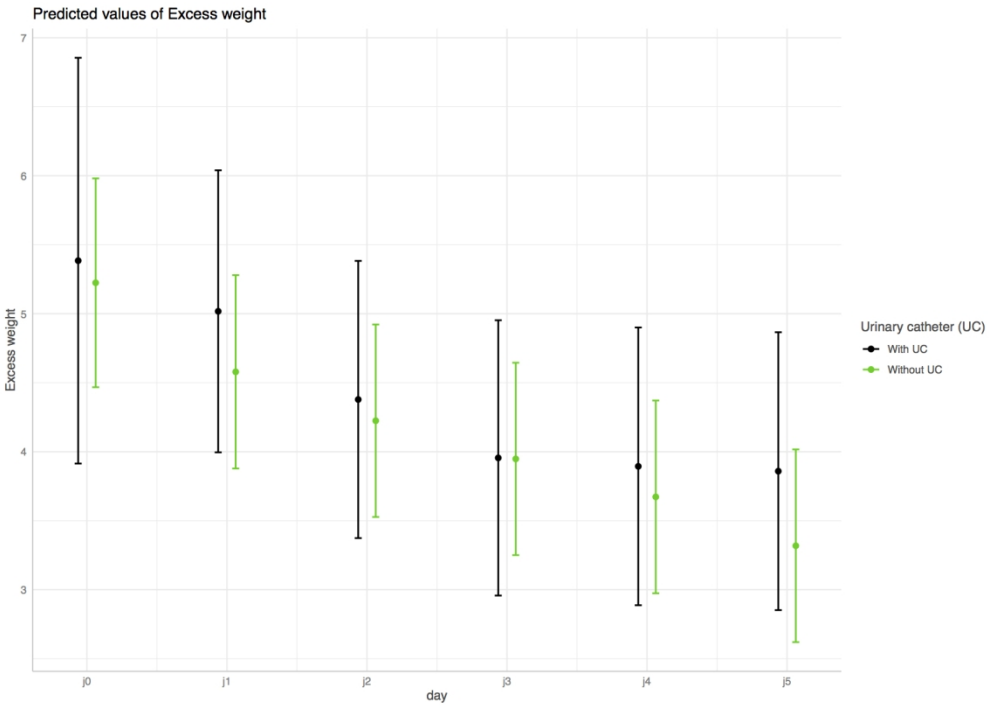
ACE, angiotensin-converting-enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blockers; CKD, chronic kidney disease by CKD-EPI classification; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure therapy; ER, emergency room; UC: urinary catheterisation

Table 2: Clinical improvements and adverse outcomes with and without urinary catheterisation. Values are numbers unless otherwise stated.

Time to clinical improvement	**With UC**	**Without UC**	**HR**	**Adjusted HR**
Time to target weight (d), median (IQR)	6 (3–7)	6 (3–7)	1.1 (0.8–1.5)	1.0 (0.7–1.5)
Time to switch/discontinuation of intravenous diuretics (d), median (IQR)	4 (2–8)	3 (1–6)	0.8 (0.7–1.0)	0.9 (0.7–1.2)
Time to discontinuation of CPAP (d), median (IQR)	4 (2–6)	4 (2–5)	1.2 (0.7–2.2)	1.1 (0.5–2.4)
Time to discontinuation of oxygen supply (d), median (IQR)	4 (2–8)	3 (1–7)	0.8 (0.6–1.0)	0.9 (0.7–1.2)
Time to adverse events	**With UC**	**Without UC**	**HR**	**Adjusted HR**
Urinary tract infection, n (%)	37 (32.7%)	46 (13.3%)	2.9 (1.8–4.8)*	2.5 (1.5–4.2)*
One-year all-cause hospital readmission, n (%)	56 (50.9%)	193 (56.9%)	1.1 (0.8–1.4)	1.1 (0.8–1.4)
One-year heart failure-related hospital readmission, n (%)	28 (25.5%)	91 (26.8%)	1.1 (0.7–1.7)	1.1 (0.7–1.7)
One-year mortality, n (%)	51 (50.0%)	101 (33.4%)	1.7 (1.2–2.4)*	1.4 (1.0–2.1)
Other secondary outcomes	**With UC**	**Without UC**	**OR**	**Adjusted OR**
Initial treatment failure	23 (26.7%)	78 (30.5%)	0.8 (0.5–1.4)	0.8 (0.4–1.4)
Low blood pressure episode - Need of saline perfusion	49 (43.7%) 24/49 (49.0)	154 (44.6%) 67/154 (43.5)	1.0 (0.6–1.5)	1.1 (0.7–1.7)
Worsening of renal function 0 1 2	 82 (74.6%) 27 (24.6%) 1 (-)	 260 (76.7%) 73 (21.5%) 6 (1.8%)	1.1 (0.7–1.8)†	1.1 (0.7–1.8)†

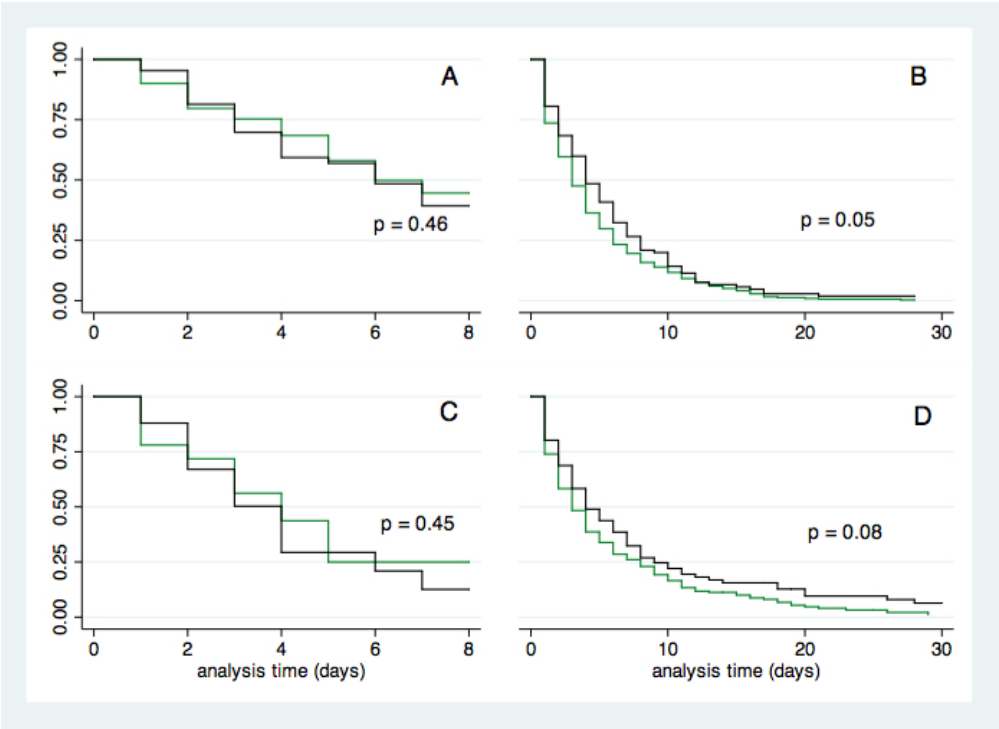
*p value < 0.05; † OR of changing to a worse category

CPAP, continuous positive airway pressure therapy; UC, urinary catheterisation



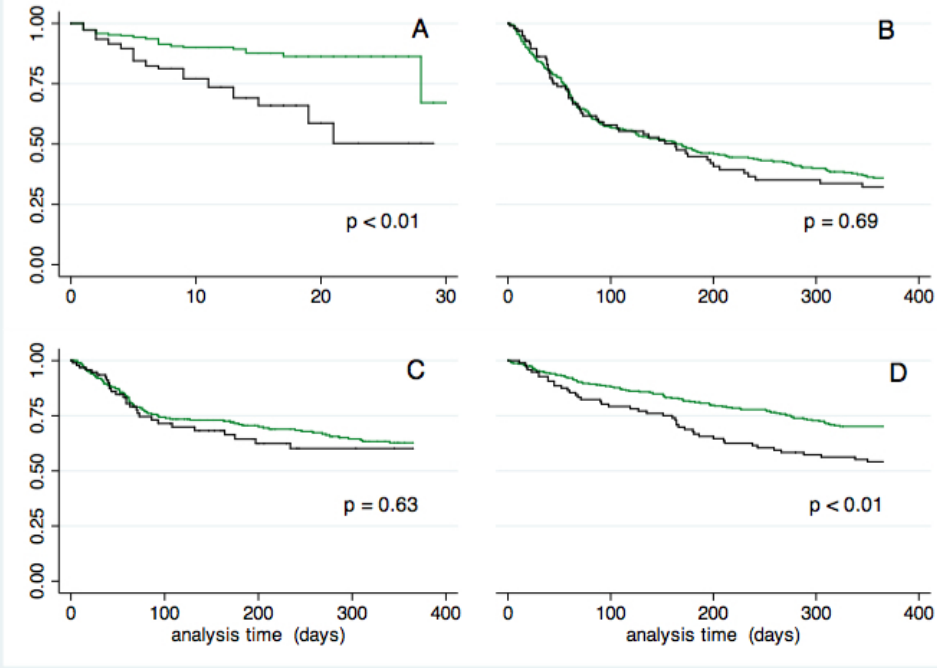
Predicted excess weight (kg) over time (days) for patients with (black line) and without (green line) urinary catheterisation (UC). Mean expected excess weights and their confidence intervals were calculated using an adjusted mixed-effects model assuming mean values for continuous predictors and a proportion of positive categorical predictors similar to the study sample. UC had no statistical effect on excess weight evolution over time (p for interaction = 0.55).

296x209mm (150 x 150 DPI)



Time to reach clinical improvement for patients with urinary catheterisation (black line) and controls (green line): (A) time to reach target weight; (B) time to discontinuation of intravenous diuretics; (C) time to discontinuation of continuous positive airway pressure therapy; and (D) time to discontinuation of oxygen supply.

244x178mm (72 x 72 DPI)



Time to reach unfavourable outcomes for patients with urinary catheterisation (black line) and controls (green line): (A) time to first urinary tract infection; (B) time to first all-cause hospital readmission; (C) time to first heart failure-related readmission; and (D) time to death.

244x178mm (72 x 72 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5	
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6	
Methods				
Study design	4	Present key elements of study design early in the paper	6	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-7	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	10-11	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9	
Bias	9	Describe any efforts to address potential sources of bias	10	
Study size	10	Explain how the study size was arrived at	NA	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-11
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	10-11
		(*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12-14, table 1-2
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	12
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Figure2-3
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Figure2-3
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table2
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16-17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Risks and benefits of urinary catheterisation during inpatient diuretic therapy for acute heart failure: A retrospective, non-inferiority, cohort study

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Title: Risks and benefits of urinary catheterisation during inpatient diuretic therapy for acute heart failure: A retrospective, non-inferiority, cohort study

Running headline: urinary catheterisation in acute heart failure.

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Number of References: 23, **Tables**: 2, **Figures**: 3, and **Appendix**: 0

Word counts: Abstract: 295; Text: 3066

Keywords: Heart-failure, diuretics, urinary catheter, non-inferiority study, hospital readmission, mortality

ABSTRACT:

Objectives: Patients with acute congestive heart failure (HF) regularly undergo urinary catheterisation (UC) at hospital admission. Little evidence exists on the real benefit of using UC in patients treated by diuretics for HF. We aimed at exploring risks and clinical benefits of UC during inpatient diuretic therapy for acute congestive HF.

Design: retrospective, non-inferiority study.

Setting: Geneva University Hospitals' (HUG) Department of Medicine, a tertiary centre.

Participants: In a cohort of HF, patients catheterised within 24h of diuretic therapy (n=113) were compared with non-catheterised patients (n=346).

Primary and secondary outcome measures: The primary endpoint was the forty-eight hours weight loss after starting diuretic therapy. Secondary endpoints were the time needed to reach target weight, discontinuation of intravenous diuretics, and resolution of respiratory failure. Safety outcomes included the time to a first urinary tract infection UTI, first hospital readmission and death.

Results: Forty-eight hours weight loss was not statistically different between groups and the adjusted difference was bellow the non-inferiority boundary of 1kg (0.43 kg (95% CI: -0.03–0.88) in favour of UC, $p < 0.01$ for non-inferiority). UC was not associated with time to reaching target weight (adjusted HR 1.0; 95%CI: 0.7–1.5), discontinuation of intravenous diuretics (aHR 0.9; 95%CI: 0.7–1.2), or resolution of respiratory failure (aHR 1.1; 95%CI: 0.5–2.4). UC increased the risk of urinary tract infection (aHR 2.5; 95%CI: 1.5–4.2). UC was not associated with hospital readmission (aHR 1.1, 95%CI: 0.8–1.4) or one-year mortality (aHR 1.4; 95%CI: 1.0–2.1).

Conclusion: In this retrospective study, with no obvious hourly diuresis-based diuretic adjustment strategy, UC insertion within 24h of initiating diuretic treatment had no impact on clinical improvement but increased risk of a urinary infection. This evidence, therefore, argues against a systematic use of UC during a diuretic therapy for HF.

‘STRENGTHS AND LIMITATIONS OF THIS STUDY’

- The present study is the first to give an insight into the hypothetical clinically relevant benefits of UC in the context of HF.
- The preceded the advent of sacubitril or SGLT2 inhibitors therapy. Nevertheless, in 2021, updated ESC guidelines did not evolve regarding diuretics or the relevance of UC insertion for the management of acute decompensate HF. .
- The study’s retrospective, observational approach only allowed us to hypothesise that urinary catheters were placed for HF management or to facilitate diuresis.
- Since patients are usually not weighed in emergency rooms, we focused on the weight change from days 1 to day 3. Thus, UC’s impact during the first 24 h of diuretic therapy was not assessed.
- A randomised prospective design, with protocols to guide rapid diuretic adaptation, would be better able to explore the UC’s real potential among HF patients. However, considering current evidence and risks, such a study may never occur.

INTRODUCTION:

Heart failure (HF) is a major, growing, worldwide public health concern, affecting 2% of the developed world's population.[1] HF results in 1.7 million consultations and over 1 million hospitalisations yearly in the USA.[2] Since acute HF is the leading cause of hospitalisations in patients ≥ 65 years old, current demography will increase hospitalisation rates and health care costs.[1, 2]

Diuretics are the mainstay treatments for volume overload.[3, 4] Randomised studies of acute congestive HF have failed to associate either low or high initial doses of diuretics, or different modes of administration (continuous vs intermittent intravenous), with clinically significant differences in outcome.[5] Nevertheless, overly aggressive or insufficient treatments can result in acute kidney injury, electrolytic imbalance, low blood pressure, prolonged hospital length of stay (LOS) or early hospital readmission.[5, 6] Assessing adequate response to diuretics, e.g. measuring diuresis, is therefore important and enables rapid treatment adjustment. This may be as or even more useful than how diuretics are initially administered.

Between one quarter [7] and one half of patients hospitalised for HF undergoes in-dwelling urinary catheter placement.[8] Indications for UC in this population include managing hypervolemia [8, 9] or improving comfort during diuretic treatment.[10] By maximising the elimination of liquids while avoiding excessive losses, UC can have a positive impact on hospital LOS, readmission rates and even death. Although the benefits of UC remain uncertain, the risks of increased infectious and non-infectious complications are well known.[8, 11, 12] A recent retrospective study of catheterised HF

patients showed no impact on LOS and an increased risk of infection.[8] Little evidence exists on UC's impact on clinically relevant improvements such as weight loss, time to improvement of respiratory failure or time to discontinuation of intravenous therapy. The present study aimed to determine the risks and clinical benefits of UC among patients hospitalised for congestive HF.

MATERIALS AND METHODS

We conducted a retrospective, non-inferiority, cohort study using a pre-existing cohort of patients admitted to Geneva University Hospitals' (HUG) Department of Medicine for acute HF.[13, 14] Patients were followed for one year or until death. Data on weight, in-hospital diuretic use, UC and predefined outcomes were obtained from paper medical charts, electronic medical records, laboratory databases and Switzerland's national deaths registry. The institutional review board approved the study and the need for informed consent to collect retrospectively information, was waived by the ethical committee (Comission cantonale d'éthique de la recherche (CCER)). Reporting and analyses were performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

STUDY POPULATION

All patients ≥ 18 years old requiring hospital admission for a primary symptom of dyspnoea and a diagnosis of acute decompensated HF between 01.01.2006 and 01.01.2010 were eligible.[13, 14] Acute decompensated HF was diagnosed from patients' clinical presentation, risk factors and treatment responsiveness or was

supported by structural or functional echocardiographic anomalies. Patients with final diagnosis other than HF that explained their dyspnoea, with low NT-proBNP level (<300ng/l), who were admitted to the intensive care unit, whose paper medical charts for the index admission were available or who did not receive diuretics during their first seven days of hospitalisation were excluded. We compared patients who underwent UC insertion within 24 h of diuretic therapy initiation with those not catheterised.

