PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risks and benefits of urinary catheterisation during inpatient diuretic therapy for acute heart failure: A retrospective, non-inferiority, cohort study
AUTHORS	John, Gregor; Arcens, Marc; Berra, Gregory; Garin, Nicolas; Carballo, David; Carballo, Sebastian; Stirnemann, Jerome

VERSION 1 – REVIEW

REVIEWER	Tomasz Imiela Postgraduate Medical School, Cardiology
REVIEW RETURNED	25-Jun-2021

GENERAL COMMENTS	John G et al. present a retrospective study on the influence of urinary catherization (UC) on the effectiveness of diuretic treatment and possible complications in patients with acute heart failure (AHF). The authors discuss a relevant topic, as routine UC in hospitalized patients with AHF is a debatable topic. I have some major and minor comments and questions regarding presented study: 1. Please provide the definition of acute decompensated heart failure used in this study. The definition should be added to the study population section. 2. The term “congestive” in the title of the manuscript should be removed, as currently the acute heart failure term is sufficient. 3. Please discuss the volume overload criteria used in this study. The clear definition of volume overload should be added to the materials and methods section. 4. Even though the study was conducted before the year 2016 , the current ESC heart failure guidelines should be cited (possibly in parallel to previous guidelines). 5. Please provide a source for loop diuretic dose conversion used in the study. 6. The topic of diuretic effectiveness is a highly debatable one. The authors choose to assess diuretic efficacy as the 48h weight loss after the initiation of diuretic therapy. Please discuss why was this particular definition of diuretic efficacy chosen. 7. In the regression model for the primary analysis, the authors decided to choose the adjustment factors based on their clinical expertise. The authors choose not to include some factors associated with diuretic resistance, like the presence of edema, basic renal function (the authors opted for the presence of acute kidney injury on admission), serum sodium and potassium. The factors associated with diuretic resistance were assessed in clinical trials – for example in the analysis of ASCEND-HF trial.[1] Please discuss. 8. It could be argued, that in clinical practice the UC might be used more frequently in patiots in more serious condition on admission. If I understand the methods section correctly, the authors decided to

	adjust the models for 1-year readmission and death for age, sex and Charlson comorbidity index score only. There are other known risk factors for poor long term prognosis in AHF patients. Why the authors considered only the mentioned factors? Please discuss. 9. Why was the low blood pressure threshold set as systolic blood pressure <100mmHg? Please discuss. 10. Please include a detailed definition for acute kidney injury and worsening of renal function in the manuscript. 11. Could the authors provide basic laboratory data regarding described population? Renal function, serum sodium, C-reactive protein and haemoglobin concentration on admission are especially important for the context of this study. 12. In the methods section the authors state, that patients were stratified according to left ventricle ejection fraction (LVEF). However, the data regarding LVEF is not shown. Please provide mentioned data. 13. The adjusted difference between UC and non-UC patients for 1-year death occurrence was not statistically significant. However, in the Figure 3 a time to death analysis presents a statistically significant difference. This is potentially a very important finding. Please discuss. 1. ter Maaten JM, Dunning AM, Valente MA, Damman K, Ezekowitz JA, Califf RM, et al. Diuretic response in acute heart failure-an analysis from ASCEND-HF. Am Heart J 2015;170(2):313-21. doi: 10.1016/j.ahj.2015.05.003

REVIEWER	Salma Balhi Department of Epidemiology and Public Health, Faculty of Medicine of Tunis, epidemiology and public health
REVIEW RETURNED	17-Oct-2021

GENERAL COMMENTS	It's too old for publication. This is a very old study covering the period 2006-2010. The data must be updated. You are talking about data over 11 years old. The field of medicine has know a lot of evolution and innovation during this period. You have a registry of patients in your hospital. Try to take a more recent period.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:
Dr. Tomasz Imiela, Postgraduate Medical School Comments to the Author:
John G et al. present a retrospective study on the influence of urinary catherization (UC) on the effectiveness of diuretic treatment and possible complications in patients with acute heart failure (AHF). The authors discuss a relevant topic, as routine UC in hospitalized patients with AHF is a debatable topic. I have some major and minor comments and questions regarding presented study:

Major Comments

Comment 1:
Please provide the definition of acute decompensated heart failure used in this study. The definition should be added to the study population section.

Answer:
- We have completed the inclusion criteria for the study. Patients were enrolled along a critical pathway, and all the patients included had a final main diagnosis of acute decompensated HF at the end of their hospital stay. The diagnosis was made using patients' clinical presentation, risk factors,

treatment responsiveness, and/or structural or functional echocardiographic anomalies. The patients with a (discharge) final diagnosis other than HF were excluded, which included those diagnosed with dyspnoea or with a low probability of heart failure due to low levels of relevant biological markers. We have changed the first paragraph of the Materials and Methods' study population subsection as follows:

- *"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 diagnoses other than HF that explained their dyspnoea, with low NT-proBNP levels (< 300 ng/l), who were admitted to the intensive care unit, whose paper medical charts for their 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 who were not catheterised."*

Comment 2:
The term "congestive" in the title of the manuscript should be removed, as currently the acute heart failure term is sufficient.

Answer:
- Thank you for this comment. We have removed "congestive" from the title.

Comment 3:
Please discuss the volume overload criteria used in this study. The clear definition of volume overload should be added to the materials and methods section.

Answer:
- We agree that "volume overload" could be misleading. We used "volume overload" as the equivalent of "hypervolemia" and not as the mechanism of ventricular overload (pressure or volume overload). We assessed hypervolemia when patient weight measured at admission was higher than their target weight (usual weight or weight at the end of therapy). This information is presented in the statistics subsection. To make this clearer, we moved this definition to the Data Collection subsection, page 7 (clean version), first paragraph:

- *"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..."*

Comment 4:
Even though the study was conducted before the year 2016, the current ESC heart failure guidelines should be cited (possibly in parallel to previous guidelines).

Answer:
- Thank you for this comment. We have added the new recommendations to the reference list. However, the specific management of diuretic treatment and the issue of urinary catheter insertion have not evolved since the preceding ESC guidelines.
- Since some important changes in the management of HF were made after the study inclusion period, we have also added the following to the Discussion section under study 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 our study's conclusions remain valid today."*

Comment 5:
Please provide a source for loop diuretic dose conversion used in the study.

Answer:
- We used the classic conversion method (**Anisman2019**). However, we made a typo in the manuscript. The torasemide was not multiplied by four, which is to convert to an oral equivalent of furosemide, but by two for iV furosemide. This reference was added on page 7 (clean version), third paragraph:

> - *"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]"*

Comment 6:
The topic of diuretic effectiveness is a highly debatable one. The authors choose to assess diuretic efficacy as the 48h weight loss after the initiation of diuretic therapy. Please discuss why was this particular definition of diuretic efficacy chosen.

