PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The efficacy and safety of furosemide for prevention of intradialytic hypotension in hemodialysis patients: protocol for a multicenter randomized controlled trial
AUTHORS	Chen, Wenwen; Wang, Fang; Zhao, Yuliang; Zhang, Ling; Chen, Zhiwen; Dai, Mingjin

VERSION 1 – REVIEW

REVIEWER	Mariano, Filippo University of Turin, Department of Medical Sciences
REVIEW RETURNED	10-Feb-2021

GENERAL COMMENTS	Wenwen C et al. proposed a two-arm multicenter RCT on patients on hemodialysis patients, aimed at evaluating the efficacy of furosemide on preventing hemodialysis hypotension. They planned an estimated sample of 430 hemodialysis patients. The treated arm will be assigned to receive oral furosemide 80mg/day, or after a two-week treatment adjusted dose of 160 mg/day if their urine volume is less than 400ml/day. The primary outcome will be intradialytic hypotension (defined in ref 3). The secondary outcomes will be hospitalization, all-cause mortality, cardiac mortality, cardiovascular events, intradialytic weight gain, dialysis symptoms, and any adverse effects. The follow-up will last one year. This trial will be conducted using a central computer-generated randomized sequence and the blinding of data analysis and outcome assessors. Thes trial will be administered a blank control, not a placebo control and dose contrast. General comment Thanks for allowing me to review this paper. This is a well-designed trial of practical interest, done with a cheap drug. Therefore, the trial has a great potential of the ratio cost-benefit. Major comments 1) I have some doubts about the planned dose of furosemide. I see the safety reason for choosing a low dose of furosemide, however, some papers demonstrated that a higher dose of furosemide means more urine output. 2) Did the Authors plan a cut-off point of urine output to stop furosemide in the treated group? In other words, when the urine output decrease below a determined value, will be the furosemide stopped? 3) Among parameters to be recorded the trial should include: Charlson comorbidity index score, the type of vascular access (AV fistula, CVC), episode of frank (or suspected) sepsis

	Minor comments 1) I think that “intradialytic weight gain” stands for “interdialytic weight gain”

REVIEWER	Mata, J Son Llàtzer Hospital, Anaesthesia
REVIEW RETURNED	15-Feb-2021

GENERAL COMMENTS	The efficacy and safety of furosemide for prevention of intradialytic hypotension in hemodialysis patients: protocol for a multicenter randomized controlled trial This is a two-arm, parallel, prospective, multicenter randomized controlled trial, which is intent to primarily examine if furosemide can reduce IDH and improve prognosis in HD patients. The research subject is interesting: Intradialytic hypotension (IDH) is a common and serious complication of hemodialysis patients (HD), with an incidence of up to 20%-30% of all dialysis sessions. The frequent occurrence of IDH increases the risk of thrombosis in vascular access, inadequate dialysis, cardiovascular disease and mortality. A number of strategies had been built to reduce the frequency and severity of IDH, including the modulation of ultrafiltration, qualitative changes in dialysate composition and lowering of dialysate temperature, while all of those reached a limited effect. No other effective pharmacological approach is recommended to addressing IDH excepting adjusting antihypertensive The effect of furosemide in dialysis has been investigated in several observational studies, unfortunately, prospective randomized studies evaluating furosemide therapy for IDH are lacking. The overall level of the paper is good. This paper has a potential to be accepted, but some questions have to be clarified or fixed before it is published. General recommendations Overall, this is a clear, concise, and well-written study protocol. The introduction is relevant and theory based. Sufficient information about the previous study findings is presented for readers to follow the present study rationale and procedures. The methods are generally appropriate, although clarification of a few details should be provided. Specific comments follow. Abstract At the end of the introduction, the objective of the study should be included. Introduction Page 5 (line 34) “No other effective pharmacological approach are recommended to addressing IDH excepting adjusting antihypertensive drugs”. It should be” “No other effective pharmacological approach is...” Page 6 (lines 41-42) “We plan to recruit participants at each HD units from March 2021 to December 2021 by the nephrologist”. According to the Trial registration record the study begins in January 2021, being the last update on November 6, 2020. Page 6 (lines 19-23) “In this study, we aim to conduct a prospective multicenter randomized controlled trial to primarily examine if furosemide can reduce IDH and improve prognosis in HD patients”.