OUTCOMES

The primary endpoint was the 48 h weight loss after starting diuretic therapy. Secondary endpoints were persistent excess weight at 72 h and at one week, the time needed to reach clinical improvement (reaching target weight (+/- 0.5 kg), discontinuation of intravenous diuretics, oxygen supply and continuous positive airway pressure (CPAP)), and hospital LOS.

Safety outcomes included the proportion of patients with a urinary tract infection (UTI), initial diuretic treatment failure, worsening kidney function and episodes of low blood pressure, and time to a first UTI, first hospital readmission and death. Initial treatment failure was defined as a need for increased doses of diuretics, or a switch from oral to intravenous diuretic therapy or from a bolus to a continuous intravenous diuretic therapy two days or more after the initiation of diuretics. Diuretic dose increases before that point were considered to be usual treatment adjustments.

DATA COLLECTION

Data extracted from medical charts included pre-admission diuretic use, micturition volumes during diuretic therapy, weight at discharge and, for the first seven days, daily information on the UC, weight, diuretics administration, clinical parameters, oxygen supply and use of CPAP therapy.

Volume overload (hypervolaemia) was defined as excess weight at diuretic therapy. We calculated excess weight by subtracting target weight from other weights measured during hospitalisation. Target weight was defined as the patient's weight at discharge or, when unavailable, the lowest weight during hospitalisation that did not result in increased creatinaemia or low blood pressure. Since patients are not always weighed on admission day, 48 h weight loss was calculated between days 1 and 3 after starting diuretic therapy (day 0). When weight on day 1 or on day 3, was missing, we took double the mean daily weight loss calculated between day 0 to day 4.

Respiratory failure was defined as the need for oxygen supply or CPAP. We noted episodes of low blood pressure (systolic pressure < 100 mmHg) and the need for saline perfusion. Daily doses of torasemide were multiplied by two and doses of oral furosemide were divided by two to convert daily diuretics use into an equivalent intravenous furosemide dosage.[15]

We obtained patients' habitual kidney function from their general practitioner.[14] Kidney function at hospital admission and during the first week was extracted from the laboratory database. We defined acute kidney injury (AKI) as any kidney function at admission lower than its usual value, and worsening kidney function (WKF) as kidney

function that decreased during hospitalisation relative to admission values.[14] AKI and WKF were scored according to the KDIGO classification. An absolute increase in the creatinine value of 26.4mmol/L, or a 1.5 to <2-fold increase over the baseline creatinine value was defined stage I. A ≥2 to <3-fold increase was defined as stage II and a ≥3-fold increase or use of dialysis was determined as stage III.

Comorbidity burdens were summarised using Charlson index, calculated using the CIM-10 codes from electronic medical charts.[16] HF types were stratified into intermediate or reduced left ventricular ejection fraction (LVEF < 49%), preserved LVEF (LVEF > 50%) and unknown LVEF.

We extracted urinary and blood culture information from the microbiology laboratory database for each febrile episode during hospitalisation. A diagnosis of UTI was defined as bacterial growth of $10E^3$ colony-forming units in a urine sample plus the corresponding symptoms of a UTI.

Information on death was obtained from Switzerland's national deaths registry and Geneva University Hospitals' (the only public hospital in the canton) electronic databases. We reviewed charts for hospital LOS, place of discharge (home vs rehabilitation centre or care home), and all-cause and HF-related hospital readmissions within one year.

PATIENT AND PUBLIC INVOLVEMENT

Patients where not involved in the study design or conduct.

STATISTICS

For our analyses, timings (day 0) were set from the first day of diuretic use, which could differ from the hospital admission day.

Primary analysis and weight evolution

Weight loss analyses during diuretic treatment were restricted to patients with volume overload. The primary analysis used a linear regression model, where the 48 h weight loss was the dependent variable and UC was the independent variable. The model was adjusted for age (continuous), sex (binary), Charlson index score (continuous), pre-admission diuretic dose (continuous), HF type (categorical), admission heart rate and blood pressure (continuous), respiratory failure (binary), weight excess at diuretic therapy (continuous), first diuretic dose (continuous), use of continuous intravenous diuretics (binary), AKI (categorical) and admission through the emergency room (binary). Adjustment factors were chosen based on clinical expertise. To reach non-inferiority, the upper confidence interval of a between-group difference had to be less than 1 kg (in favour of UC). The 1 kg boundary was arbitrarily chosen as a clinically relevant threshold. Unilateral T-test served to test non-inferiority.

We performed three sensitivity analyses for the main outcome. Firstly, multiple imputation method was used to replace missing values. Missing data, which were all 5% or less, were inspected to ensure that the missing at random assumption was reasonable. Imputation involved all baseline responders and utilised the variables in the adjusted models. Missing data were imputed using chained equations. Twenty imputed datasets were generated and parameter estimates were combined using Rubin's rules. The second sensitivity analysis excluded patients with urinary retention. The third matched catheterised patients 1:1 to non-catheterised patients according to sex and the closest value (< 10%) of a propensity score. The score included all the

variables mentioned above except sex. A paired t-test was used to test mean differences.

We used linear regression, adjusted for confounders, to explore associations between UC and persistent weight excess at 72 h and one week. We also tested the interaction between UC and time in a mixed-effects model adjusted for the factors mentioned above. A random intercept for each patient accounted for repeated measures across days. The mean expected excess weights of patients with and without UC was calculated assuming mean values for continuous predictors and a proportion of positive categorical predictors similar to the study sample.

Clinical improvements, safety outcomes and other analyses

The unadjusted impact of UC on time-dependent outcomes was analysed using Kaplan–Meier survival analysis and an unweighted, two-sided, log-rank test to compare groups. Analysis of target weight was restricted to patients with volume overload. Analyses of intravenous diuretics, oxygen supply and CPAP were restricted to patients receiving those therapies. Multivariate Cox models were adjusted for age, sex and Charlson comorbidity index score. For target weight and the time needed to discontinue intravenous diuretics, Cox models were further adjusted for all the confounding factors in the primary analysis. The proportional hazards assumption was verified using Schoenfeld residuals and a visual inspection of the log-minus-log plots.

The association between UC and LOS was tested using a linear regression model adjusted for confounding factors and in which LOS was log-transformed to correct for

skewed data. Logistic regression was used to adjust binary outcomes for confounders. Comparisons of characteristics between groups were performed using the chi-squared test or Fisher's exact test, where appropriate, for categorical variables. The Mann–Whitney test was used for continuous variables as these were not normally distributed. Except for the primary outcomes, all analyses were two-sided, with a significance level set at 5%. All analyses were performed using STATA, version 12.0, and R statistical software, Version 4.0.0.[17]

RESULTS

Of 640 potential participants in the HF register, 174 had no available paper medical chart and 7 had had no diuretic therapy within the first 7 days, leaving a cohort of 459 patients of whom 113 underwent UC within the first 24 h (24.6%). Only four of these patients had documented urinary retention. Catheterised patients were older, more often women, more frequently experienced respiratory failure or AKI, and received higher initial diuretic doses (**Table 1**). Urinary catheters were placed for a median of 4 days (IQR: 2–8). Diuresis was recorded more often among patients with UC (58.0%) than patients without (41.2%, $p < 0.01$).

EXCESS WEIGHT UNDER DIURETIC THERAPY

At diuretic therapy initiation, 342 patients carried excess weight and were included in the primary analysis. In adjusted linear regressions, being catheterised was not associated with significantly greater 48 h weight loss than not being catheterised (0.43 Kg in favour of UC (95% CI: -0.03–0.88)). The upper confidence interval of

between-group difference was bellow the non-inferiority boundary of 1 kg ($p < 0.01$ for non-inferiority).

In sensitivity analysis, the results were in line with the primary analysis. The difference in 48 h weight loss, after multiple imputation for missing values, was 0.33 kg (95% CI: -0.1–0.76; $p < 0.01$ for non-inferiority). Excluding patients with urinary retention (n = 4) did not change the results (data not shown). In the last sensitivity analysis, 64 patients with UC were matched with 64 patients without one (none had urinary retention). The difference in weight loss was 0.29 kg (95% CI: -0.3–0.88; $p < 0.01$ for non-inferiority).

Patients with UC did not have a statistically lower persistent excess weight at 72 h: the difference was 0.27 kg (95% CI: -0.52–1.1; $p = 0.50$) in unadjusted and 0.24 kg (95% CI: -0.17–0.64; $p < 0.001$ for non-inferiority) in adjusted linear regression. At one week, the excess weight difference between patients with and without UC was -0.09 kg (95% CI: -1.0–0.8; $p = 0.84$) in unadjusted and -0.14 kg (95% CI: -0.89–0.60; $p = 0.01$ for non-inferiority) in adjusted linear regression. Similarly, there was no statistically significant interaction between UC and daily excess weight changes in the mixed-effects model ($p = 0.55$; **Figure 1**).

CLINICAL IMPROVEMENT

Time to reach target weight and time needed to discontinue CPAP were not statistically different between patients with and without UC in both unadjusted and adjusted analysis (**Figure 2, Table 2**). UC tended to be associated with a longer time to discontinuation of an intravenous diuretic or discontinuation of oxygen supply (**Figure 2**), but the associations disappeared after adjustment for confounders (**Table 2**).

The median hospital LOS was identical for patients with and without UC (12 days, IQR: 9–18). However, fewer UC patients were discharged directly home from hospital (57.3% vs 73.7%; adjusted OR 0.6 (95% CI: 0.3–0.9; $p < 0.01$)).

SAFETY OUTCOMES

The proportions of initial treatment failures, low blood pressure episodes and patients with worsening kidney function were not statistically different between groups (**Table 2**).

All-cause and HF-related readmissions were not statistically different between patients with and without UC (**Table 2** and **Figure 3**). Half the patients with UC and one third without UC were dead at one year. The difference was not statistically significant after adjustment (**Table 2**).

UC patients were at a higher risk of suffering from a UTI, and this association persisted in adjusted analyses (**Table 2** and **Figure 3**). Multiple UTIs occurred in 9 UC patients (8.0%) and in 5 patients without UC (1.2%, $p < 0.01$). Patients with a UTI had a longer hospital LOS (15 days (IQR: 10–21) vs 11 days (IQR: 8–17), $p < 0.001$) and an increased one-year mortality rate (52.5% vs 34.0%, adjusted HR 1.5; 95% CI: 1.1–2.3; $p = 0.038$).

DISCUSSION AND CONCLUSION

Among patients admitted to medical wards for acute HF, initial weight loss was not different for the strategy of abstaining from UC compared to UC placement within the first 24 h. Besides, UC had no impact on clinical improvement such as the time needed to reach target weight, discontinue intravenous diuretics or improve respiratory failure, and hospital LOS. Furthermore, UC did not prevent excessive diuresis resulting in low blood pressure episodes or worsening kidney function. However, UC was associated with a higher risk of a UTI.

There are few appropriate indications for UC,[11] and 7% to 50% of UCs are done outside these indications.[18, 19] Rates of UC subsequent to HF vary greatly and could be very high. In one study, more than half of haemodynamically stable patients underwent UC.[8] The rationale for UC in HF is weak yet somehow based on beliefs that it facilitates urine elimination and increases comfort by decreasing toilet visits. However, there is good evidence that UC does not increase the comfort of patients undergoing diuretic therapy, even at high dosages.[10] Most guidelines on UC good practice do not list HF as a standard indication.[20] Through their *Choosing Wisely* campaigns, Swiss and American authorities recommend avoiding in-dwelling UC for urine output monitoring in stable patients who can void or for patient or staff convenience.[21, 22] Indication lists, authorities' recommendations and financial penalties have reduced the overall inappropriate use of UC.[11] An American study showed that the proportion of UC among HF patients decreased by 8% between 2009 and 2014.[7]

Catheter-associated UTIs (CAUTIs) are the second most common infections associated with patients hospitalised for HF after *Clostridium*-related infections.[23] Previous reports among HF patients found associations between CAUTI and increased risks of discharge to a skilled care facility, longer hospital LOS, higher total hospital costs and in-hospital mortality.[8, 23] Condom catheters are a better option when diuresis affects older patients with a disability: they lead to fewer complications,[24] are more comfortable and are less painful than UC.[10]

The present study is the first to give an insight into the hypothetical clinically relevant benefits of UC in the context of HF. Using a register of prospective records and significant adjustments to potential confounding factors (some collected retrospectively) further strengthened our findings. However, the study has limitations. Firstly, the cohort preceded some important advances in HF management (e.g.: sacubitril treatment or SGLT2 inhibitors) that may have changed readmission risk and mortality. Nevertheless, there were no changes in the 2021 ESC guidelines concerning the management of acute HF using diuretics, or the relevance of UC insertion in this indication.[25] We thus believe that out study's conclusions remain valid today. Secondly, the study's retrospective, observational approach only allowed us to hypothesise that urinary catheters were placed for HF management or to facilitate diuresis. To minimise these issues, we only selected UCs which occurred in the first 24 h of diuretic therapy. Thirdly, since patients are usually not weighed in emergency rooms, we focused on the weight change from days 1 to day 3. Thus, UC's impact during the first 24 h of diuretic therapy was not assessed. A randomised prospective design, with protocols to guide rapid diuretic adaptation, would be better able to explore the UC's real potential among HF patients. However, considering current evidence and

risks, such a study may never occur. It is of note that records of the amount of urine passed were only available for half of the patients, with or without UC. Thus, checking for adequate diuresis after treatment with diuretics might be a simpler, safer recommendation than UC for improved HF management. Finally, some medical charts could not be retrieved, but their unavailability was random and unrelated to their UC status or outcomes. Thus, there is little risk that unavailable charts biased the results.

In this retrospective study, with no obvious hourly diuresis-based diuretic adjustment strategy, UC within 24 h of diuretic therapy initiation had no proven impact on the clinically relevant outcomes of time to reach target weight, time to resolve respiratory failure and hospital LOS. The lack of benefits and the increased risk of a UTI preclude systematic UC for the management of HF.

DATA AVAILABILITY

The database, variable explanation, and Stata do-file (in Word format) are available at request to gregor.john@h-ne.ch.

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AUTHORS CONTRIBUTIONS

G.J., **S.C.**, **N.G., D.C.** and **J.S.**: planned the study (protocol). **M.A.** and **G.B.** collected the data. **G.J.** and **J.S.** performed the analyses. **G.J.** wrote the manuscript. All authors reviewed and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

ABBREVIATIONS

AKI: acute kidney injury

CI: confidence interval

CPAP: continuous positive airway pressure HF: heart failure

HR: hazard ratio

HUG: Geneva University Hospitals

KDIGO: Kidney Disease: Improving Global Outcomes

LVEF: left ventricular ejection fraction

OR: odds ratioUC: urinary catheterisation

UTI: urinary tract infection

Figure 1: Predicted excess weight for patients with (black line) and without (green line) urinary catheterisation (UC). Mean expected excess weights and their confidence intervals were calculated using an adjusted mixed-effects model assuming mean values for continuous predictors and a proportion of positive categorical predictors similar to the study sample. UC had no statistical effect on excess weight evolution over time (*p* for interaction = 0.55).

Figure 2: Time to reach clinical improvement for patients with urinary catheterisation (black line) and controls (green line): (A) time to reach target weight; (B) time to discontinuation of intravenous diuretics; (C) time to discontinuation of continuous positive airway pressure therapy; and (D) time to discontinuation of oxygen supply.

Figure 3: Time to reach unfavourable outcomes for patients with urinary catheterisation (black line) and controls (green line): (A) time to first urinary tract infection; (B) time to first all-cause hospital readmission; (C) time to first heart failure-related readmission; and (D) time to death.

Table 1: Characteristics of participants with and without urinary catheterisation (UC). Only UC within 24 h of diuretic therapy initiation was considered. Values are numbers (percentage) unless otherwise stated.