Answer:
- In most hospitals, the effectiveness of HF treatment is measured based on the patient's clinical evolution and day-on-day weight difference. We hypothesised that the UC could give information on hourly diuresis and thus its impact on the patient's initial clinical evolution (the first few days). An overly-long period of observation would eventually give time for both strategies (with or without urinary catheter insertion) to resolve the weight overload (and thus result in no difference), and an overly-short period would entail the risk of only having a small difference. Thus, around 48 h seemed to us to be the appropriate window for a primary analysis.

Indeed, this 48 h window has also already been used in other studies on diuretic effectiveness, based on randomised studies: the DOSE-AHF study (**Shah2012**), the RELAX-AHF study (**Voors2014**) and the ASCEND-HF study (**Ter Maaten2015**).

In a secondary analysis, we also evaluated diuretics effectiveness (like weight evolution) over other periods (such as at day 3 and day 7) and the interactions between weight and time (using a mixed-effects model with repeated measures) and the time to reach target weights.

Comment 7:
In the regression model for the primary analysis, the authors decided to choose the adjustment factors based on their clinical expertise. The authors choose not to include some factors associated with diuretic resistance, like the presence of edema, basic renal function (the authors opted for the presence of acute kidney injury on admission), serum sodium and potassium. The factors associated with diuretic resistance were assessed in clinical trials – for example in the analysis of ASCEND-HF trial. [1] Please discuss.
1. ter Maaten JM, Dunning AM, Valente MA, Damman K, Ezekowitz JA, Califf RM, et al. Diuretic response in acute heart failure-an analysis from ASCEND-HF. Am Heart J 2015;170(2):313-21. doi: 10.1016/j.ahj.2015.05.003

Answer:
- Thank you for this comment and reference. We chose to include variables that could influence both the risk of urinary catheter insertion and weight loss under diuretic therapy and, in fact, these included most of the important factors also found in the ASCEND-HF study. In the table below, we present the factors associated with diuretics effectiveness in three important studies alongside the factors included in our study. Certain factors were not included in our analysis, however:

1. Our database did not collect information on ethnicity. The proportion of patients of African or Asian origin is relatively small in Geneva, however, with the vast majority being Caucasian.
2. Although information on the presence of oedema was not collected in the database, the analysis of diuretic responsiveness was restricted to patients with a weight excess (compared to their target

weight), and thus most of them would have had oedema. Furthermore, the analysis was adjusted for the weight excess (in kg) at diuretic therapy.
3. At admission, AKI criteria were chosen instead of creatininemia because acute kidney failure deserves close diuresis monitoring and high creatininemia could be a patient's usual value (chronic).
4. Baseline potassium levels were not collected in the study and thus cannot be included in the analysis. However, there are no rational grounds for associating potassium levels with urinary catheter insertion.
5. Sodium levels were collected but were not initially planned for inclusion in the analysis.

Following your comments, we performed a new sensitivity analysis (below) by including sodium and creatininemia at admission (instead of AKI) in the regression model for the primary outcome. The results showed the same results as the primary analysis: a weight loss difference of **0.38 Kg (95% CI: -0.08 to 0.83, *p*-value for non-inferiority of < 0.01)** between patients with and without a urinary catheter.

Table: 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 submitted manuscript

Factors		**Studies**			
Category	**Variable**	**ASCEND-HF**	**RELAX-AHF**	**DOSE-AHF**	**Our study**
Diuretics	Home loop diuretics	Home loop diuretics (chronic use) use	-	Home loop diuretics (dose)	Dose of chronic diuretic treatment
	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
General characteristics	Sex	Female sex	-	-	Female sex
	Age	-	-	-	Age
	Ethnicity	Ethnicity	Ethnicity	-	NA[1]
Weight and oedema	Oedema	Oedema	Oedema	-	NA[2]
	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
Comorbid conditions	Diabetes	Diabetes	-	-	Charlson comorbidities index
	Hyperlipidaemia	Hyperlipidaemia	-	-	
	Atrial Fibrillation	-	Atrial Fibrillation	-	
	Percutaneous	-	Percutaneous intervention	-	

	intervention				
	Hyperthyroid	-	Hyperthyroid	-	
Laboratory	Renal function	baseline (at admission) creatininemia	BUN	baseline (at admission) creatininemia	Grade of acute renal injury (0–3)[3]
	Baseline potassium	Baseline potassium	Baseline potassium	-	NA[4]
	Baseline sodium at admission	Baseline sodium at admission	Baseline sodium at admission	-	Not included[5]
	Uric acid	-	Uric acid	-	NA
	Aspartate aminotransferase	-	Aspartate aminotransferase	-	NA
	Total protein (g(l))	-	Total protein (g(l))	-	NA

* No Bumetanide use during the study
** Database did not collect ethnicity; proportion of patients of African or Asian origin is relatively small in Geneva, most being Caucasian.
*** 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)

Comment 8:
It could be argued, that in clinical practice the UC might be used more frequently in patients in more serious condition on admission. If I understand the methods section correctly, the authors decided to adjust the models for 1-year readmission and death for age, sex and Charlson comorbidity index score only. There are other known risk factors for poor long term prognosis in AHF patients. Why the authors considered only the mentioned factors? Please discuss.

Answer:
- Age and, to a lesser extent, sex were associated with the risk of urinary catheter insertion. Age, sex and Charlson comorbidity index were also associated with readmission and mortality, and they also explained the difference observed between patients with and without a UC. Since adjustment for the cited variables resulted in a non-statistically-significant difference, adding further adjustment variables would not have increased the pertinence of the results.
- Following your comments, we performed a new sensitivity analysis (below) adding haemoglobin and natremia at admission, renal function, FEVG, and systolic function (**Sanderson2016** and **DeVore2021**) to age, comorbidities and sex. 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 still not statistically significant.

Comment 9:
Why was the low blood pressure threshold set as systolic blood pressure <100mmHg? Please discuss.

Answer:
- We agree that it is common to consider a severe decrease in blood pressure to be < 90 mmHg. However, we wanted to explore hypotensive episodes, which are lower than patients' usual TA, which could potentially alter decisions on or dosages of diuretic treatment. Nevertheless, in order to catch significant low blood pressure incidents, we also recorded episodes that were sufficiently severe as to deserve a saline perfusion (**Table 2**). There was no difference between groups for these two measure of low blood pressure episode.

Comment 10:
Please include a detailed definition for acute kidney injury and worsening of renal function in the manuscript.

Answer:
An acute decrease of kidney function was defined as either acute kidney injury (AKI), if present at admission, or as WRF, if it appeared within 7 days after admission. Severity was graded according to the KDIGO classification. In this classification, an absolute increase in the creatinine value of 26.4 mmol/L, or a relative 1.5 to <2-fold increase over the baseline creatinine value defines AKI or WRF stage I. A ≥2 to <3-fold increase defines AKI or WRF stage II, and a ≥3-fold increase or use of dialysis determines AKI or WRF stage III. s
We added the following text to the last paragraph of page 7 (clean version) and first paragraph of page 8 (clean version):

- *"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 values 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 the use of dialysis was determined as stage III."*

Comment 11:
Could the authors provide basic laboratory data regarding described population? Renal function, serum sodium, C-reactive protein and haemoglobin concentration on admission are especially important for the context of this study.

Answer:

- We added these to Table 1 under admission characteristics.

Comment 12:

In the methods section the authors state, that patients were stratified according to left ventricle ejection fraction (LVEF). However, the data regarding LVEF is not shown. Please provide mentioned data.

Answer:

- We have added data on LVEF to Table 1.

Comment 13:

The adjusted difference between UC and non-UC patients for 1-year death occurrence was not statistically significant. However, in the Figure 3 a time to death analysis presents a statistically significant difference. This is potentially a very important finding. Please discuss.

Answer:

- Thank you for this comment. This is true: the difference is statistically significant. This increased mortality has been observed in several studies and meta-analyses of observational studies (**John2016**).

However, patients with urinary catheters are usually older, sicker, and more often men. When these factors are taken into account, the association between UC insertion and death is no longer significant (a confusion effect). Thus, the effect seems to be driven mostly by patients' comorbidities (**John2020**).

Reviewer #2:

Dr. Salma Balhi, Department of Epidemiology and Public Health, Faculty of Medicine of Tunis

Comments to the Author:

Major Comments

Comment 1:

It's too old for publication. This is a very old study covering the period 2006-2010. The data must be updated. You are talking about data over 11 years old. The field of medicine has know a lot of evolution and innovation during this period. You have a registry of patients in your hospital. Try to take a more recent period.

Answer:

- We agree that this study was performed on an old dataset. We chose this retrospective cohort because it was available and had already collected many of the variables useful for our study. The process of finding financial support (2017) to carry it out and to collect new variables from different sources and paper medical charts took a long time. The analysis ended in late 2019. The publication process was then further slowed, of course, by the COVID-19 pandemic since all the authors were (and still are) working in Internal Medicine Departments combatting the crisis.
- Unfortunately, we are unable to update the data. Although a registry on HF is actually open at Geneva University Hospitals, some of the specific variables needed by our study, such as about urinary catheterisation, daily weight, daily diuretic doses, acute renal injuries, urinary tract infections or readmissions, are not directly available from that registry. Updating our results would require collecting these variables from each individual patient record (after having received permission from the relevant ethics committees). Since the time before resubmission is limited and we do not have the financial support to perform these time-consuming tasks, we are unfortunately unable to act on your suggestion.
- Nevertheless, we remain convinced that our results are still valid today. The diuretic management of patients hospitalised for acute decompensated HF and the recommendations on urinary catheter insertion for this specific indication have not evolved between the study inclusion period and the 2021

ESC guidelines on heart failure. Besides, although newly available drugs have an impact on the symptoms of HF, hospital admission risk and mortality risk, they do not alter requirements for or the performance of intravenous diuretics (at least in the first few days) in cases of acute decompensated HF (**Damman2020**). Thus, we believe that our study is valid and gives valuable information on the impact (or lack of impact) of urinary catheter insertion on acute heart failure management, especially regarding overload resolution under diuretics. Because the benefits of UC insertion are unproven, our findings are of utmost importance since the risk of a urinary tract infection or a traumatic complication of UC insertion carry significant burdens on hospitalised patients and hospitals. The results (and conclusions) of our study have the potential to improve future guidelines and prevent nosocomial infections from the unnecessary insertion of UCs.

- We added a paragraph in the study limitations to remind readers that the dataset is old. We also acknowledged the flaws of a retrospective study.
- In the discussion section's paragraph on limitations, we added:
- *"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 our study's conclusions remain valid today."*
- We also changed the second point of the 'Study strengths and limitations' section.

  "The cohort preceded the advent of sacubitril or SGLT2 inhibitor therapy. Nevertheless, in 2021, updated ESC guidelines did not evolve regarding diuretics or the relevance of UC insertion for the management of acute decompensated HF."

VERSION 2 – REVIEW

REVIEWER	Tomasz Imiela Postgraduate Medical School, Cardiology
REVIEW RETURNED	15-Dec-2021

GENERAL COMMENTS	I would like to congratulate the authors for the time and effort put in the revision process for the manuscript. I am satisfied with the extensive answers provided by the authors. My last point: please include additional sensitivity analysis, mentioned in the answers for Comment 7 and Comment 8 in the manuscript.

REVIEWER	Salma Balhi Department of Epidemiology and Public Health, Faculty of Medicine of Tunis, epidemiology and public health
REVIEW RETURNED	09-Dec-2021

GENERAL COMMENTS	I really appreciated the statistical analysis part of your manuscript. Title : delete a retrospective, non-inferiority cohort study. It's a personal choice but I prefer : «Risks and benefits of urinary catheterisation during inpatient diuretic therapy for acute heart failure ». It's not attractive for the reader to put « retrospective study » in the title. I. INTRODUCTION 1. HF results in 1.7 million consultations and over 1 million hospitalisations yearly in the USA.[2] Give recent estimation of HF in Switzerland, if you have. HF is a major public health in the world and in your coutry. 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]