Characteristic	**Cohort (N = 459)**	**With UC (N = 113)**	**Without UC N = 346)**	***P* value**
Age (y), median (IQR)	81 (73–86)	83.5 (76–89)	80 (71–85)	< 0.001
Male	248 (55.2%)	52 (47.3%)	196 (57.8%)	0.053
Admitted through ER	398 (86.7%)	97 (85.8%)	301 (87.0%)	0.754
Night-time admission (19h00–07h00)	169 (36.8%)	37 (32.7%)	132 (38.1%)	0.301
Current smoker	79 (18.0%)	18 (17.3%)	61 (18.1%)	0.844*
High blood pressure	331 (73.7%)	83 (73.7%)	248 (73.2%)	0.709
Diabetes	135 (30.1%)	34 (30.9%)	101 (29.8%)	0.812
Myocardial infarct	27 (6.1%)	6 (5.5%)	21 (6.3%)	0.762*
FEVG<50%	203 (45.2%)	46 (40.7%)	157 (45.4%)	0.686
Stroke	52 (11.8%)	18 (16.1%)	34 (10.2%)	0.076*
Peripheral vascular disease	76 (17.2%)	23 (21.1%)	53 (15.9%)	0.242*
Dementia	30 (6.8%)	9 (8.3%)	21 (6.3%)	0.482*
COPD	66 (14.7%)	16 (14.5%)	50 (14.7%)	0.958*
Oncological disease	32 (7.2%)	8 (7.3%)	24 (7.2%)	0.963*
Liver disease	24 (5.4%)	7 (6.4%)	17 (5.1%)	0.598*
CKD II III IV V	 174 (38.7%) 154 (34.4%) 22 (4.9%) 2 (0.5%)	 39 (35.4%) 40 (36.4%) 6 (5.5%) 0	 135 (39.2%) 114 (33.6%) 16 (4.7%) 2 (0.6%)	0.380
Charlson comorbidity index, median (IQR)	3 (1–4)	3 (2–4)	3 (1–4)	0.115
Pre-admission medication				
ACE/ARB	290 (64.6%)	65 (59.1%)	225 (66.4%)	0.165
Beta-blocker	204 (45.4%)	49 (44.5%)	155 (45.7%)	0.829
Aldosterone inhibitor	62 (13.8%)	14 (12.7%)	48 (14.2%)	0.753*
Diuretics	239 (52.1%)	66 (58.4%)	173 (50.0%)	0.120
Admission characteristics				
Median sodium level (mmol/l) at admission (IQR)	137 (134-140)	137 (133-139)	138 (135-140)	0.022
Median NT-proBNP level (ng/l) at admission (IQR)	6377 (3069-13254)	7700 (4080-16204)	6206 (2700-12101)	0.124
Median haemoglobin level (g/l) at admission (IQR)	123 (109-137)	119 (107-133)	125 (110-138)	0.115
Median creatinin level (mmol/l) at admission (IQR)	107 (85-148)	116 (89-197)	104 (83-138)	0.005
Heart rate (beat/min), median (IQR)	81 (70–94)	82.5 (70–91)	80 (69.5–95)	0.785
Mean blood pressure (mmHg), median (IQR)	90 (80–100)	88.3 (78.3–100)	90 (80.3–100)	0.162
AKI I II III	 143 (31.5%) 24 (5.3%) 5 (1.1%)	 46 (41.8%) 9 (8.2%) 3 (2.7%)	 97 (28.6%) 15 (4.4%) 2 (0.6%)	0.002*
Respiratory failure: - Needs oxygen supply - CPAP	371 (80.8%) 365 (79.5%) 75 (16.3%)	105 (92.9%) 104 (92.0%) 27 (23.9%)	266 (76.9%) 261 (75.4%) 48 (13.9%)	< 0.001*
Volume overload - Target weight (kg), median (IQR)	342 (74.5%) 69.2 (58.1–80.8)	86 (76.1%) 70 (58–81.4)	256 (74.0%) 68.7 (58.6–80.5)	0.654
Intravenous therapy	431 (93.9%)	108 (95.6%)	323 (93.4%)	0.391*
Continuous intravenous diuretic therapy	42 (9.2%)	15 (13.4%)	27 (7.8%)	0.076*

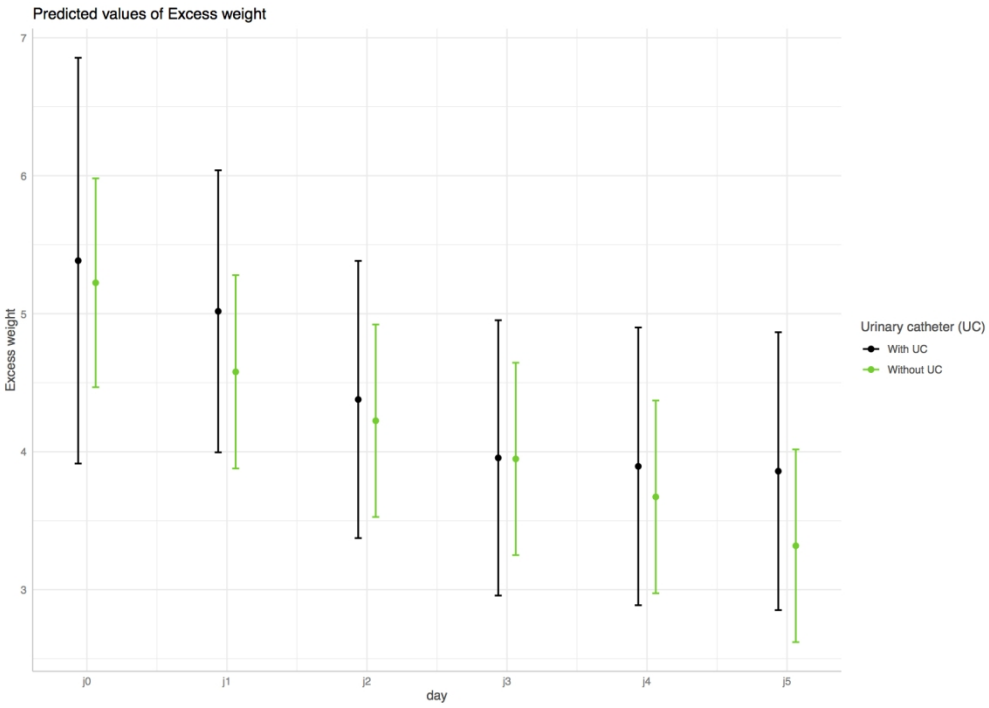
Initial diuretic doses (mg), median (IQR)	40 (30–80)	60 (40–90)	40 (20–60)	< 0.001
* Fischer test ACE, angiotensin-converting-enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blockers; CKD, chronic kidney disease by CKD-EPI classification; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure therapy; ER, emergency room; UC: urinary catheterisation				

Table 2: Clinical improvements and adverse outcomes with and without urinary catheterisation. Values are numbers unless otherwise stated.

Time to clinical improvement	**With UC**	**Without UC**	**HR**	**Adjusted HR**
Time to target weight (d), median (IQR)	6 (3–7)	6 (3–7)	1.1 (0.8–1.5)	1.0 (0.7–1.5)
Time to switch/discontinuation of intravenous diuretics (d), median (IQR)	4 (2–8)	3 (1–6)	0.8 (0.7–1.0)	0.9 (0.7–1.2)
Time to discontinuation of CPAP (d), median (IQR)	4 (2–6)	4 (2–5)	1.2 (0.7–2.2)	1.1 (0.5–2.4)
Time to discontinuation of oxygen supply (d), median (IQR)	4 (2–8)	3 (1–7)	0.8 (0.6–1.0)	0.9 (0.7–1.2)
Time to adverse events	**With UC**	**Without UC**	**HR**	**Adjusted HR**
Urinary tract infection, n (%)	37 (32.7%)	46 (13.3%)	2.9 (1.8–4.8)*	2.5 (1.5–4.2)*
One-year all-cause hospital readmission, n (%)	56 (50.9%)	193 (56.9%)	1.1 (0.8–1.4)	1.1 (0.8–1.4)
One-year heart failure-related hospital readmission, n (%)	28 (25.5%)	91 (26.8%)	1.1 (0.7–1.7)	1.1 (0.7–1.7)
One-year mortality, n (%)	51 (50.0%)	101 (33.4%)	1.7 (1.2–2.4)*	1.4 (1.0–2.1)
Other secondary outcomes	**With UC**	**Without UC**	**OR**	**Adjusted OR**
Initial treatment failure	23 (26.7%)	78 (30.5%)	0.8 (0.5–1.4)	0.8 (0.4–1.4)
Low blood pressure episode - Need of saline perfusion	49 (43.7%) 24/49 (49.0)	154 (44.6%) 67/154 (43.5)	1.0 (0.6–1.5)	1.1 (0.7–1.7)
Worsening of renal function 0 1 2	 82 (74.6%) 27 (24.6%) 1 (-)	 260 (76.7%) 73 (21.5%) 6 (1.8%)	1.1 (0.7–1.8)†	1.1 (0.7–1.8)†

*p value < 0.05; † OR of changing to a worse category

CPAP, continuous positive airway pressure therapy; UC, urinary catheterisation



Predicted excess weight for patients with (black line) and without (green line) urinary catheterisation (UC). Mean expected excess weights and their confidence intervals were calculated using an adjusted mixed-effects model assuming mean values for continuous predictors and a proportion of positive categorical predictors similar to the study sample. UC had no statistical effect on excess weight evolution over time (p for interaction = 0.55).

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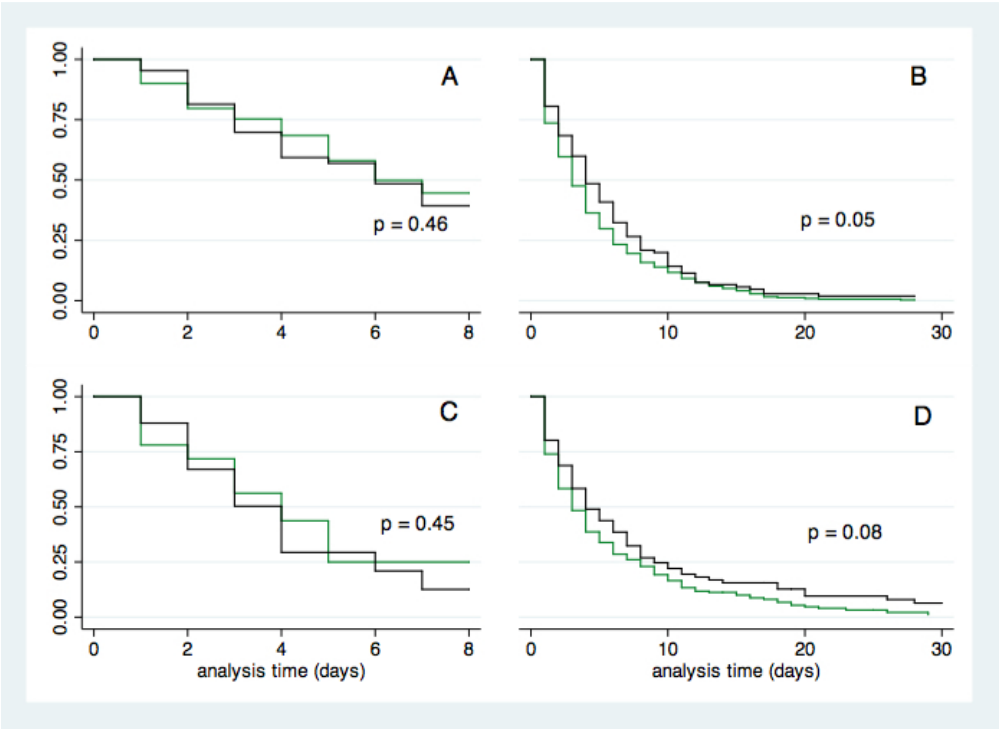

Time to reach clinical improvement for patients with urinary catheterisation (black line) and controls (green line): (A) time to reach target weight; (B) time to discontinuation of intravenous diuretics; (C) time to discontinuation of continuous positive airway pressure therapy; and (D) time to discontinuation of oxygen supply.

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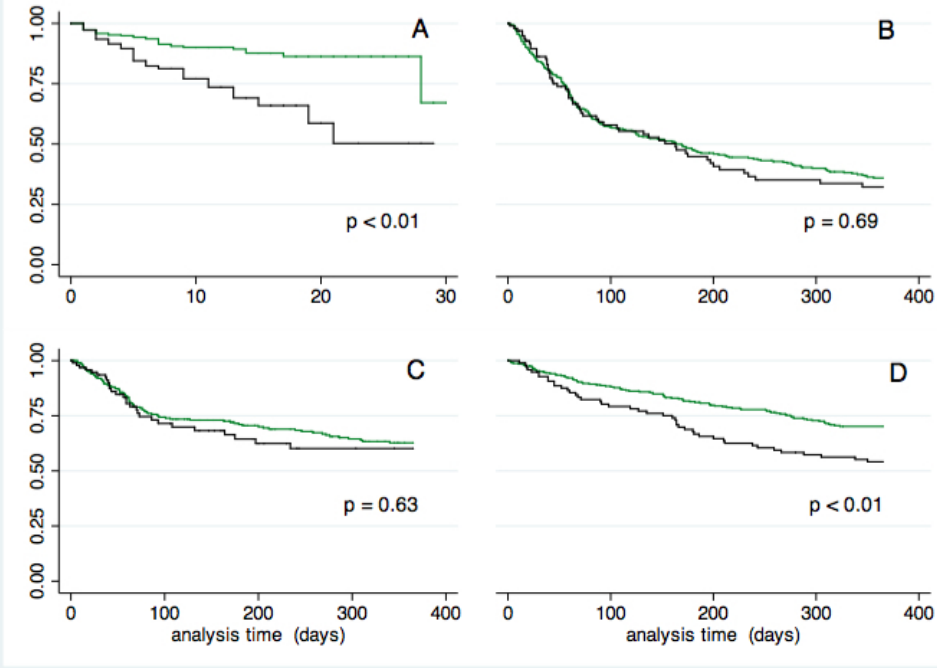

Time to reach unfavourable outcomes for patients with urinary catheterisation (black line) and controls (green line): (A) time to first urinary tract infection; (B) time to first all-cause hospital readmission; (C) time to first heart failure-related readmission; and (D) time to death.

244x178mm (72 x 72 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5	
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6	
Methods				
Study design	4	Present key elements of study design early in the paper	6	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6-7	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	10-11	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9*	
Bias	9	Describe any efforts to address potential sources of bias	10	
Study size	10	Explain how the study size was arrived at	NA	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-11
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	10-11
		(*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12-14, table 1-2
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	12
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Figure2-3
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Figure2-3
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table2
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16-17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Risks and benefits of urinary catheterisation during inpatient diuretic therapy for acute heart failure: A retrospective, non-inferiority, cohort study

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Title: Risks and benefits of urinary catheterisation during inpatient diuretic therapy for acute heart failure: A retrospective, non-inferiority, cohort study

Running headline: urinary catheterisation in acute heart failure.

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ABSTRACT:

Objectives: Patients with acute congestive heart failure (HF) regularly undergo urinary catheterisation (UC) at hospital admission. We hypothesised that UC has no clinical benefits with regard to weight loss during inpatient diuretic therapy for acute congestive HF and increases the risk of urinary tract infection (UTI).

Design: Retrospective, non-inferiority study.

Setting: Geneva University Hospitals' Department of Medicine, a tertiary centre.

Participants: In a cohort of HF patients, those catheterised within 24 h of diuretic therapy (n=113) were compared with non-catheterised patients (n=346).

Primary and secondary outcome measures: The primary endpoint was weight loss 48 h after starting diuretic therapy. Secondary endpoints were time needed to reach target weight, discontinuation of intravenous diuretics, and resolution of respiratory failure. Complications included the time to a first UTI, first hospital readmission and death.

Results: 48 h weight loss was not statistically different between groups and the adjusted difference was bellow the non-inferiority boundary of 1 kg (0.43 kg (95% CI: -0.03–0.88) in favour of UC, $p < 0.01$ for non-inferiority). UC was not associated with time to reaching target weight (adjusted HR 1.0; 95%CI: 0.7–1.5), discontinuation of intravenous diuretics (aHR 0.9; 95%CI: 0.7–1.2), or resolution of respiratory failure (aHR 1.1; 95%CI: 0.5–2.4). UC increased the risk of UTI (aHR 2.5; 95%CI: 1.5–4.2) but was not associated with hospital readmission (aHR 1.1, 95%CI: 0.8–1.4) or one-year mortality (aHR 1.4; 95%CI: 1.0–2.1).

Conclusion: In this retrospective study, with no obvious hourly diuresis-based diuretic adjustment strategy, weight loss without UC was not inferior to weight loss after UC

within 24 h of initiating diuretic treatment. UC had no impact on clinical improvement and increased the risk of UTI. This evidence, therefore, argues against the systematic use of UC during a diuretic therapy for HF.

‘STRENGTHS AND LIMITATIONS OF THIS STUDY’

- The present study is the first to give an insight into the hypothetical clinically relevant benefits of UC in the context of HF.
- The preceded the advent of sacubitril or SGLT2 inhibitors therapy. Nevertheless, in 2021, updated ESC guidelines did not evolve regarding diuretics or the relevance of UC insertion for the management of acute decompensate HF.
- The study’s retrospective, observational approach only allowed us to hypothesise that urinary catheters were placed for HF management or to facilitate diuresis.
- Since patients are usually not weighed in emergency rooms, we focused on the weight change from days 1 to day 3. Thus, UC’s impact during the first 24 h of diuretic therapy was not assessed.
- A randomised prospective design, with protocols to guide rapid diuretic adaptation, would be better able to explore the UC’s real potential among HF patients. However, considering current evidence and risks, such a study may never occur.