	□ Reformulate this sentence 3. 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. □ You need reference 4. Between one quarter [7] and one half of patients hospitalised for HF undergoes indwelling urinary catheter placement [8] □ Between one quarter [7] and one half of patients [8] hospitalised for HF undergoes indwelling urinary catheter placement. 5. UC can have a positive impact on hospital LOS, readmission rates and even death. □ You need reference 6. the risks of increased infectious and non-infectious complications are well known. □ Cite some of most frequent infectious and non-infectious complications in the literature II. Methods 1. I prefer the term « patients and methods » or simply « methods » (instead of materials and methods) as the title of this section. 2. The first paragraph of this section is usually called « study design » □ In this section, it is necessary to mention type, setting, period of this study and the consent of patients. 3. 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. □ This paragraph must be put in the section « data collection », not in study design. 4. All patients ≥ 18 years old □ Reformulate □ For Example : all patients older than 18 years during the study period 5. Acute decompensated HF was diagnosed from patients' clinical presentation, risk factors and treatment responsiveness or was supported by structural or functional echocardiographic anomalies. □ I think that the right word is « and was supported » not « or was supported ». 6. whose paper medical charts for the index admission were available □ Again the right word is « unvailable » not « available » 7. between 01.01.2006 and 01.01.2010 were eligible □ Reformulate □ Were followed during a period of ….. years from January 2006 to January 2010. 8. 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. □ When you talk about UTI, treatment failure, kidney dyfunction…. Do we call them safety outcomes ? it's complicated outcomes 9. Page 8 of 59 □ Add title of section « variable definition » 10. 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. On what basis did you choose these criteria. Statistics 11. Adjustment factors were chosen based on clinical expertise adjustment factors should be selected through a review of the literature and not only from clinical experience. You must be very careful in the choice of these adjustment variables. Removing or adding any variable can change the entire analysis. 11. The third matched catheterised patients 1:1 to non-catheterised patients according to sex. I am not an expert in the field of cardiology but I think that it is necessary to match the gender and also the stage of heart failure. We can not match a patient having intermediate or reduced left ventricular ejection fraction with another having a preserved left ventricular ejection fraction. 12. major question: You have compared patients with HF underoing urinary catheterization with those without urinary catheterization. Did you use the same type of catheter for these patients? Because the type of catheter including the material according to the literature (e.g. for intermittent catheterization) influences the risk of infectious and traumatic complications. This can lead to a measurement bias in your study III. Results section 1. Write a paragraph at the beginning of the result section on which you describe the socio-demographic characteristics of your study population and then you talk about patients undergoing UC. 2. MAJOR QUESTION : - A total, 113 underwent UC within the first 24 h - In the last sensitivity analysis, 64 patients with UC were matched with 64 patients without one (none had urinary retention). Why you don't match 113 patient undergoing UC with 113 without one (why you choose only 64 patients)? 3. I am not a cardiologist but I think that it is not the urinary catheterization that will lower the weight of patients. It's mainly due to the correct treament prescription and the route of administration. IV. Discussion 1. There are few appropriate indications for UC, Cite some of this indications, the most frequent 2. Based on the discussion of your study's methodology, your have just one strength and four weaknesses. Try to enrich the strength part of the study

REVIEWER	Cherry Lim Mahidol-Oxford Tropical Medicine Research Unit, Microbiology
REVIEW RETURNED	29-Mar-2022

GENERAL COMMENTS	The authors performed analyses on observational data to explore the risk and impact of UC on weight loss (primary outcome) in patients with acute congestive HF. The statistical approaches used included linear regression model (to examine the impact of UC on

	weight loss), and cox regression models (to examine the impact of UC on time to target weight, and time to changes in therapies). Major comments Please discuss why a non-inferiority analysis was chosen. What are the rational for performing a non-inferiority analysis in an observational study? Please discuss the additional benefits of using non-inferiority analysis in the context of this study. In a trial, non-inferiority design has been done for ethical reasons when a new treatment has to compete with pre-existing effective standard treatment. However, it is not clear from the manuscript if this is an applicable reason for an observational data to be analysed similarly here. Please clarify the rational. Moreover, non-inferiority often has several statistical complexities. For instance, the selection of non-inferiority margin (which would determine the sample size needed of a trial; and when the margin was not selected appropriately, "biocreep phenomenon" would be expected [1]); and interpretation of results may not be straightforward (in non-inferiority trials the question asked is whether the new intervention is worse than the current standard or not). In the abstract, the authors stated the aim was to explore "risks and clinical benefits of UC during inpatient diuretic therapy for acute congestive HF", please clarify why a non-inferiority analysis was chosen/needed to answer the stated objectives, and please clarify the conclusion accordingly, if authors chose a non-inferiority analysis. Moreover, please provide a justification for the choice of the non-inferiority margin. Also, it would be useful to include a power calculation if non-inferiority analysis was used, in the manuscript or in the appendix. Please clarify whether or not the linearity assumptions were made for the continuous variables (especially pre-admission diuretic dose; first diuretic dose, and Charlson's comorbidities index scores), and if the assumptions were tested. Minor: It would be useful for readers to visualize how patients were selected into the analysis, if authors could include a flowchart. Please provide the results of the linear regression model in a table form (either in the main manuscript or appendix). This would be useful for readers to visualize the assumptions made in the model and to interpret the results. Please clarify whether the results in the last column of table 2 was estimated from model that adjusted for all the 12 confounders or just age, sex, and CCI; you may need to add a footnote for the table on what variables were adjusted for. Moreover, it would be useful to do sensitivity analyses to see the deviation of results from models with only subset of confounders vs those from models with the full list of pre-defined confounders. Please add unit for "Excess weight" in the first graph, and add label for the x-axis. Please provide the plots of Schoenfeld residuals and log-minus-log in the appendix. This will be helpful for users to visualize and interpret the proportional hazard assumptions of the analyses in this study. Discussion:

	Please elaborate the choice of using weight loss as outcome as oppose to using net fluid loss/creatinine level. Also, please clarify how robust "targeted weights" of patients defined in this study were to represent the weight of patients when they were not volume overloaded, especially for patients who died within the hospital. For instance, do patients who died within a short time interval after admission met their true target weight before death (i.e. how many patients died with volume overloaded)? "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." Please clarify the meaning of "hypothetical clinically relevant benefits of UC". It was not clear how "prospective records" were collected when data used in the analysis was from 2006-2010. Reference [1] D'Agostino RB., et al (2003) Stat Med;22:169-86.

VERSION 2 – AUTHOR RESPONSE

Reviewer #2:
Dr. Salma Balhi, Department of Epidemiology and Public Health, Faculty of Medicine of Tunis

Comment 1:
I really appreciated the statistical analysis part of your manuscript.

Answer: - Thank you very much. We truly appreciate your comment.

Comment 2:
Title : delete a retrospective, non-inferiority cohort study.

- It's a personal choice but I prefer : «Risks and benefits of urinary catheterisation during inpatient diuretic therapy for acute heart failure ». It's not attractive for the reader to put « retrospective study » in the title.

Answer:
- We appreciate your comment. However, BMJ Open asked to state the design of the study already in the title. Thus, we cannot change it.

Comment 3:
HF results in 1.7 million consultations and over 1 million hospitalisations yearly in the USA.[2]

- Give recent estimation of HF in Switzerland, if you have.
- HF is a major public health in the world and in your coutry.

Answer:
- Unfortunately, there is no nation-wide register for heart failure in Switzerland. However, it has been estimated that approximately 200,000 patients suffer from heart failure in Switzerland, based on surveys in neighbouring countries (**Savares**, Card Fail Rev 2017, references at the end of the letter). And, of course, cardiovascular disease is still the leading cause of death in our country.

We decided to update the references and to give European data, which would be more appropriate for the BMJ Open audience and better describes the Swiss situation. We changed the first paragraph to:

" *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] "

Comment 4:
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]

- Reformulate this sentence

Answer:
- We changed the first paragraph as mentioned in the previous comment.

Comment 5:
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.