INTRODUCTION:

Heart failure (HF) is a major public health concern, affecting 2% of the developed world's population.[1] Patients with HF are hospitalised about once a year, on average.[2] Due to population aging and the growing prevalence of comorbidities, the absolute number of hospital admissions for HF is expected to increase by as much as 50% over the next 25 years.[1, 3, 4]

Diuretics are the mainstay treatments for volume overload.[5, 6] Nevertheless, overly aggressive or insufficient treatments can result in acute kidney injury, electrolytic imbalance, low blood pressure, prolonged hospital length of stay (LOS) or early hospital readmission.[7, 8] Assessing adequate response to diuretics, e.g. measuring diuresis, is therefore important and enables rapid treatment adjustment. This may be as or even more useful than how diuretics are initially administered.[7, 9]

Between one quarter [10] and one half of patients [11] hospitalised for HF undergoes in-dwelling urinary catheter placement (UC). The rationale for UC in this population sometimes includes managing hypervolemia [11, 12] or improving comfort during diuretic treatment.[13] By maximising the elimination of liquids while avoiding excessive losses, UC could theoretically have a positive impact on hospital LOS, readmission rates and even death. Although the benefits of UC remain uncertain, the risks of increased urinary tract infections (UTI) and traumatic complications are well known.[11, 14, 15] A recent retrospective study of catheterised HF patients showed no impact on LOS and an increased risk of infection.[11] Little evidence exists on UC's impact on clinically relevant improvements such as weight loss, time to improvement

of respiratory failure or time to discontinuation of intravenous therapy. The present study aimed to determine the risks and clinical benefits of UC among patients hospitalised for congestive HF, with the a priori hypothesis that HF management with UC is not better than without it.

PATIENTS AND METHODS

We conducted a retrospective, non-inferiority, cohort study using a pre-existing cohort of patients admitted to Geneva University Hospitals' Department of Medicine for acute HF between 01.01.2006 and 01.01.2010.[16, 17] Patients were followed for one year or until death. The institutional review board approved the study and the need for informed consent to collect retrospectively information, was waived by the ethics committee (Comission cantonale d'éthique de la recherche (CCER)). Reporting and analyses were performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

STUDY POPULATION

All patients aged 18 years old or more, requiring hospital admission for a primary symptom of dyspnoea and a diagnosis of acute decompensated HF were eligible.[16, 17] Acute decompensated HF was diagnosed from patients' clinical presentation, risk factors and treatment responsiveness and/or was supported by structural or functional echocardiographic anomalies. Patients with a final diagnosis other than HF that explained their dyspnoea, with a low NT-proBNP level (<300ng/l), who were admitted to the intensive care unit, whose paper medical charts for the index admission were

unavailable or who did not receive diuretics during their first seven days of hospitalisation were excluded. We compared patients who underwent UC insertion within 24 h of diuretic therapy initiation with those not catheterised.

Outcomes

The primary endpoint was the 48 h weight loss after starting diuretic therapy. Secondary endpoints were persistent excess weight at 72 h and at one week, the time needed to reach clinical improvement (reaching target weight (+/- 0.5 kg), discontinuation of intravenous diuretics, oxygen supply and continuous positive airway pressure (CPAP)), and hospital LOS.

Complications included the proportion of patients with UTI, initial diuretic treatment failure, worsening kidney function and episodes of low blood pressure, and time to a first UTI, first hospital readmission and death. Initial treatment failure was defined as a need for increased doses of diuretics, or a switch from oral to intravenous diuretic therapy or from a bolus to a continuous intravenous diuretic therapy two days or more after the initiation of diuretics. Diuretic dose increases before that point were considered to be usual treatment adjustments.

Data collection and variable definition

Data extracted from medical charts included pre-admission diuretic use, micturition volumes during diuretic therapy, weight at discharge and, for the first seven days, daily

information on the UC, weight, diuretics administration, clinical parameters, oxygen supply and use of CPAP therapy.

Volume overload (hypervolaemia) was defined as excess weight at diuretic therapy. We calculated excess weight by subtracting target weight from other weights measured during hospitalisation. Target weight was defined as the patient's weight at discharge or, when unavailable, the lowest weight during hospitalisation that did not result in increased creatinaemia or low blood pressure. Since patients are not always weighed on admission day, 48 h weight loss was calculated between days 1 and 3 after starting diuretic therapy (day 0). When weight on day 1 or on day 3 was missing, we took double the mean daily weight loss calculated between day 0 and day 4.

Respiratory failure was defined as the need for oxygen supply or CPAP. We noted episodes of low blood pressure (systolic pressure < 100 mmHg) and the need for saline perfusion. Daily doses of torasemide were multiplied by two and doses of oral furosemide were divided by two to convert daily diuretics use into an equivalent intravenous furosemide dosage.[18]

We obtained patients' habitual kidney function from their general practitioner.[17] Kidney function at hospital admission and during the first week was extracted from the laboratory database. We defined acute kidney injury (AKI) as any kidney function at admission lower than its usual value, and worsening kidney function (WKF) as kidney function that decreased during hospitalisation relative to admission values.[17] AKI and WKF were scored according to the KDIGO classification. An absolute increase in the

creatinine value of 26.4 mmol/L, or a 1.5 to <2-fold increase over the baseline creatinine value was defined stage I. A ≥2 to <3-fold increase was defined as stage II and a ≥3-fold increase or use of dialysis was determined as stage III.

Comorbidity burdens were summarised using Charlson index, calculated using the CIM-10 codes from electronic medical charts.[19] HF types were stratified into intermediate or reduced left ventricular ejection fraction (LVEF < 49%), preserved LVEF (LVEF > 50%) and unknown LVEF.

We extracted urinary and blood culture information from the microbiology laboratory database for each febrile episode during hospitalisation. A diagnosis of UTI was defined as bacterial growth of $10E^3$ colony-forming units in a urine sample plus the corresponding symptoms of a UTI.

Information on death was obtained from Switzerland's national deaths registry and Geneva University Hospitals' (the only public hospital in the canton) electronic databases. We reviewed charts for hospital LOS, place of discharge (home vs rehabilitation centre or care home), and all-cause and HF-related hospital readmissions within one year.

PATIENT AND PUBLIC INVOLVEMENT

Patients were not involved in the study design or conduct.

STATISTICS

For our analyses, timings (day 0) were set from the first day of diuretic use, which could differ from the hospital admission day.

Primary analysis and weight evolution

Weight loss analyses during diuretic treatment were restricted to patients with volume overload (Figure S1). The primary analysis used a linear regression model, where the 48 h weight loss was the dependent variable and UC was the independent variable. The model was adjusted for age, sex, Charlson index score, pre-admission diuretic dose, HF type, admission heart rate and blood pressure, respiratory failure, weight excess at diuretic therapy, first diuretic dose, use of continuous intravenous diuretics, AKI and admission through the emergency room, based on previous studies (Table S1). [9, 20, 21] To reach non-inferiority, the upper confidence interval of a between-group difference had to be less than 1 kg (in favour of UC). This threshold was determined based on daily minimal clinically significant weight loss of 0.5 kg (1 kg in 2 days; Statistics S1).[22] Unilateral T-test served to test non-inferiority.

We performed five sensitivity analyses on the main outcome (Statistics S2). Firstly, a multiple imputation method was used to replace missing values. The second matched catheterised patients 1:1 with non-catheterised patients according to sex and the closest value (< 10%) of a propensity score. The score included all the variables mentioned above except sex. A paired t-test was used to test mean differences. The third sensitivity analysis excluded patients with urinary retention. The fourth replaced AKI at admission with creatininemia and blood sodium. The last sensitivity analysis split the continuous confounding variables at their median.

We used linear regression, adjusted for confounders, to explore associations between UC and persistent weight excess at 72 h and one week. We also tested the interaction between UC and time in a mixed-effects model adjusted for the factors mentioned above. A random intercept for each patient accounted for repeated measures across days. The mean expected excess weights of patients with and without UC was calculated assuming mean values for continuous predictors and a proportion of positive categorical predictors similar to the study sample.

Clinical improvements and complications

The unadjusted impact of UC on time-dependent outcomes was analysed using Kaplan–Meier survival analysis and an unweighted, two-sided, log-rank test to compare groups. Analysis of target weight was restricted to patients with volume overload. Analyses of intravenous diuretics, oxygen supply and CPAP were restricted to patients receiving those therapies. Multivariate Cox models were adjusted for age, sex and Charlson comorbidity index score. For target weight and the time needed to discontinue intravenous diuretics, Cox models were further adjusted for all the confounding factors in the primary analysis. The proportional hazards assumption was verified using Schoenfeld residuals and a visual inspection of the log-minus-log plots (Statistics S3).

The association between UC and LOS was tested using a linear regression model adjusted for confounding factors and in which LOS was log-transformed to correct for skewed data. Logistic regression was used to adjust binary outcomes for confounders. Comparisons of characteristics between groups were performed using the chi-squared test or Fisher's exact test, where appropriate, for categorical

variables. The Mann–Whitney test was used for continuous variables as these were not normally distributed. Except for the primary outcomes, all analyses were two-sided, with a significance level set at 5%. All analyses were performed using STATA, version 12.0, and R statistical software, Version 4.0.0.[23]

RESULTS

Of 640 potential participants in the HF register, 174 had no available paper medical chart and 7 had had no diuretic therapy within the first 7 days, leaving a cohort of 459 patients of whom 113 underwent UC within the first 24 h (24.6%). Only four of these patients had documented urinary retention. Catheterised patients were older, more often women, more frequently experienced respiratory failure or AKI, and received higher initial diuretic doses (**Table 1**). Urinary catheters were placed for a median of 4 days (IQR: 2–8). Diuresis was recorded more often among patients with UC (58.0%) than patients without (41.2%, $p < 0.01$).

EXCESS WEIGHT UNDER DIURETIC THERAPY

At diuretic therapy initiation, 342 patients carried excess weight and were included in the primary analysis (Figure S1). In adjusted linear regressions, being catheterised was not associated with significantly greater 48 h weight loss than not being catheterised (0.43 Kg in favour of UC (95% CI: -0.03–0.88)). The upper confidence interval of between-group difference was bellow the non-inferiority boundary of 1 kg ($p < 0.01$ for non-inferiority).

In sensitivity analysis, the results were in line with the primary analysis (Table S2). In the propensity score-matched analysis, 64 patients with UC were matched with 64 patients without a catheter (none had urinary retention). The difference in weight loss was 0.29 kg (95% CI: -0.3–0.88; $p < 0.01$ for non-inferiority).

Patients with UC did not have a statistically lower persistent excess weight at 72 h: the difference was 0.27 kg (95% CI: -0.52–1.1; $p = 0.50$) in unadjusted and 0.24 kg (95% CI: -0.17–0.64; $p < 0.001$ for non-inferiority) in adjusted linear regression. At one week, the excess weight difference between patients with and without UC was -0.09 kg (95% CI: -1.0–0.8; $p = 0.84$) in unadjusted and -0.14 kg (95% CI: -0.89–0.60; $p = 0.01$ for non-inferiority) in adjusted linear regression. Similarly, there was no statistically significant interaction between UC and daily excess weight changes in the mixed-effects model ($p = 0.55$; **Figure 1**).

CLINICAL IMPROVEMENT

Time to reach target weight and time needed to discontinue CPAP were not statistically different between patients with and without UC in both unadjusted and adjusted analysis (**Figure 2, Table 2**). UC tended to be associated with a longer time to discontinuation of an intravenous diuretic or discontinuation of oxygen supply (**Figure 2**), but the associations disappeared after adjustment for confounders (**Table 2**).

The median hospital LOS was identical for patients with and without UC (12 days, IQR: 9–18). However, fewer UC patients were discharged directly home from hospital (57.3% vs 73.7%; adjusted OR 0.6 (95% CI: 0.3–0.9; $p < 0.01$)).

COMPLICATIONS

The proportions of initial treatment failures, low blood pressure episodes and patients with worsening kidney function were not statistically different between groups (**Table 2**).

All-cause and HF-related readmissions were not statistically different between patients with and without UC (**Table 2** and **Figure 3**). Half the patients with UC and one third without UC were dead at one year. The difference was not statistically significant after adjustment (**Table 2**).

UC patients were at a higher risk of suffering from a UTI, and this association persisted in adjusted analyses (**Table 2** and **Figure 3**). Multiple UTIs occurred in 9 UC patients (8.0%) and in 5 patients without UC (1.2%, $p < 0.01$). Patients with a UTI had a longer hospital LOS (15 days (IQR: 10–21) vs 11 days (IQR: 8–17), $p < 0.001$) and an increased one-year mortality rate (52.5% vs 34.0%, adjusted HR 1.5; 95% CI: 1.1–2.3; $p = 0.038$).

DISCUSSION AND CONCLUSION

Among patients admitted to medical wards for acute HF, the strategy of abstaining from UC did not lead to inferior initial weight loss when compared to the strategy of UC placement within the first 24 h. Besides, UC had no impact on clinical improvement such as the time needed to reach target weight, discontinue intravenous diuretics or improve respiratory failure, and hospital LOS. Furthermore, UC did not prevent excessive diuresis resulting in low blood pressure episodes or worsening kidney function, and it was associated with a higher risk of a UTI.

There are few appropriate indications for UC,[14] and 7% to 50% of UCs are done outside these indications (Table S3).[24, 25] Rates of UC subsequent to HF vary greatly and could be very high. In one study, more than half of haemodynamically stable patients underwent UC.[11] The rationale for UC in HF is weak yet somehow based on beliefs that it facilitates urine elimination and increases comfort by decreasing toilet visits. However, there is good evidence that UC does not increase the comfort of patients undergoing diuretic therapy, even at high dosages.[13] Most guidelines on UC good practice do not list HF as a standard indication.[26] Through their *Choosing Wisely* campaigns, Swiss and American authorities recommend avoiding in-dwelling UC for urine output monitoring in stable patients who can void or for patient or staff convenience.[27, 28] Indication lists, authorities' recommendations and financial penalties have reduced the overall inappropriate use of UC.[14] An American study showed that the proportion of UC among HF patients decreased by 8% between 2009 and 2014.[10]

Catheter-associated UTIs (CAUTIs) are the second most common infections associated with patients hospitalised for HF after *Clostridium*-related infections.[29] Previous reports among HF patients found associations between CAUTI and increased risks of discharge to a skilled care facility, longer hospital LOS, higher total hospital costs and in-hospital mortality.[11, 29] Condom catheters are a better option when diuresis affects older patients with a disability: they lead to fewer complications,[30] are more comfortable and are less painful than UC.[13]

The present study is the first to consider association between UC and clinically relevant outcomes in the context of HF. Using a register and significant adjustments to potential confounding factors further strengthened our findings. However, the study has limitations. Firstly, the cohort preceded some important advances in HF management (e.g.: sacubitril treatment or SGLT2 inhibitors) that may have changed readmission risk and mortality. Nevertheless, there were no changes in the 2021 ESC guidelines concerning the management of acute HF using diuretics, or the relevance of UC insertion in this indication.[3] We thus believe that our study's conclusions remain valid today. Secondly, the study's retrospective, observational approach only allowed us to hypothesise that urinary catheters were placed for HF management. To minimise these issues, we only selected UCs which occurred in the first 24 h of diuretic therapy. Thirdly, since patients are usually not weighed in emergency rooms, we focused on the weight change from days 1 to day 3. Thus, UC's impact during the first 24 h of diuretic therapy was not assessed. A randomised prospective design, with protocols to guide rapid diuretic adaptation, would be better able to explore the UC's real potential among HF patients. However, considering current evidence and risks, such a study may never occur. It is of note that records of the amount of urine passed were only

available for half of the patients, with or without UC. Thus, checking for adequate diuresis after treatment with diuretics might be a simpler, safer recommendation than UC for improved HF management. Finally, some medical charts could not be retrieved, but their unavailability was random and unrelated to their UC status or outcomes. Thus, there is little risk that unavailable charts biased the results.

In this retrospective study, with no obvious hourly diuresis-based diuretic adjustment strategy, weight loss without UC was not inferior to weight loss after UC within 24 h of initiating diuretic treatment. UC had no impact on the clinically relevant outcomes of time to reach target weight, time to resolve respiratory failure and hospital LOS. The lack of benefits and the increased risk of a UTI preclude systematic UC for the management of HF.

DATA AVAILABILITY

The database, variable explanation, and Stata do-file (in Word format) are available at request to gregor.john@rhne.ch.