- You need reference

Answer:
- We added two references and changed slightly the paragraph to go straight to the point:
"…This may be as or even more useful than how diuretics are initially administered.[7, 9]"

Comment 6:
Between one quarter [7] and one half of patients hospitalised for HF undergoes indwelling urinary catheter placement [8]

- Between one quarter [7] and one half of patients [8] hospitalised for HF undergoes indwelling urinary catheter placement.

Answer:
- We made the proposed changes. Thank you.

Comment 7:
UC can have a positive impact on hospital LOS, readmission rates and even death.

- You need reference

Answer:
- This is an hypothesis that has not been proved by our analysis. So, we decided to change the "can" by "could theoretically". We also added references that confirm that rapid overload management can affect clinical evolution and risk of future hospital readmission.

Comment 8:
the risks of increased infectious and non-infectious complications are well known.

- Cite some of most frequent infectious and non-infectious complications in the literature

Answer:
- The infectious complication is the urinary tract infection (that can be lower infection (cystitis, prostatitis,…), upper infection (pyelonephritis), and, rarely sepsis / choc). The most frequent mechanical complications are obstruction, hematuria, and pain. We provided references for those readers that would be interested in finding reviews on the subject.
We changed the paragraph to

- "*Although the benefits of UC remain uncertain, the risks of increased urinary tract infections (UTI) and traumatic complications are well known."*

Comment 9:
I prefer the term « patients and methods » or simply « methods » (instead of materials and methods) as the title of this section.

Answer:
- We made the changes. Thank you.

Comment 10:
The first paragraph of this section is usually called « study design »

- In this section, it is necessary to mention type, setting, period of this study and the consent of patients.

Answer:
- Except for the period (that was previously in the population section), all the key elements of the "study design" section are in the first paragraph. We added the period of inclusion in the paragraph:
- "*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 between 01.01.2006 and 01.01.2010*..."

Comment 11:
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.

- This paragraph must be put in the section « data collection », not in study design.

Answer:
- This information was in both sections and was thus redundant. Since the manuscript length was too long, we decided to erase the summary sentence in the first paragraph of the method section.

Comment 12:
All patients ≥ 18 years old

- Reformulate
- For Example : all patients older than 18 years during the study period

Answer:
- We changed to *"All patients aged 18 years old or more* …"

Comment 13:
Acute decompensated HF was diagnosed from patients' clinical presentation, risk factors and treatment responsiveness or was supported by structural or functional echocardiographic anomalies.

- I think that the right word is « and was supported » not « or was supported ».

Answer:
- Since patients could have a diagnosis with symptoms, elevate biomarkers, and clinical response to treatment, abnormal echocardiography was not mandatory for the diagnosis. We changed the sentence to "…*treatment responsiveness and/or was supported by*…"

Comment 14:
Whose paper medical charts for the index admission were available

- Again the right word is « unvailable » not « available »

Answer:
- You are right. Thank you for having pointing out this typo.

Comment 15:
between 01.01.2006 and 01.01.2010 were eligible

- Reformulate
- Were followed during a period of ….. years from January 2006 to January 2010.

Answer:
- We changed the place of this sentence and moved it to the first paragraph of the methods section (as you recommended). In the first paragraph section (the "study design") we added:

- "*.. using a pre-existing cohort of patients admitted to HUG Departement of Medicine for acute HF between 01.01.2006 and 01.01.2010*."
- We consequently changed the first sentence of the "study population" subsection to:
-"*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]* "

Comment 16:
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.
When you talk about UTI, treatment failure, kidney dyfunction…. Do we call them safety outcomes ? it's complicated outcomes

Answer:
- The term "safety outcomes" was chosen to parallel interventional studies. However, we decided to change it to "complications".

Comment 17:
Page 8 of 59 : Add title of section « variable definition »

Answer:
- Thank you for this suggestion. However, in this section, the paragraphs are mixt between "variable definition" and "Data collection". Thus, we decided to change the entire section name "Data collection" to "Data collection and variable definition".

Comment 18:
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. On what basis did you choose these criteria.

Answer:
- These are the standard clinical criteria used to appreciate the patient improvement, when they are admitted to the hospital for acute heart failure. In such, results of our study can be directly transposed to the every-day practice.

Comment 19:
Adjustment factors were chosen based on clinical expertise

- adjustment factors should be selected through a review of the literature and not only from clinical experience.
- You must be very careful in the choice of these adjustment variables. Removing or adding any variable can change the entire analysis.

Answer:
- We addressed this point in the first review process but did not changed accordingly the sentence on variable choice in the manuscript. The adjustment variables were gathered from the major studies dealing with diuretics and fluid loss in HF. The "clinical expertise" was on the choice of factors from this list that would also be related to UC placement. We changed the sentence and added the references. Finally, we provided in the appendix, a table comparing the different variable used in the 3 main studies in the field and our variables (**Table S1**). Since the nature of the variable is now given in the appendix, we also decided to simplify the paragraph, by erasing the format of the 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]*"

Comment 20:
The third matched catheterised patients 1:1 to non-catheterised patients according to sex. I am not an expert in the field of cardiology but I think that it is necessary to match the gender and also the stage

of heart failure. We can not match a patient having intermediate or reduced left ventricular ejection fraction with another having a preserved left ventricular ejection fraction.

Answer:
- We used left ventricular ejection fraction determined by echocardiography in the propensity score used to match the patients. We also used this variable to adjust the association between UC and 48h weight loss in the main analysis. However, the primary analysis and the sensitivity analysis deal with the first days of weight loss. The preserved and reduced LVEF have a greater impact on clinical evolution in a longer period. Nevertheless, we took into account this variable.

Comment 21:
major question: You have compared patients with HF underoing urinary catheterization with those without urinary catheterization. Did you use the same type of catheter for these patients?
Because the type of catheter including the material according to the literature (e.g. for intermittent catheterization) influences the risk of infectious and traumatic complications. This can lead to a measurement bias in your study

Answer:
- This is true, intermittent and supra-pubic catheter (for prolonged use) have lower risk of infectious and mechanical complications. In our study, patients had indwelling, trans-urethral catheters for a median of 4 days.

We acknowledge that patients in the non-UC management group could have received an UC later during their hospital stay. Nevertheless, the vast majority of patients that received a urinary catheter was in the UC group. Furthermore, there is no rational to believe that patient in one or the other group received different type of catheters. Finally, since some controls (non-UC management) could had received an UC later on, the analysis of the association between the UC groups and UTI was very conservative. Besides, this fact could only had blurred the association rather than having created a spurious one.

Comment 22:
Results section. Write a paragraph at the beginning of the result section on which you describe the socio-demographic characteristics of your study population and then you talk about patients undergoing UC.