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ETHICAL STATEMENT

The institutional review board of Geneva university hospital

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AUTHORS CONTRIBUTIONS

G.J., **S.C.**, **N.G.**, **D.C.** and **J.S.**: planned the study (protocol). **M.A.** and **G.B.** collected the data. **G.J.** and **J.S.** performed the analyses. **G.J.** wrote the manuscript. All authors reviewed and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

ABBREVIATIONS

AKI: acute kidney injury

CI: confidence interval

CPAP: continuous positive airway pressure HF: heart failure

HR: hazard ratio

KDIGO: Kidney Disease: Improving Global Outcomes

LVEF: left ventricular ejection fraction

OR: odds ratio

UC: urinary catheterisation

UTI: urinary tract infection

ONLINE SUPPLEMENTS

Statistic S1: Choice of non-inferiority boundary and sample size calculation

Statistic S2: Sensitivity analysis

Statistic S3: Proportional assumption and test

Table S1: Choice of adjustment variable

Table S2: Sensitivity analysis results

Table S3: List of indications for urinary catheter insertion per the Swiss 'Progress! Safe urinary catheterization' programme

Figure S1: Study flow-chart

Figure 1: Predicted excess weight (kg) over time (days) for patients with (black line) and without (green line) urinary catheterisation (UC). Mean expected excess weights and their confidence intervals were calculated using an adjusted mixed-effects model assuming mean values for continuous predictors and a proportion of positive categorical predictors similar to the study sample. UC had no statistical effect on excess weight evolution over time (*p* for interaction = 0.55).

Figure 2: Time to reach clinical improvement for patients with urinary catheterisation (black line) and controls (green line): (A) time to reach target weight; (B) time to discontinuation of intravenous diuretics; (C) time to discontinuation of continuous positive airway pressure therapy; and (D) time to discontinuation of oxygen supply.

Figure 3: Time to reach unfavourable outcomes for patients with urinary catheterisation (black line) and controls (green line): (A) time to first urinary tract infection; (B) time to first all-cause hospital readmission; (C) time to first heart failure-related readmission; and (D) time to death.

Table 1: Characteristics of participants with and without urinary catheterisation (UC). Only UC within 24 h of diuretic therapy initiation was considered. Values are numbers (percentage) unless otherwise stated.

Characteristic	**Cohort (N = 459)**	**With UC (N = 113)**	**Without UC N = 346)**	***P* value**
Age (y), median (IQR)	81 (73–86)	83.5 (76–89)	80 (71–85)	< 0.001
Male	248 (55.2%)	52 (47.3%)	196 (57.8%)	0.053
Admitted through ER	398 (86.7%)	97 (85.8%)	301 (87.0%)	0.754
Night-time admission (19h00–07h00)	169 (36.8%)	37 (32.7%)	132 (38.1%)	0.301
Current smoker	79 (18.0%)	18 (17.3%)	61 (18.1%)	0.844*
High blood pressure	331 (73.7%)	83 (73.7%)	248 (73.2%)	0.709
Diabetes	135 (30.1%)	34 (30.9%)	101 (29.8%)	0.812
Myocardial infarct	27 (6.1%)	6 (5.5%)	21 (6.3%)	0.762*
LVEF<50%	203 (45.2%)	46 (40.7%)	157 (45.4%)	0.686
Stroke	52 (11.8%)	18 (16.1%)	34 (10.2%)	0.076*
Peripheral vascular disease	76 (17.2%)	23 (21.1%)	53 (15.9%)	0.242*
Dementia	30 (6.8%)	9 (8.3%)	21 (6.3%)	0.482*
COPD	66 (14.7%)	16 (14.5%)	50 (14.7%)	0.958*
Oncological disease	32 (7.2%)	8 (7.3%)	24 (7.2%)	0.963*
Liver disease	24 (5.4%)	7 (6.4%)	17 (5.1%)	0.598*
CKD II III IV V	 174 (38.7%) 154 (34.4%) 22 (4.9%) 2 (0.5%)	 39 (35.4%) 40 (36.4%) 6 (5.5%) 0	 135 (39.2%) 114 (33.6%) 16 (4.7%) 2 (0.6%)	0.380
Charlson comorbidity index, median (IQR)	3 (1–4)	3 (2–4)	3 (1–4)	0.115
Pre-admission medication				
ACE/ARB	290 (64.6%)	65 (59.1%)	225 (66.4%)	0.165
Beta-blocker	204 (45.4%)	49 (44.5%)	155 (45.7%)	0.829
Aldosterone inhibitor	62 (13.8%)	14 (12.7%)	48 (14.2%)	0.753*
Diuretics	239 (52.1%)	66 (58.4%)	173 (50.0%)	0.120
Admission characteristics				
Median sodium level (mmol/l) at admission (IQR)	137 (134-140)	137 (133-139)	138 (135-140)	0.022
Median NT-proBNP level (ng/l) at admission (IQR)	6377 (3069-13254)	7700 (4080-16204)	6206 (2700-12101)	0.124
Median haemoglobin level (g/l) at admission (IQR)	123 (109-137)	119 (107-133)	125 (110-138)	0.115
Median creatinin level (mmol/l) at admission (IQR)	107 (85-148)	116 (89-197)	104 (83-138)	0.005
Heart rate (beat/min), median (IQR)	81 (70–94)	82.5 (70–91)	80 (69.5–95)	0.785
Mean blood pressure (mmHg), median (IQR)	90 (80–100)	88.3 (78.3–100)	90 (80.3–100)	0.162
AKI I II III	 143 (31.5%) 24 (5.3%) 5 (1.1%)	 46 (41.8%) 9 (8.2%) 3 (2.7%)	 97 (28.6%) 15 (4.4%) 2 (0.6%)	0.002*
Respiratory failure: - Needs oxygen supply - CPAP	371 (80.8%) 365 (79.5%) 75 (16.3%)	105 (92.9%) 104 (92.0%) 27 (23.9%)	266 (76.9%) 261 (75.4%) 48 (13.9%)	< 0.001*
Volume overload - Target weight (kg), median (IQR)	342 (74.5%) 69.2 (58.1–80.8)	86 (76.1%) 70 (58–81.4)	256 (74.0%) 68.7 (58.6–80.5)	0.654
Intravenous therapy	431 (93.9%)	108 (95.6%)	323 (93.4%)	0.391*
Continuous intravenous diuretic therapy	42 (9.2%)	15 (13.4%)	27 (7.8%)	0.076*

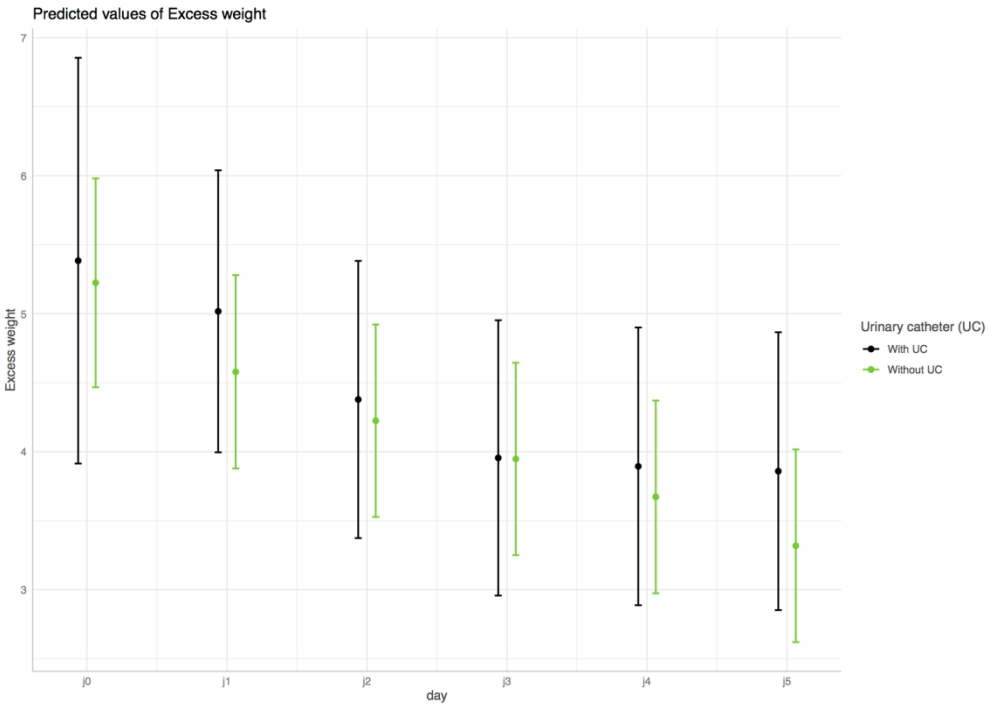
Initial diuretic doses (mg), median (IQR)	40 (30–80)	60 (40–90)	40 (20–60)	< 0.001
* Fischer test ACE, angiotensin-converting-enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blockers; CKD, chronic kidney disease by CKD-EPI classification; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure therapy; ER, emergency room; LVEF: left ventricular ejection fraction; UC: urinary catheterisation				

Table 2: Clinical improvements and adverse outcomes with and without urinary catheterisation. Values are numbers unless otherwise stated.

Time to clinical improvement	**With UC**	**Without UC**	**HR**	**Adjusted HR***
Time to target weight (d), median (IQR)	6 (3–7)	6 (3–7)	1.1 (0.8–1.5)	1.0 (0.7–1.5)
Time to switch/discontinuation of intravenous diuretics (d), median (IQR)	4 (2–8)	3 (1–6)	0.8 (0.7–1.0)	0.9 (0.7–1.2)
Time to discontinuation of CPAP (d), median (IQR)	4 (2–6)	4 (2–5)	1.2 (0.7–2.2)	1.1 (0.5–2.4)
Time to discontinuation of oxygen supply (d), median (IQR)	4 (2–8)	3 (1–7)	0.8 (0.6–1.0)	0.9 (0.7–1.2)
Time to adverse events	**With UC**	**Without UC**	**HR**	**Adjusted HR†**
Urinary tract infection, n (%)	37 (32.7%)	46 (13.3%)	2.9 (1.8–4.8)‡	2.5 (1.5–4.2)‡
One-year all-cause hospital readmission, n (%)	56 (50.9%)	193 (56.9%)	1.1 (0.8–1.4)	1.1 (0.8–1.4)
One-year heart failure-related hospital readmission, n (%)	28 (25.5%)	91 (26.8%)	1.1 (0.7–1.7)	1.1 (0.7–1.7)
One-year mortality, n (%)	51 (50.0%)	101 (33.4%)	1.7 (1.2–2.4)‡	1.4 (1.0–2.1)
Other secondary outcomes	**With UC**	**Without UC**	**OR**	**Adjusted OR†**
Initial treatment failure	23 (26.7%)	78 (30.5%)	0.8 (0.5–1.4)	0.8 (0.4–1.4)
Low blood pressure episode - Need of saline perfusion	49 (43.7%) 24/49 (49.0)	154 (44.6%) 67/154 (43.5)	1.0 (0.6–1.5)	1.1 (0.7–1.7)
Worsening of renal function 0 1 2	 82 (74.6%) 27 (24.6%) 1 (-)	 260 (76.7%) 73 (21.5%) 6 (1.8%)	1.1 (0.7–1.8)‖	1.1 (0.7–1.8) ‖

* Models were adjusted for age (continuous), sex (binary), Charlson index score (continuous), pre-admission diuretic dose (continuous), HF type (categorical), admission heart rate and blood pressure (continuous), respiratory failure (binary), weight excess at diuretic therapy (continuous), first diuretic dose (continuous), use of continuous intravenous diuretics (binary), AKI (categorical) and admission through the emergency room (binary); † Models were adjusted for age (continuous), sex (binary), Charlson index score (continuous); ‡ p value < 0.05; || OR of changing to a worse category;

CPAP, continuous positive airway pressure therapy; UC, urinary catheterisation



Predicted excess weight (kg) over time (days) for patients with (black line) and without (green line) urinary catheterisation (UC). Mean expected excess weights and their confidence intervals were calculated using an adjusted mixed-effects model assuming mean values for continuous predictors and a proportion of positive categorical predictors similar to the study sample. UC had no statistical effect on excess weight evolution over time (p for interaction = 0.55).

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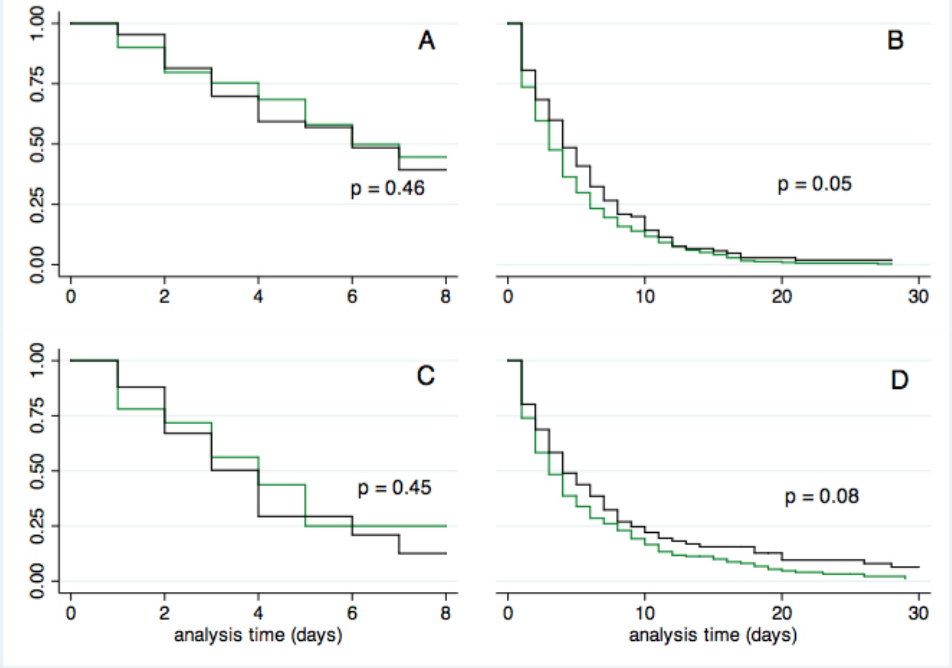

Time to reach clinical improvement for patients with urinary catheterisation (black line) and controls (green line): (A) time to reach target weight; (B) time to discontinuation of intravenous diuretics; (C) time to discontinuation of continuous positive airway pressure therapy; and (D) time to discontinuation of oxygen supply.

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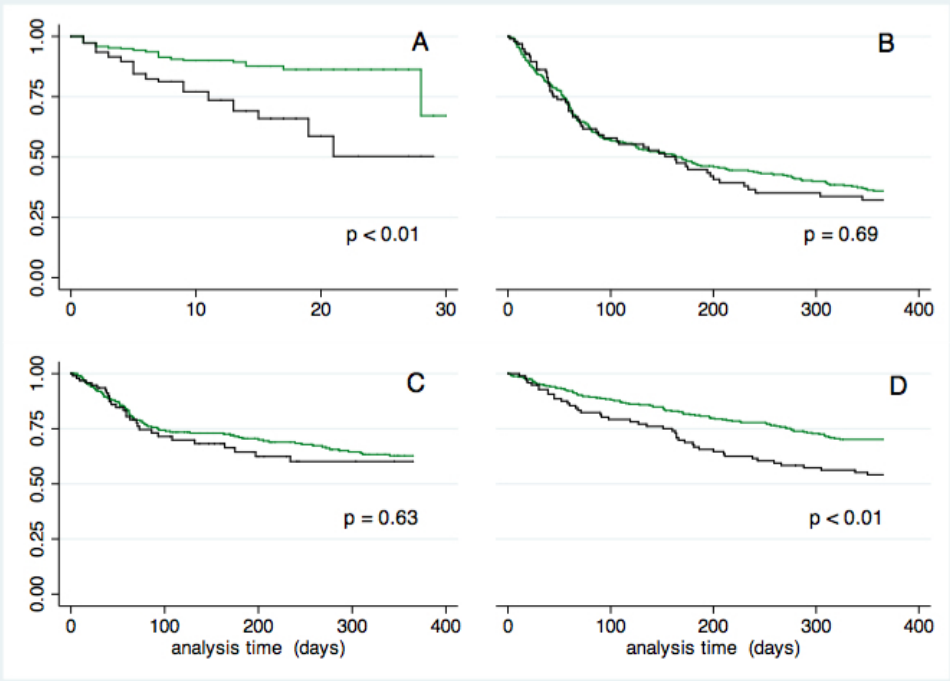

Time to reach unfavourable outcomes for patients with urinary catheterisation (black line) and controls (green line): (A) time to first urinary tract infection; (B) time to first all-cause hospital readmission; (C) time to first heart failure-related readmission; and (D) time to death.