Answer:
- Socio-demographic characteristics of the study population are available in the **table 1**. Since, we were above the word limit, we decided not to add a description of characteristics that can be appreciated elsewhere (redundant information). We feel that the most important point here is the differences between the two subgroups (with and without UC).

Comment 23:
MAJOR QUESTION :
- A total, 113 underwent UC within the first 24 h
- In the last sensitivity analysis, 64 patients with UC were matched with 64 patients without one (none had urinary retention).

Why you don't match 113 patient undergoing UC with 113 without one (why you choose only 64 patients)?

Answer:
- To construct the propensity score, we used characteristics that are different in patients with and without UC. Consequently, patients in the two groups will aggregate in the opposite direction and will be difficult to match for extreme values of the score. This is a common limitation of matching analysis with propensity scores (or matching in general). Nevertheless, this is only a sensitivity analysis, and the results confirmed the primary analysis.

Comment 24:
I am not a cardiologist but I think that it is not the urinary catheterization that will lower the weight of patients. It's mainly due to the correct treament prescription and the route of administration.

Answer:
- This is true, but assessment of treatment response is important for hypervolemia resolution. One could argue that UC could help to rapidly appreciate the diuresis and thus to adapt (if needed) the treatment. We work on risk of UC. The project was mainly planned to demonstrate that there is no rational for a systematic UC insertion in this situation. We wanted to add evidence on the risk of this practice. We changed slightly the Introduction section last paragraph to better describe the study aim, by adding:
- "*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.*"

Comment 25:
Discussion There are few appropriate indications for UC, Cite some of this indications, the most frequent

Answer:
- We decided to add in the appendix the main appropriate reason to insert a UC (**Table S3**).

Comment 26:
Based on the discussion of your study's methodology, your have just one strength and four weaknesses. Try to enrich the strength part of the study

Answer:
- Thank you for your encouragement. However, we were above the word limitation. We believe that the strength of the study will be noticed by the reader and preferred to point out some limitations.

Reviewer #1:
Dr. Tomasz Imiela, Postgraduate Medical School Comments to the Author:

Comment 1:
I would like to congratulate the authors for the time and effort put in the revision process for the manuscript. I am satisfied with the extensive answers provided by the authors.

Answer:
- Thank you for helping us in the improvement of the manuscript

Comment 2:
My last point: please include additional sensitivity analysis, mentioned in the answers for Comment 7 and Comment 8 in the manuscript.
Answer:
- We needed to add several information and analysis in the manuscript. Due to word limitation, we were unable to add the sensitive analysis on your Comment 7 and 8 in the main text. We add them in the appendix **statistics S2** and **Table S2**.

Reviewer #3:
Dr. Cherry Lim, Mahidol-Oxford Tropical Medicine Research Unit, University of Oxford Comments to the Author:
The authors performed analyses on observational data to explore the risk and impact of UC on weight loss (primary outcome) in patients with acute congestive HF. The statistical approaches used included linear regression model (to examine the impact of UC on weight loss), and cox regression models (to examine the impact of UC on time to target weight, and time to changes in therapies).

Comment 1:
Major comments
Please discuss why a non-inferiority analysis was chosen. What are the rational for performing a non-inferiority analysis in an observational study? Please discuss the additional benefits of using non-inferiority analysis in the context of this study. In a trial, non-inferiority design has been done for

ethical reasons when a new treatment has to compete with pre-existing effective standard treatment. However, it is not clear from the manuscript if this is an applicable reason for an observational data to be analysed similarly here. Please clarify the rational. Moreover, non-inferiority often has several statistical complexities. For instance, the selection of non-inferiority margin (which would determine the sample size needed of a trial; and when the margin was not selected appropriately, "biocreep phenomenon" would be expected [1]); and interpretation of results may not be straightforward (in non-inferiority trials the question asked is whether the new intervention is worse than the current standard or not). In the abstract, the authors stated the aim was to explore "risks and clinical benefits of UC during inpatient diuretic therapy for acute congestive HF", please clarify why a non-inferiority analysis was chosen/needed to answer the stated objectives, and please clarify the conclusion accordingly, if authors chose a non-inferiority analysis. Reference[1] D'Agostino RB., et al (2003) Stat Med;22:169-86.

Answer:

- Non-inferiority is more often found in clinical trials. Nevertheless, this design is also possible in observational studies (**B Hiemstra** and al. in BMC clinical research methodology 2019). Besides, it is increasingly used in observational studies (**S Stoke** and al. in BMJ Open 2021; **H Moseson** and al. In The Lancet 2021).

- UC has long been used in HF to help manage diuretic therapy, with no study to support this practice. One study found no statistically significant difference between UC and patient without UC on LOS. In fact, we work on the field of UC complications and stewardship/good practice of UC. Our study aimed to prove that there are no benefits in HF. A superiority study would have only resulted in a non-statistically significant p value (as it is observed in our results). However, non-significant p value does not mean that there is no clinically significant difference between the two strategies... it means the study fail to demonstrate a statistically difference ("negative study"). We wanted to demonstrate that this practice (UC) is not better than HF management without UC, with a statistical test. Thus, we opted for a non-inferiority design.

We agree that the abstract and our introduction could appear too enthusiastic for UC use in HF, and could be paradoxically interpreted as a real desire to demonstrate a positive impact of UC in this indication. Thus, we made several changes throughout the manuscript in order to be more coherent with the non-inferiority design:

- In the abstract, we changed the objectives to :

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

- We also changed the conclusion of the abstract to:

"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"

- In the main manuscript in the last paragraph of introduction we changed slightly the text to better shows that the benefits of UC is only theoretical. We also changed the sentence on study aim to :

- "*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.*"

- In the discussion section, we changed the first sentence of the first paragraph to: "*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.*"

- We changed the last paragraph of the discussion section to:

> "*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 …"*

Comment 2:

Major comments. Moreover, please provide a justification for the choice of the non-inferiority margin. Also, it would be useful to include a power calculation if non-inferiority analysis was used, in the manuscript or in the appendix.

Answer:
- The non-inferiority cut-off is based on daily minimal weight loss under diuretic therapy of 500 grams (=1Kg in 2 days), acknowledge by guidelines on HF management (**J Ezekowitz** Can J Cardiol 2017). 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".

- We calculated a sample size, which was part of the first manuscript but as the sample was mainly driven by the available database, and due to word limitation in the manuscript, we had to delete the sample size calculation. We decided to add its calculation and some comments on non-inferiority boundary choice in the appendix (**Statistics S1**).

Comment 3:
Major comments: Please clarify whether or not the linearity assumptions were made for the continuous variables (especially pre-admission diuretic dose; first diuretic dose, and Charlson's comorbidities index scores), and if the assumptions were tested.