244x178mm (72 x 72 DPI)

Risks and benefits of urinary catheterisation during inpatient diuretic therapy for acute heart failure: A retrospective, non-inferiority, cohort study

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Supplemental Materials

Statistic S1: Choice of non-inferiority boundary and sample size calculation

The non-inferiority cut-off was based on daily minimal weight loss under diuretic therapy of 500 grams (=1Kg in 2 days), acknowledge by guidelines on HF management.[1] Thus, a therapy achieving less than this target of weight loss would be considerate to have no or only minimal effect and would be increased (or changed). Similarly, two treatments resulting in weight loss difference under this minimal daily significant weight loss would be considerate to have "no clinically relevant difference".

The sample size was calculated based on an expected mean weight loss during the first days of 4.2 litters (SD 3.2) under diuretic therapy [2], and a clinically relevant difference of 1 litter between groups (for the UC group). This resulted in 376 patients (one third with an UC) needed to demonstrate non-inferiority with a one-sided significant level of 0.05 and a power of 90%.

Table S1: The variables associated with diuretics effectiveness in three studies (ASCEND-HF; RELAX-AHF; DOSE-AHF) compared to the variables included as adjustments in the multivariable models of our study.

Factors		Studies			
Category	**Variable**	**ASCEND-HF** [6]	**RELAX-AHF** [7]	**DOSE-AHF** [8]	**Our study**[1]
Diuretics	Home loop diuretics	Home loop diuretics (chronic use) use	-	Home loop diuretics (dose)	Home loop diuretics (dose) use
	Continuous vs intermittent	-	-	Type of therapy (continuous vs intermittent)	Type of therapy (continuous vs intermittent)
	Initial IV diuretic dose	Loop diuretic	-	Initial IV diuretic dose	Initial IV diuretic dose
	Bumetanide use	Bumetanide use	-	-	NA[2]
General characteristics	Sex	Female sex	-	-	Female sex
	Age	-	-	-	Age
	Ethnicity	Ethnicity	Ethnicity	-	NA[3]
Weight and oedema	Oedema	Oedema	Oedema	-	NA[4]
	Baseline weight	Baseline weight	Baseline weight	Baseline weight	Baseline weight
Vital signs/ Haemodynamics	Blood pressure	Systolic and diastolic blood pressure	Diastolic blood pressure	-	Systolic blood pressure
	Heart rate	-	-	-	Heart rate
	Body temperature	-	Body temperature	-	NA
	Respiratory rate	-	Respiratory rate	-	Respiratory failure (hypoxemia and/or non-invasive respiratory therapy)
Heart failure severity	Dyspnoea	Orthopnoea	Dyspnoea	-	
	HF hospitalisation last year	-	HF hospitalisation last year	-	NA
	NT-proBNP	-	NT-proBNP (median vs < median)	-	Not included
	LVEF	-	LVEF (no effect)	-	LVEF (> 50% vs < 50% vs unknown)
	Mode of hospital admission	-	-	-	Admission through ER
	Diabetes	Diabetes	-	-	Charlson comorbidities index

Comorbid conditions	Hyperlipidaemia	Hyperlipidaemia	-	-	
	Atrial Fibrillation	-	Atrial Fibrillation	-	
	Percutaneous intervention	-	Percutaneous intervention	-	
	Hyperthyroid	-	Hyperthyroid	-	
Laboratory	Renal function	baseline (at admission) creatininemia	BUN	baseline (at admission) creatininemia	Grade of acute renal injury at admission (0–3)
	Baseline potassium	Baseline potassium	Baseline potassium	-	NA
	Baseline sodium at admission	Baseline sodium at admission	Baseline sodium at admission	-	Not included
	Uric acid	-	Uric acid	-	NA
	Aspartate aminotransferase	-	Aspartate aminotransferase	-	NA
	Total protein (g/l)	-	Total protein (g/l)	-	NA

1) The model was adjusted for age (continuous), sex (binary), Charlson index score (continuous), pre-admission diuretic dose (continuous), HF type (categorical), admission heart rate and blood pressure (continuous), respiratory failure (binary), weight excess at diuretic therapy (continuous), first diuretic dose (continuous), use of continuous intravenous diuretics (binary), AKI (categorical) and admission through the emergency room (binary). Adjustment factors were chosen based on clinical expertise. To reach non-inferiority, the upper confidence interval of a between-group difference had to be less than 1 kg (in favour of UC). Unilateral T-test served to test non-inferiority; **2**) No Bumetanide use during the study; **3**) Database did not collect ethnicity; proportion of patients of African or Asian origin is relatively small in Geneva, most being Caucasian; **4**) Although the presence of oedema was not collected in the database, the analysis of diuretic responsiveness was restricted to patients with weight excess (compared to their target weight) and thus most of them would have had oedema.
NA: not assessed (not collected during the study)

Statistic S2: Sensitive analyses:

We performed several sensitivity analyses for the main outcome. Firstly, multiple imputation method was used to replace missing values. Missing data, which were all 5% or less, were inspected to ensure that the missing at random assumption was reasonable. Imputation involved all baseline responders and utilised the variables in the adjusted models. Missing data were imputed using chained equations. Twenty imputed datasets were generated and parameter estimates were combined using Rubin's rules. The second sensitivity analysis excluded patients with urinary retention. The third matched catheterised patients 1:1 to non-catheterised patients according to sex and the closest value (< 10%) of a propensity score. The score included all the variables mentioned above except sex. A paired t-test was used to test mean differences.

The fourth replaced AKI at admission by creatininemia and blood sodium. In the last analysis the continuous confounding variables were split in the median (results in **Table S2**).

It could be hypothesized that the "no difference" observed in the time to reach target weight could come from a wrong estimation of the weight to "target". Patients could die before to reach their "true" target weight, and the lowest weight (close to death) would be retained as the "study target weight". We decided to add a sensitive analysis, excluding patients that died within the first week of hospital admission, or patients that attaint the target weight less than 5 days before to die (16 patients in total). The results of this sensitive analysis was in line with the main result: adjusted HR for time to reach target weight was 0.97 (95%CI: 0.64-1.44, p=0.87).

For readmission and mortality, we performed one sensitivity analysis adding haemoglobin and natremia at admission, chronic renal function, LVEF, and systolic blood pressur to age, comorbidities and sex. [3 4] The adjusted hazard ratios for one-year readmission and one-year mortality were 1.02 (95% CI: 0.65–1.61; p = 0.93) and 1.27 (95% CI: 0.87–1.86; p = 0.22), respectively. The difference was not statistically significant and comforted the analyses in the main manuscript.

Table S2: Sensitive analysis for the main outcome. Numbers are coefficient of the linear regression (95%CI).					
	Model 1	Model 2	Model 3	Model 4	Model 5
Urinary catheter	0.43 (-0.03-0.88)*	0.42 (-0.04-0.88)*	0.43 (-0.03-0.87)*	0.38 (-0.08-0.83)*	0.36 (-0.08-0.80)*
age	-0.01 (-0.02-0.01)	-0.06 (-0.02-0.01)	-0.23 (-0.60-0.15)	-0.05 (-0.02-0.01)	-0.01 (-0.02-0.01)
sex	-0.32 (-0.73-0.08)	-0.32 (-0.73-0.08)	-0.35 (-0.76-0.07)	-0.39 (-0.81-0.02)	-0.35 (-0.74-0.03)
Charlson index	0.04 (-0.07-0.14)	0.04 (-0.06-0.14)	-0.01 (-0.41-0.38)	0.04 (-0.07-0.14)	0.02 (-0.08-0.12)
Chronic diuretic dose	-0.003 (-0.008-0.003)	-0.002 (-0.008-0.003)	0.16 (-0.22-0.55)	-0.002 (-0.007-0.004)	-0.003 (-0.007-0.003)
LVEF<50% (vs LVEF>50%) Unassessed FEVG	-0.32 (-0.76-0.11) -0.23 (-0.67-0.29)	-0.31 (-0.75-0.13) -0.25 (-0.75-0.25)	-0.29 (-0.73-0.15) -0.26 (-0.76-0.24)	-0.33 (-0.77-0.11) -0.27 (-0.76-0.23)	-0.31 (-0.73-0.11) -0.25 (-0.74-0.23)
admission heart rate	0.005 (-0.005-0.015)	0.005 (-0.005-0.015)	0.10 (-0.28-0.48)	0.004 (-0.006-0.014)	0.005 (-0.005-0.015)
Systolic blood pressure	0.006 (-0.002-0.015)	0.006 (-0.002-0.015)	0.09 (-0.28-0.45)	0.007 (-0.001-0.016)	0.005 (-0.004-0.013)
respiratory failure	-0.19 (-0.67-0.29)	-0.19 (-0.67-0.29)	-0.12 (-0.60-0.37)	-0.19 (-0.67-0.30)	-0.12 (-0.58-0.35)
weight excess at diuretic therapy	0.18 (0.12-0.24)	0.18 (0.12-0.24)	1.09 (0.71-1.47)	0.18 (0.12-0.24)	0.18 (0.12-0.23)
first diuretic dose	0.001 (-0.004-0.004)	0.001 (-0.004-0.004)	-0.18 (-0.62-0.25)	0.001 (-0.003-0.005)	0.001 (-0.003-0.004)
use of continuous intravenous diuretics	0.20 (-0.41-0.80)	0.19 (-0.41-0.79)	0.16 (-0.45-0.77)	0.05 (-0.55-0.64)	0.09 (-0.48-0.68)
AKI 1 AKI 2 AKI 3	-0.51 (-0.91—0.10) -0.83 (-1.76-0.09) -1.40 (-3.0-0.22)	-0.55 (-0.95—0.14) -0.85 (-1.77-0.08) -0.74 (-2.6-1.09)	-0.59 (-0.99—0.18) -0.82 (-1.72-0.07) -1.20 (-2.83-0.42)	-	-0.50 (-0.89—0.11) -0.69 (-1.62-0.23) -1.35 (-2.9-0.20)
admission through the emergency room	-0.02 (-0.58-0.54)	-0.001 (-0.56-0.56)	0.16 (-0.39-0.71)	-0.08 (-0.64-0.48)	0.02 (-0.51-0.56)
Admission blood sodium	-	-	-	-0.03 (-0.01-0.06)	-
Admission creatininemia	-	-	-	-0.003 (-0.005--0.0005)	-

*p value for non-inferiority <0.05

Model 1: main analysis diuretic chronic dose, diuretic first admission dose, age, Charlson index, systolic blood pressure, heart rate, weight excess at diuretic therapy as continuous variables in the model; **Model 2:** same as Model 1, but excluding the patients with urinary retention; **Model 3:** Continuous variables dichotomized (less vs mediane or more); **Model 4:** same as Model 1 but, admission blood sodium (continuous) and creatininemia (continuous) instead of AKI; **Model 5:** same as Model 1 but with multiple imputation of missing values.

AKI: acute kidney injury; LVEF: Left ventricular ejection fraction

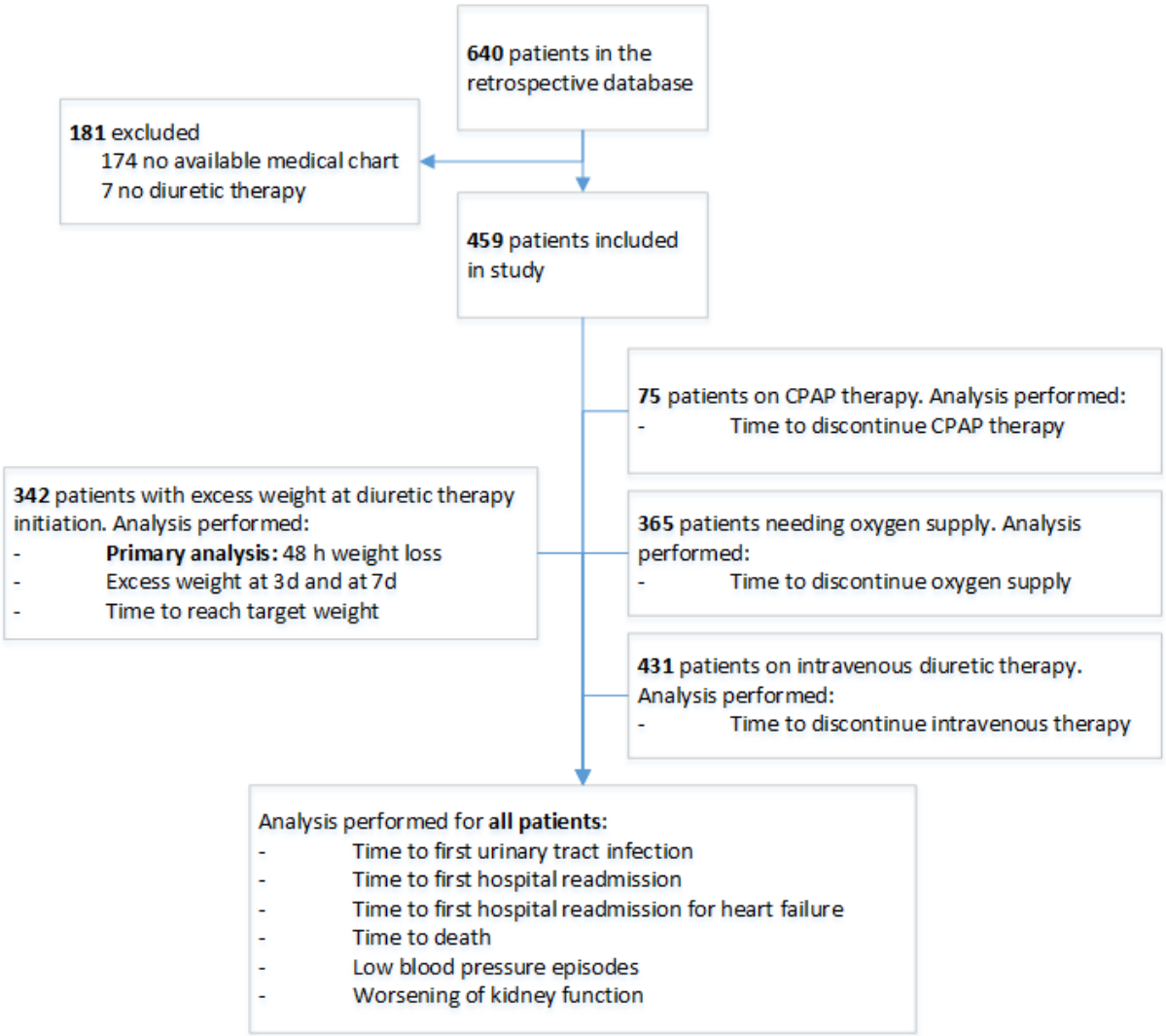

Figure S1: Study flow-chart. D=days; H = hours; CPAP= continuous positive pressure

Table S3: List of indications for urinary catheter insertion per the Swiss 'Progress! Safe urinary catheterization' programme, adapted with permission from A. Schweiger et al. / Journal of Hospital Infection 106 (2020) 364e371 [9]

Indication	Specification	Examples
Urinary retention	_ Acute urinary retention regardless of aetiology _ Symptomatic chronic outlet obstruction plus >300 mL residual urine	_ Benign hyperplasia of prostate gland, urethral strictures, bladderstones _ Drug induced (anticholinergics, opioids, antidepressants)
Measurement of urine volume/fluid balance	_ At regular intervals (hourly or as defined by hospitals) plus direct consequence on treatment of patients _ Fluid balance if patient weight not measurable on a daily basis	_ Haemodynamic instability, severe rhabdomyolysis _ Coma, sedated and ventilated patient
Surgery	_ Long surgery (>4 h) _ Peri-interventional: need for empty bladder during surgery, removal of catheter after surgery necessary if no other indication present _ Surgery in urogenital or pelvic floor region _ Epidural/peridural anaesthesia	
Pressure ulcers plus urinary incontinence	_ Stage III or IV pressure ulcers or skin transplants in sacral/ perineal region plus urinary incontinence after exhaustion of alternative strategies for urinary management	
Prolonged immobilization	_ Immobilization for medical reasons, especially for pain management, after exhaustion of alternative strategies for urinary management	_ Acute fractures with severe pain due to patient movement (pelvic fractures, fracture of the neck of the femur) _ Haemodynamic instability possibly caused by movement of the patient _ Transient immobility after specific interventions
Palliative care plus comfort	_ Palliative care plus abnormal bladder function plus/or inability for regular voiding after exhaustion of alternative strategies for urinary management _ High burden of suffering plus wish of informed patient (or relatives)	

Statistic S3: Proportional hazard assumption for univariate and multivariate models:

The log-minus-log plots are shown in the *Figure S2* for all the **univariate association** between "urinary catheter" and time to event analyses (target weight, discontinuation of intravenous diuretic therapy, discontinuous of CPAP therapy, discontinuation of oxygen supply, time to hospital readmission, time to first urinary tract infection, and time to death. We also performed the Schoenfled residuals test and tested the interaction between "urinary catheter" and Time in a time-varying covariate cox model. For both test, proportional assumption is plausible when the p value is more than 0.05. We added the results of the test in each individual graphs. Based on the three tests, proportional assumption seemed to be reasonable for all the univariate cox regressions.