Answer:
- We appreciated the linear association between all these variables and the weight loss with visual inspection of the scatter plots and its linear fitted line (**Figure below**). We did not perform other tests. However, most of these variables were used as continuous variables in the regression model predicting fluid loss (**Table S1**) in previous studies like the DOSE-AHF study (**Shah2012**), the RELAX-AHF study (**Voors2014**) and the ASCEND-HF study (**Ter Maaten2015**). As a sensitive analysis, we decided to perform a new analysis with continuous variables split in their median value (less than median=0, median or higher value =1). The results were added to the appendix (**Table S2**) and were similar to the main analysis with a weight loss difference of **0.42 Kg (95% CI: -0.03 to 0.87, *p*-value of = 0.07, and *p*-value for non-inferiority of = 0.006)** between patients with and without a urinary catheter.

Of note, we used the pre identified confounding variables (clinical choice and previous publications), and not based on p values on univariate regression.

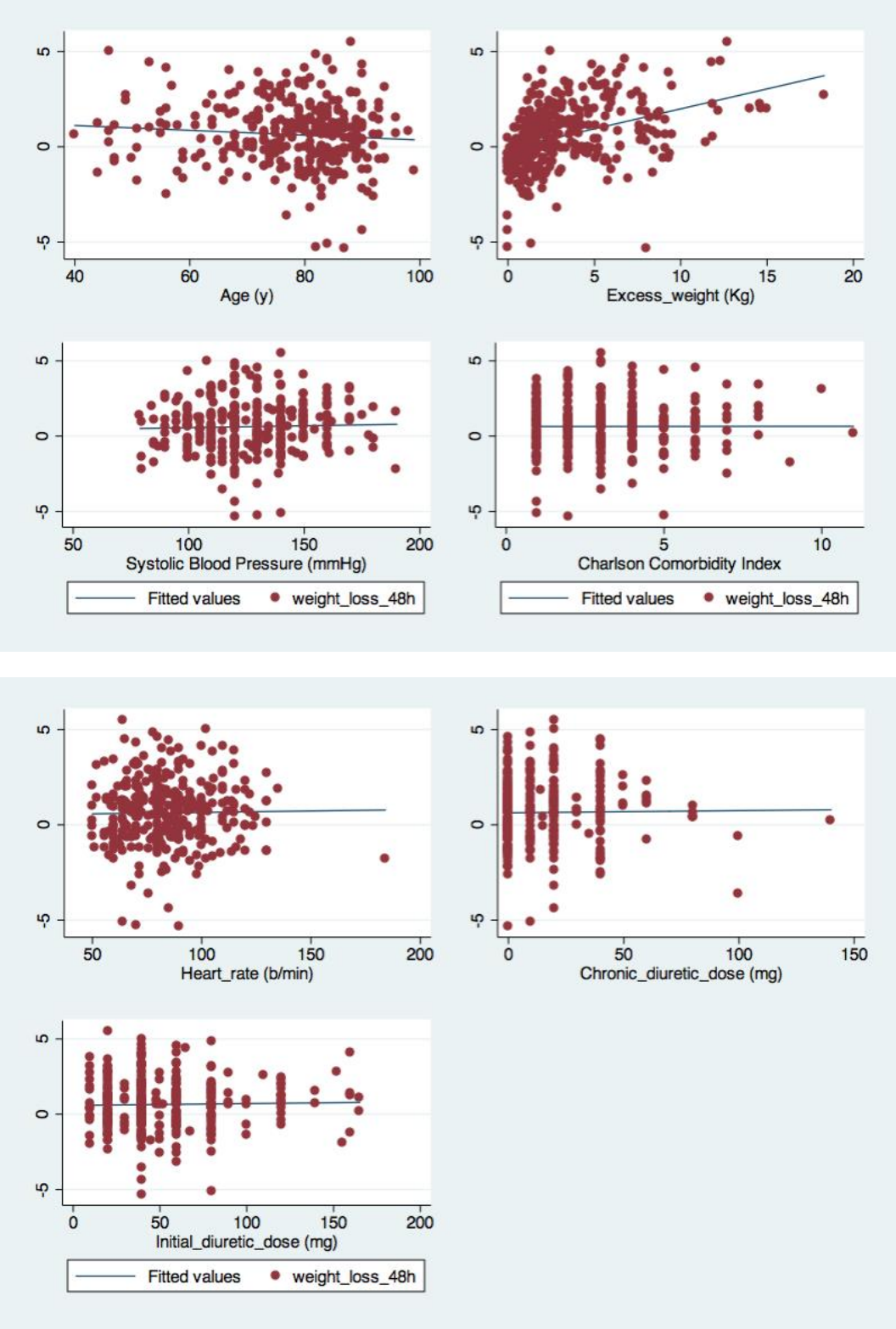
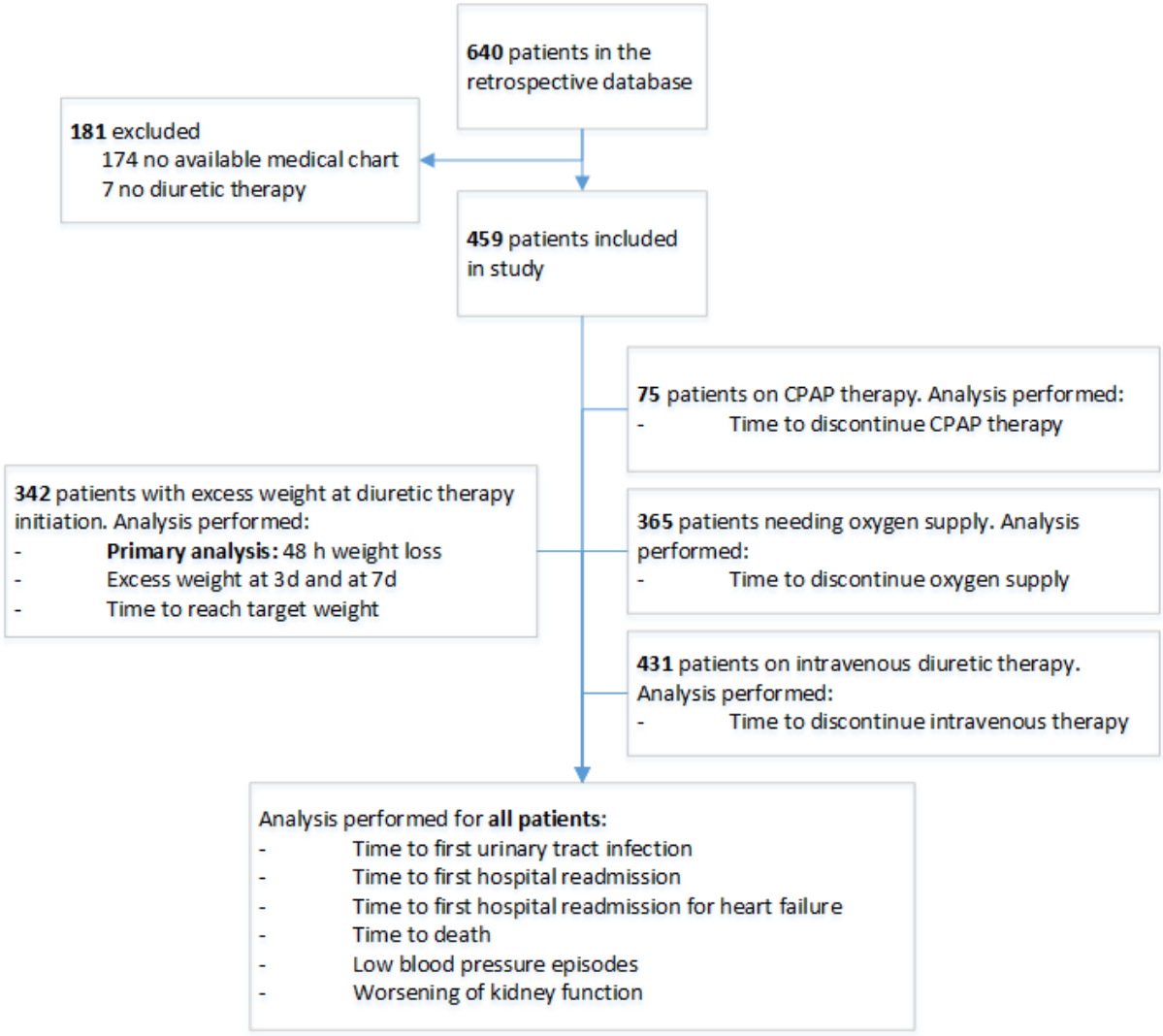