The slopes of the Schoenfeld residuals and p values of all covariates for the seven models can be found in *Table S4*. For the test, a p value of <0.05 excludes proportional hazard assumption. Because appreciation of the proportional assumption on the test only can be difficult, we also provided Schoenfeld residuals plots with their fitted line for all the models, and all the covariates (*Figure S3-9*).

Urinary catheter showed proportional hazard in all the **multivariable models**. However, in the model on time to target-weight, three covariates violated the proportional hazard assumption (weight excess at beginning of diuretic therapy, reduced left ventricular ejection fraction, and continuous intravenous therapy). Since, these variables were only used for adjustment, and the association between main variable (urinary catheter and time to reach target weight) were not statistically significant in unadjusted and adjusted analysis, we left these adjusting variables unchanged in the model assuming a mean effect over time of these variables as proposed by Allison.[5] Nevertheless, we also performed a sensitivity analysis taking into account the time variation effect of the 3 variables in a time-varying covariates Cox model, (tvc option in Stata). The model confirmed the interaction between the three covariates and time ($p < 0.05$), but did not change the effect of Urinary catheter on the outcome (*Table S5*).

For the "time to discontinue CPAP therapy" model, Charlson comorbid index score violated the proportional hazard. In the time-dependant covariate model, the interaction term (time*CCI), was not statistically significant (*Table S5*).

Table S4: Proportional-hazards assumption based on Schoenfeld residuals (P value of the phtest in Stata,) and slop of the regression line (rho).

	Target weight		I.V. diuretics		CPAP		Oxygen		UTI		Readmission		Death	
	rho	P value	rho	P value	rho	P value	rho	P value	rho	P value	rho	P value	rho	P value
	0.06	0.43	0.01	0.77	0.17	0.25	0.02	0.68	0.04	0.73	0.02	0.70	-0.02	0.85
Urinary catheter	0.04	0.57	0.02	0.60	0.14	0.28	-0.002	0.97	0.09	0.44	0.02	0.69	-0.01	0.87
age	0.01	0.87	0.01	0.86	-0.16	0.27	0.04	0.45	-0.01	0.92	0.11	0.08	-0.08	0.31
sex	-0.04	0.57	-0.02	0.63	-0.15	0.28	-0.06	0.28	-0.24	0.05	-0.12	0.07	0.09	0.25
Charlson index	0.11	0.12	0.06	0.19	-0.41	0.01*	-0.02	0.69	-0.09	0.43	0.001	0.98	0.07	0.46
Chronic diuretic dose	-0.11	0.16	0.03	0.41	0.17	0.32	-0.04	0.34	-	-	-	-	-	-
LVEF<50% (vs LVEF>50%) Unassessed LVEF	-0.16 -0.005	0.02* 0.94	0.02 0.02	0.71 0.66	0.07 0.05	0.62 0.73	0.03 0.03	0.63 0.65	-	-	-	-	-	-
admission heart rate	0.05	0.49	0.02	0.73	-0.17	0.23	0.003	0.34	-	-	-	-	-	-
Systolic blood pressure	0.01	0.87	0.10	0.05	0.26	0.06	0.06	0.95	-	-	-	-	-	-
respiratory failure	-0.06	0.40	-0.06	0.25	-	-	-	-	-	-	-	-	-	-
weight excess at diuretic therapy	0.24	0.001*	0.16	0.16	0.07	0.62	0.06	0.30	-	-	-	-	-	-
first diuretic dose	0.003	0.61	0.04	0.35	-0.22	0.12	0.02	0.76	-	-	-	-	-	-
use of continuous intravenous diuretics	-0.16	0.02*	0.09	0.08	0.09	0.61	0.01	0.84	-	-	-	-	-	-
AKI 1 AKI 2 AKI 3	-0.07 0.04 -0.02	0.31 0.57 0.73	-0.02 0.04 0.01	0.70 0.43 0.77	0.13 - 0.003 -	0.37 0.98 -	0.10 0.04 0.05	0.10 0.53 0.39	-	-	-	-	-	-
admission through the emergency room	-0.12	0.08	-0.04	0.42	0.07	0.61	0.08	0.17	-	-	-	-	-	-

* violation of the proportional hazard assumption (p value <0.05). AKI: acute kidney injury; CPAP: continuous positive airways pressure therapy; I.V.: intravenous; LVEF: Left ventricular ejection fraction; UTI: urinary tract infection.

Table S5: Sensitive analysis for the model on time to reach target weight and CPAP, including time-varying covariates. Number are HR (95%CI)				
	Time to target weight		Time to discontinue CPAP	
	Standard Cox regression model	Cox with time-varying covariates model	Standard Cox regression model,	Cox with time-varying covariates model
Urinary catheter	1.0 (0.7-1.5)	1.0 (0.7-1.4)	1.1 (0.5-2.4)	1.1 (0.5-2.3)
Age	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (0.9-1.0)	1.0 (0.9-1.0)
Sex	0.7 (0.5-1.0)	0.7 (0.5-1.0)	1.4 (0.7-2.8)	1.4 (0.7-2.8)
Systolic blood pressure	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Heart rate	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Respiratory failure	0.9 (0.6-1.4)	0.9 (0.6-1.4)	-	-
Reduced LVEF Severity not assessed	1.0 (0.6-1.4) 1.9 (1.2-2.8)*	1.8 (0.9-3.6) 1.8 (1.2-2.7)	0.7 (0.3-1.5) 0.8 (0.3-2.2)	0.7 (0.3-1.5) 0.9 (0.3-2.3)
Charlson	1.0 (0.9-1.1)	1.0 (0.9-1.1)	1.0 (0.8-1.3)	1.4 (0.9-2.1)
Weight excess	0.6 (0.5-0.6)*	0.4 (0.3-0.5)*	1.0 (0.9-1.1)	1.0 (0.9-1.1)
Chronic diuretic	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Initial diuretic	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Continuous IV	1.7 (0.9-3.2)	5.1 (1.7-15.7)*	0.3 (0.1-2.1)	0.3 (0.1-2.4)
Elective admission	1.0 (0.6-1.8)	1.0 (0.5-1.6)	0.6 (0.1-2.7)	0.7 (0.1-3.1)
AKIN 1 AKIN 2 AKIN 3	0.9 (0.6-1.3) 1.1 (0.5-2.6) 1.1 (0.4-3.4)	0.9 (0.6-1.3) 1.0 (0.5-2.3) 1.2 (0.4-3.6)	1.7 (0.8-3.9) 1.6 (0.6-4.7) -	1.6 (0.7-3.7) 1.4 (0.5-4.2) -
Time varying covariates				
Reduced LVEF		0.8 (0.7-0.9)*		-
Weight excess		1.1 (1.0-1.2)*		-
Continuous IV		0.7 (0.5-0.9)*		-
Charlson		-		0.9 (0.8-1.0)
*p value <0.05 AKI: acute kidney injury; CPAP: continuous positive airways pressure therapy; I.V.: intravenous; LVEF: Left ventricular ejection fraction; UTI: urinary tract infection.				

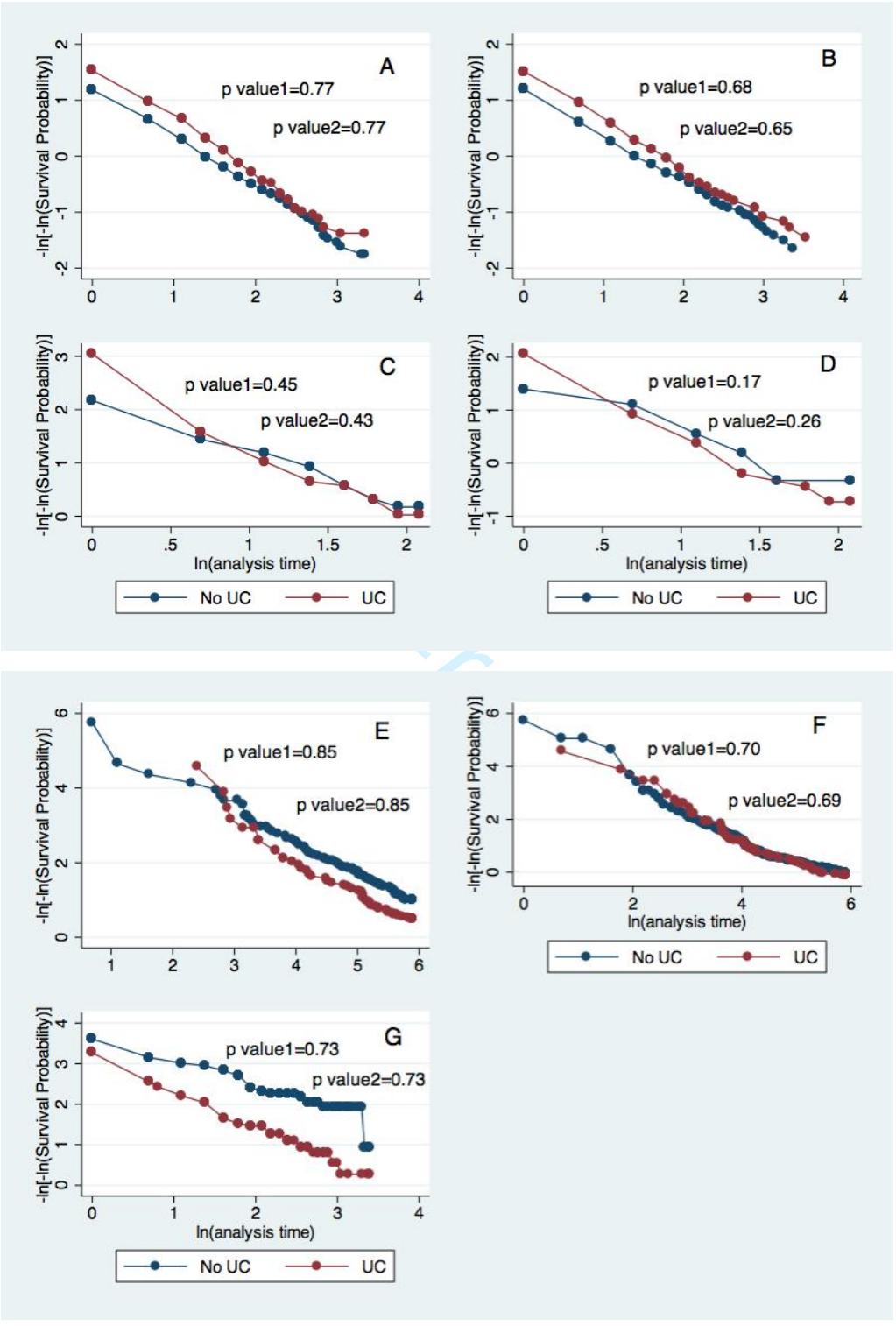

Figure S2:. log-minus-log plots for urinary catheter (UC) and the different time to event outcomes. Two tests were also used to assess the proportional hazard assumption: first the Schoenfeld residuals (**p value1**) and, second, the interaction between "urinary catheter" and time in a time-varying covariate cox regression (**p value2**). For the tow tests the p value need to be more than 0.05. **Panel A:** time to stop intravenous diuretic therapy; **Panel B:** time to stop oxygen supply; **Panel C:** time to reach target weight; **Panel D:** time to stop CPAP therapy; **Panel E:** time to death; **Panel F:** time to first hospital readmission; **Panel G:** time to first urinary tract infection.

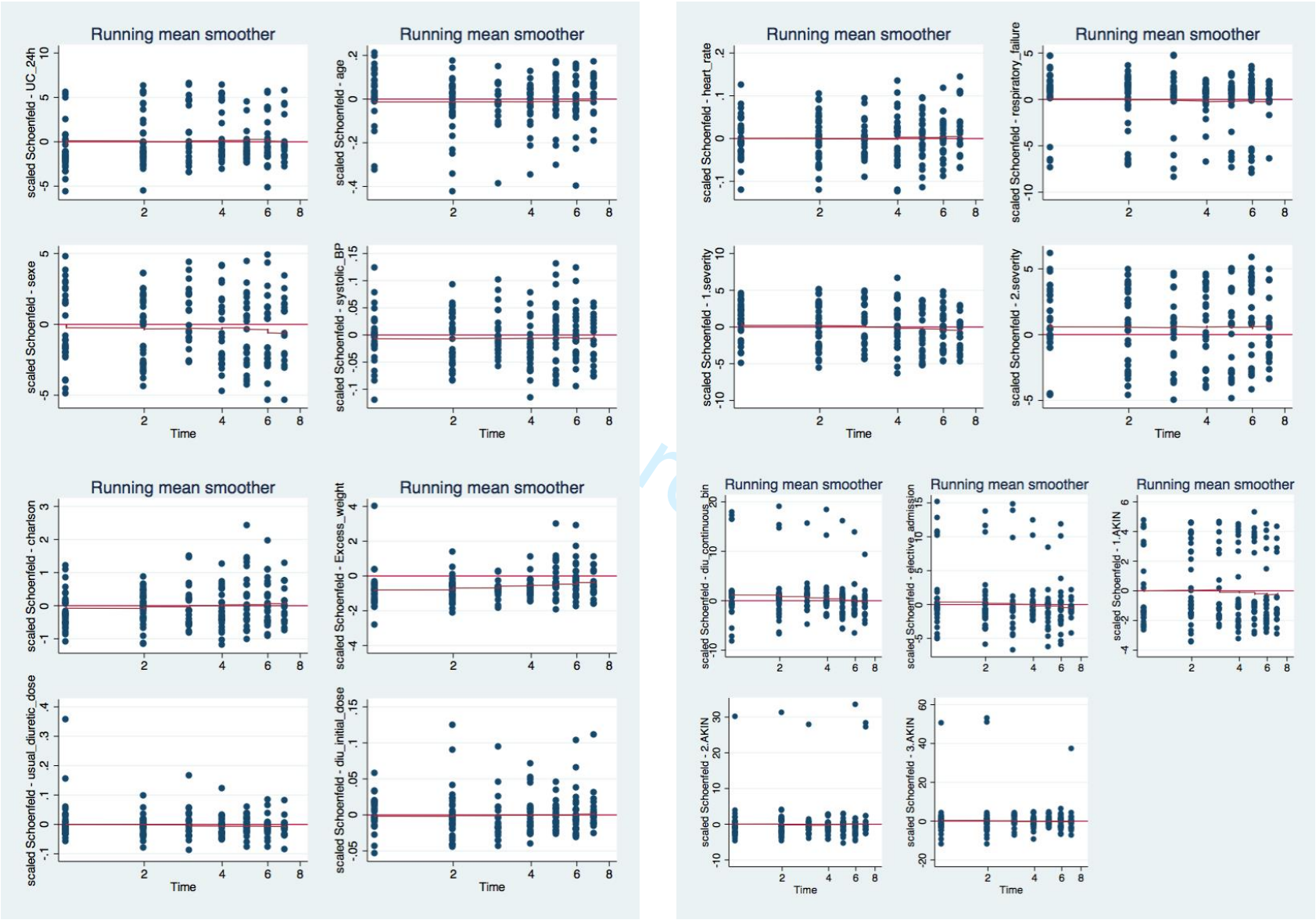

Figure S3: Schoenfeld residuals plots over Time for urinary catheterisation (UC) and covariates in the model for time to reach target weight.