Figure: linear regression of adjustment variable and 48h weight loss (kg). For visual convenience, « usual diuretic therapy dose » and « initial diuretic dose » were restricted to the 99% of their values (excluding the 1% highest values).

Comment 4:

It would be useful for readers to visualize how patients were selected into the analysis, if authors could include a flowchart.

Answer:
- This is a very good advice. We added a flow chart in the appendix (we are limited by the number of figure/table admitted in the main manuscript).



Comment 5:
Please provide the results of the linear regression model in a table form (either in the main manuscript or appendix). This would be useful for readers to visualize the assumptions made in the model and to interpret the results.

Answer:
- We add this in the appendix (**Table S2**), since we were limited by the number of figure/table admitted in the main manuscript.

Comment 6:
a) Please clarify whether the results in the last column of table 2 was estimated from model that adjusted for all the 12 confounders or just age, sex, and CCI; you may need to add a footnote for the table on what variables were adjusted for.
b) Moreover, it would be useful to do sensitivity analyses to see the deviation of results from models with only subset of confounders vs those from models with the full list of pre-defined confounders.

Answer:

a) Thank you for this comment. We agree that the table could be misleading since the models are not all adjusted for the same confounding factors. We added footnotes to better identified the variable used.
b) This is an interesting proposition. However, the results, except for urinary tract infection, show no statistically significant association between urinary catheter (the only variable of interest in the model) and the different outcome in univariate and models adjusted for the predefined variables. Thus, we decided not to add other analysis.

Comment 7:
Please add unit for "Excess weight" in the first graph, and add label for the x-axis.

Answer:
- We added the requested information in the figure legend.

Comment 8:
Please provide the plots of Schoenfeld residuals and log-minus-log in the appendix. This will be helpful for users to visualize and interpret the proportional hazard assumptions of the analyses in this study.

Answer:
- We added in the appendix (**Figure S2**) the log-minus-log plots for 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 graphs and two tests, proportional assumption appeared to be reasonable for all the univariate analyses.

For the multivariable models, since there are seven models and many covariates, we added a **table** in the appendix (**Table S4**), summarizing all the slopes of the Schoenfeld residuals, and the p value of the test (<0.05 excluding proportional hazard). 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 of these variables over time, as proposed by Allison (**Allison** 2010). 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. We added these two analyses in the appendix.

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.

Comment 9:

a) Please elaborate the choice of using weight loss as outcome as oppose to using net fluid loss/creatinine level.

b) Also, please clarify how robust "targeted weights" of patients defined in this study were to represent the weight of patients when they were not volume overloaded, especially for patients who died within the hospital. For instance, do patients who died within a short time interval after admission met their true target weight before death (i.e. how many patients died with volume overloaded)?

Answer:

- a) The 24 h urine output was not available in the database and we couldn't calculate the fluid loss. We rather used change in weight on a daily basis as a marker of water loss (just like in daily practice).

- b) This is a very interesting question. It could be hypothesized that the "no difference" in time to reach the target weight observed in the study 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".

In the study, 36 patients (8%) died during the hospital stay, 10 without volume overload and 26 with overload. More patients in the UC group died during the first week (5.4%) than patient in the non-UC group (1.7%, p=0.04). Thus, this "falsely determination of Target weight" would be more often seen in patients with UC, than patients without UC. Since, this would result in a higher target weight than the "true target weight", the time to reach the goal would be shorter. This would play in favour of UC and against the strategy without UC.

Furthermore, only 5 patients with volume overload died without reaching the Target weight, and all of this patients died after a LOS of 10 days or more. For patients that reach their target weight, only 2 patients died less than 48h after having reach the target weight. Thus, this seems to have only marginal impact on data.

- Could patients be wrongly classified as having no "overload" because they died before having a Target weight? A very small fraction of patients without volume overload died during the hospital stay

(7%). Furthermore, only 4 in the UC group and 2 in the non UC group died within the first week. Within this 7 days window, patients with known volume overload generally attaint their target weight (see result **Table 2**). So, patients dying after this first seven days must have a target weight determined (if in volume overload). Thus, this potential bias doesn't seem to have play a major role in the study.

- For the main analysis, since the outcome is a difference in weights between day one and day three, it is not affected by the determination of the target weight.

- For the time to reach target weight analysis, 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 of 0.97 (95%CI: 0.64-1.44). This sensitivity analysis was added to the appendix (**Statistic S2**)

Comment 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." Please clarify the meaning of "hypothetical clinically relevant benefits of UC". It was not clear how "prospective records" were collected when data used in the analysis was from 2006-2010.

Answer:
- We agree that these two sentences could be complicated and decided to change them to:
-*"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."*

VERSION 3 – REVIEW

REVIEWER	Tomasz Imiela Postgraduate Medical School, Cardiology
REVIEW RETURNED	15-Jun-2022

GENERAL COMMENTS	Again I would like to congratulate the authors for the time and effort put in the revision process for the manuscript. In my opinion the manuscript is eligible for publication.