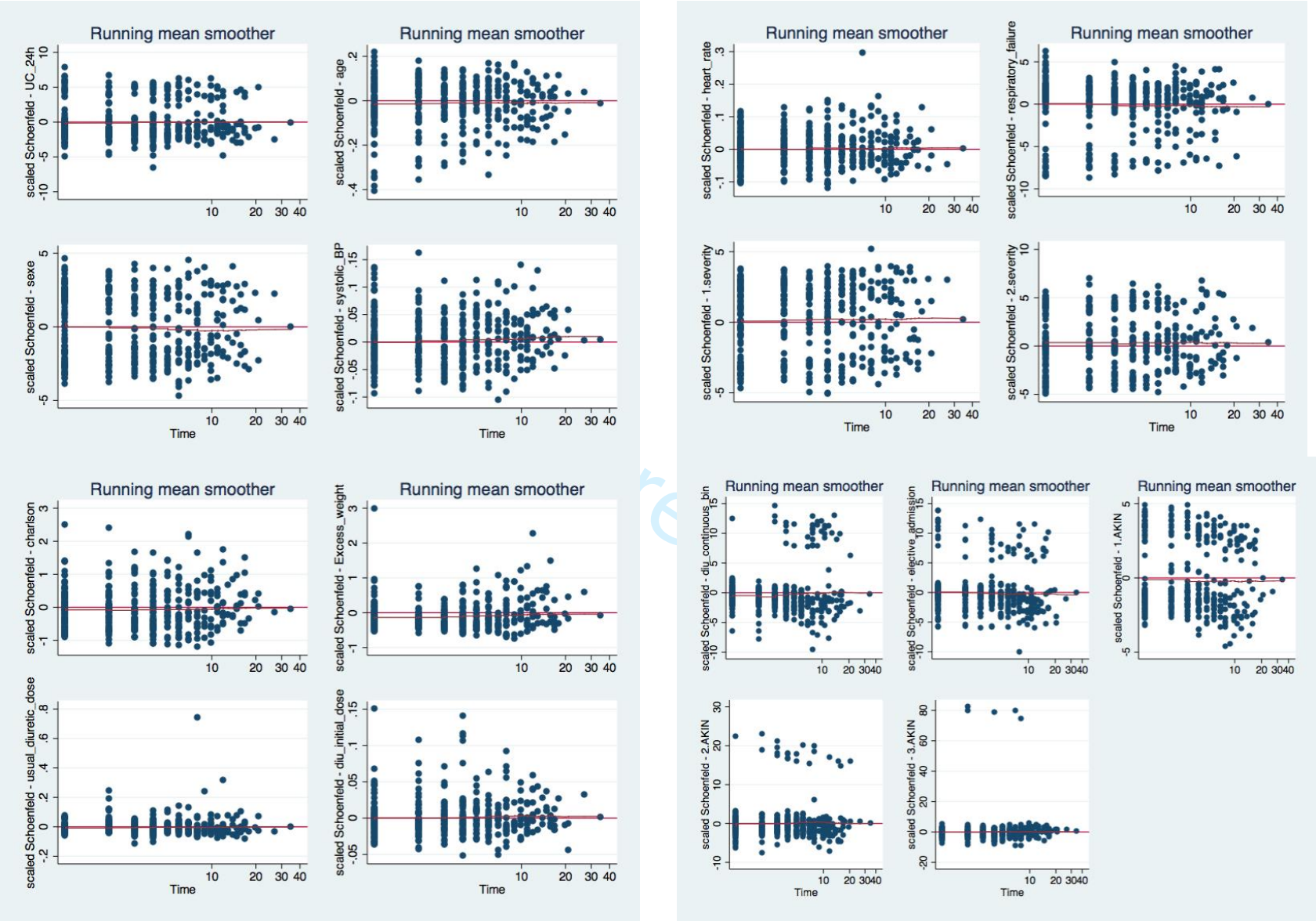

Figure S4: Schoenfeld residuals plots over Time for urinary catheter (UC) and covariates in the model of time for discontinue intravenous diuretic therapy.

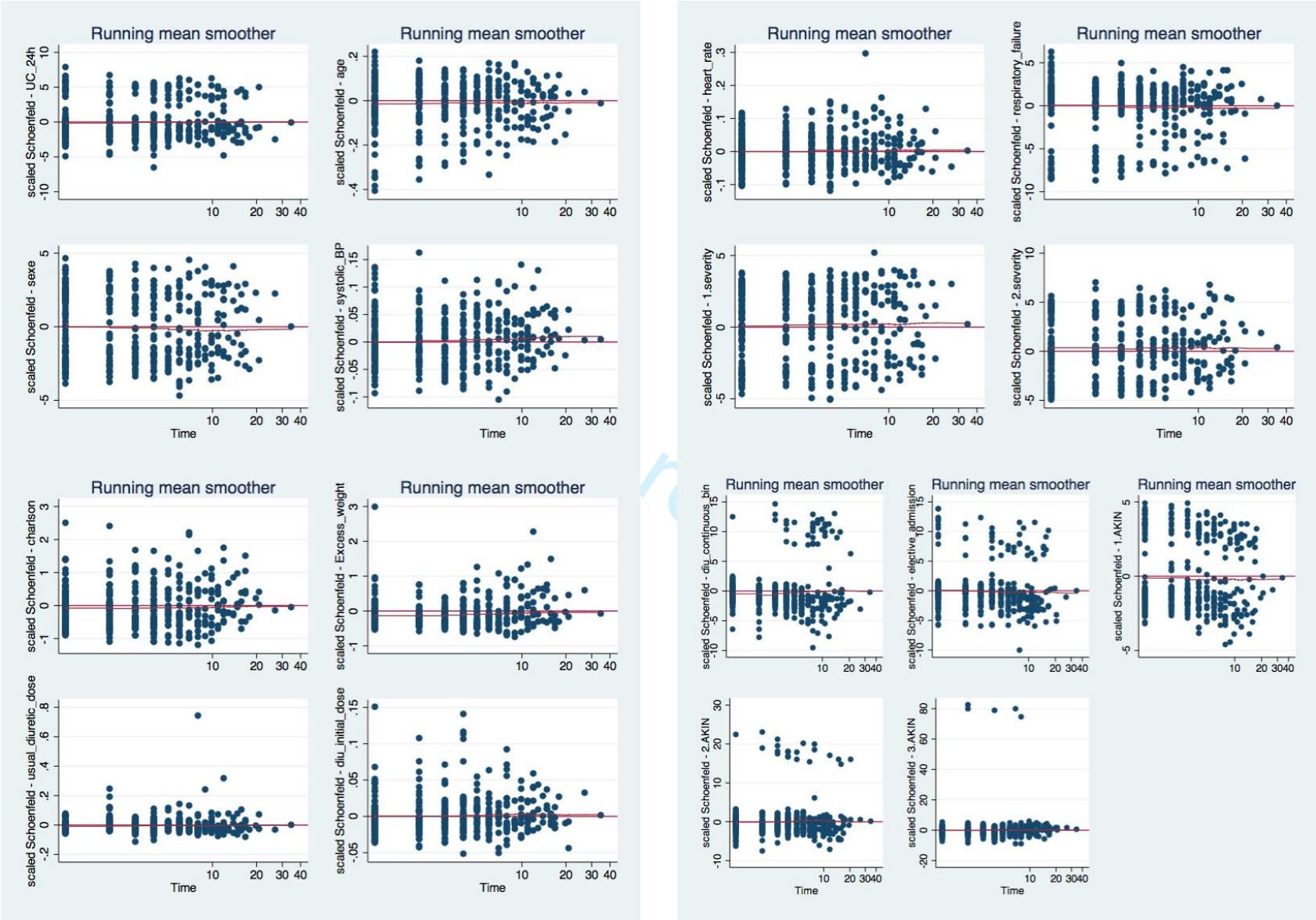

Figure S5: Schoenfeld residuals plots over Time for urinary catheter (UC) and covariates in the model of time to discontinue CPAP.

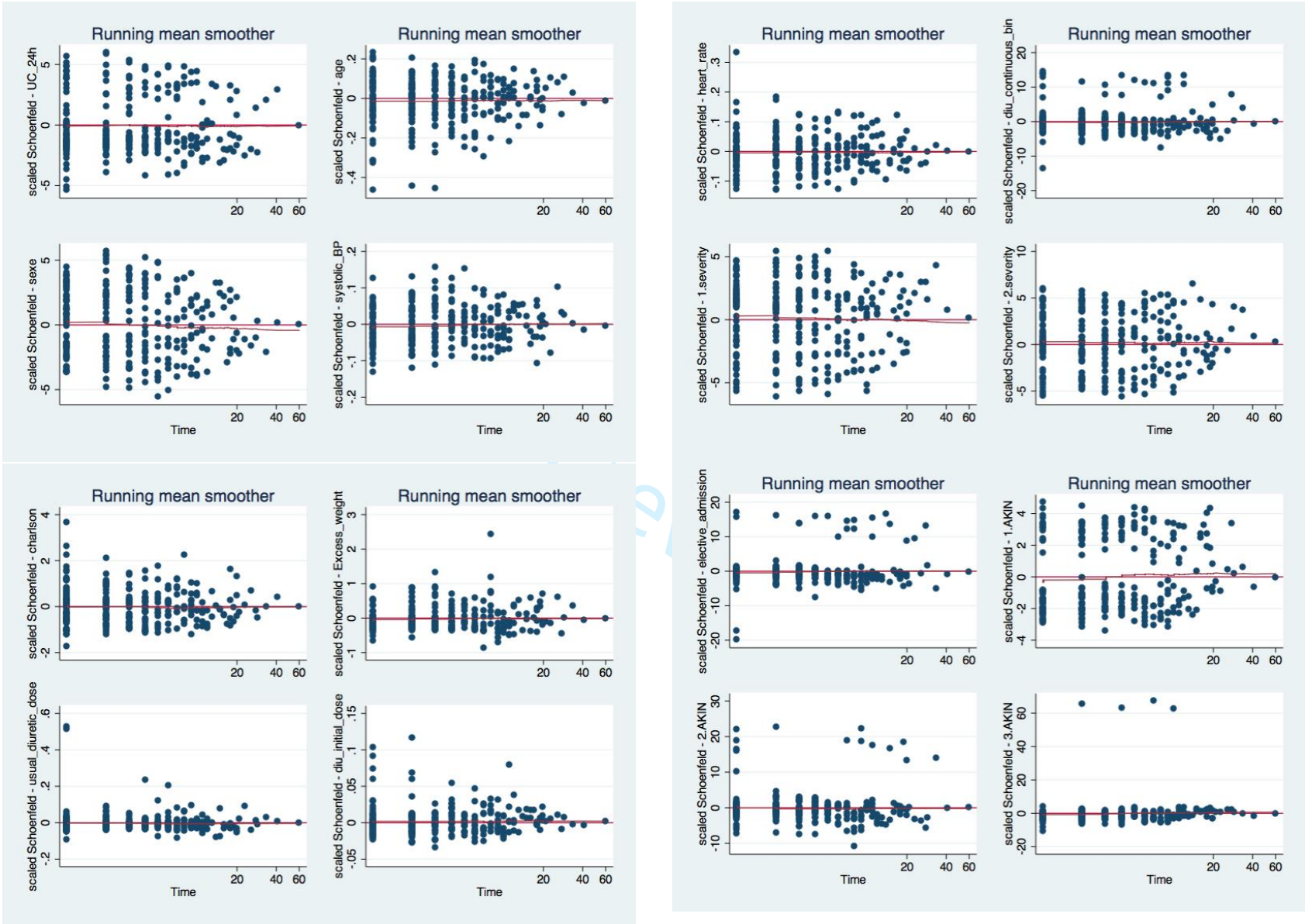

Figure S6: Schoenfeld residuals plots over Time for urinary catheter (UC) and covariates in the model for time until oxygen supply discontinuatione.

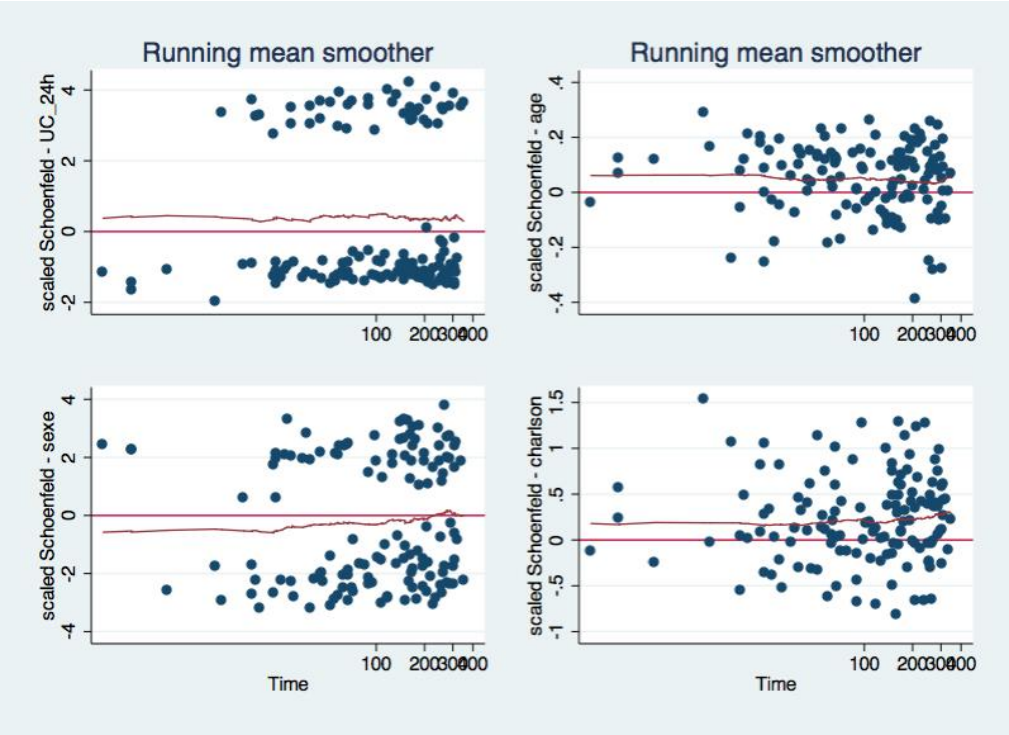

Figure S7: Schoenfeld residuals plots over Time for urinary catheter (UC) and covariates in the model for time to death.

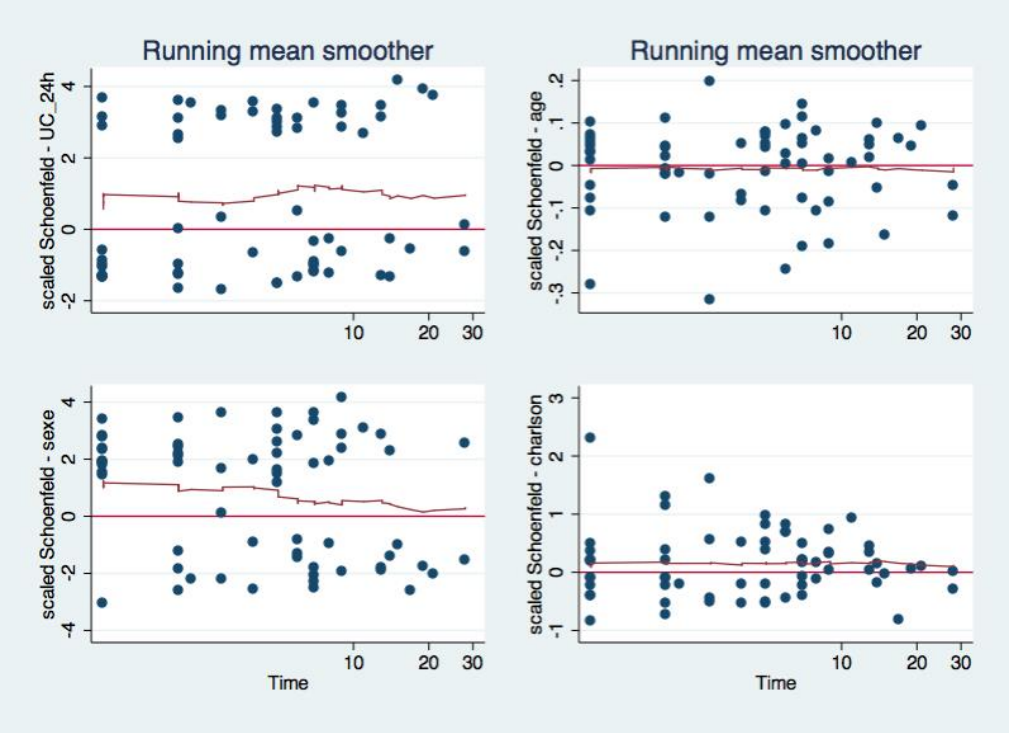

Figure S8: Schoenfeld residuals plots over Time for urinary catheter (UC) and covariates in the model for time to first urinary tract infection.

Figure S9: Schoenfeld residuals plots over Time for urinary catheter (UC) and covariates in the model for time to first hospital readmission.

References:

1. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, et al. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. *Can J Cardiol* 2017;33(11):1342-433.
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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	
Objectives	3	State specific objectives, including any prespecified hypotheses	5	
Methods				
Study design	4	Present key elements of study design early in the paper	5	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	10	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*	
Bias	9	Describe any efforts to address potential sources of bias	9 and supplements statistics	

Study size	10	Explain how the study size was arrived at	supplements statistics

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-11
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	6 and 9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	10-11
		(*e*) Describe any sensitivity analyses	9 and supplemental statistics
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11-12, table1-2, supplemental flow chart
		(b) Give reasons for non-participation at each stage	supplemental flow chart
		(c) Consider use of a flow diagram	supplemental flow chart
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	12
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Figure2-3
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Figure2-3
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table2

	(*b*) Report category boundaries when continuous variables were categorized
	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12 and supplemental data
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.