	The aim of the study should include: “HD patients with residual renal function (RRF)”, since only those patients in HD with RRF of more than 200 ml orine output per day are included in the study. Diuretics commonly are prescribed only to patients who have some urine output, and previous studies showed an association between improved clinical status and quality of life in HD patients and the presence of RRF. The association between lower mortality and diuretic use shown in this analysis may simply reflect the known survival benefit conferred by RRF. It is possible that diuretic use helps preserve RRF by minimizing hypotensive episodes during dialysis, and the resultant preserved RRF improves survival. In addition, hypotension during dialysis is the most common complication of HD and is associated consistently with greater morbidity and mortality.8 Volume managed gradually with diuretics instead of intermittently when confined to HD treatments could help minimize hypotension during HD and thus improve survival. Similarly, use of a diuretic in an HD patient may improve volume management by removing fluid between dialysis treatments and minimizing IDWG. Greater IDWG was associated with lower survival. In this analysis, both lower IDWG and higher survival were associated with diuretic use. Methods and analysis Page 7 (lines 8-13) The inclusion criteria are as follows: participants who have been treated with HD three times a week for more than 3 months, with residual renal function (RRF) of more than 200 ml urine output per day, and consent to participate in the study. RRF is defined by a yes/no answer to the question at study entry: “Did the patient have RRF (ie, urine output _ _200 mL/d or 1 cup/d) on or before the enrollment date?” RRF also was collected every 4 months afterward (which asked about the most recent month). What is the temporary reference of the RRF? Was RRF based on a 24-hour urine collection? Page 8 (lines 41-47): “The definition of IDH is systolic blood pressure (BP) <90 mmHg (among patients with predialysis systolic BP<160 mmHg) or systolic BP <100 mmHg (among patients with predialysis BP>160 mmHg)” Flythe JE et al. J Am Soc Nephrol 2015; 26(3):724-34. In the same referenced article says: BP ≥ 160 mmHg. Page 9 (lines 56-60) Why hospitalization, all cause mortality, cardiac mortality, cardiovascular events are collected in the basal period? If they presented any of these events they would not be included in the study Page 10 (lines 33-37) According to the previous study, the rate of intradialytic hypotension was 0.25, compared to the control group, the OR that furosemide could reduce the rate of IHD was 0.55 (DOPPS report) It should be noted that the greater reduction in hypotensive events observed in the DOPPS report could be the result of the effects of other classes of diuretics as well as differences in international prescription patterns, such as usage of higher doses, or international HD treatment practices. Furthermore and offering perhaps the most likely explanation for the discrepancy, the studies used different definitions of intradialytic hypotension, with the present study using a more strict, nadir-based definition.(Hypertensive episodes were defined at study entry as a change in predialysis to postdialysis systolic blood pressure (SBP) greater than 30 mm Hg and a postdialysis SBP less than 100 mm Hg.)

	Page 11 (lines 19-20) Subgroup analyses will be conducted according to the level of pre-diaysis systolic BP (<160 vs >160 mmHg), years of diaysis (<3 years vs 3-5years vs >5 years) and residual renal function (yes vs no). The limitations of subgroup analyses are well established—false positives due to multiple comparisons, false negatives due to inadequate power, and limited ability to inform individual treatment decisions because patients have multiple characteristics that vary simultaneously. Trialists, reviewers, and editors should carefully consider such issues when making the essential scientific distinction between primary (that is, hypothesis testing) and secondary (that is, hypothesis generating) subgroup analyses.4 A positive, hypothesis testing analysis can directly influence patient care whereas a positive hypothesis generating analysis only calls for confirmatory research. The sensitivity of a subgroup analysis is its statistical power: the probability of finding a true difference between groups if one exists. Most large clinical trials are powered to find a clinically meaningful difference between treatment and control groups around 80-90% of the time. Compared with the power for the trial's main effect, most subgroup analyses have much less statistical power to identify subgroup effects. Power might often be closer to 20-30% for subgroup effect sizes similar in magnitude to the main treatment effect sizes (that is, a relative odds ratio for a subgroup treatment that is equal to the odds ratio for the overall treatment)8 9 Thus, the sample size needed to adequately contrast treatment effects measured in two different subgroups is much larger than the sample needed to distinguish an overall treatment effect from the null. Just as statistical power can be thought of as the sensitivity of a trial, the specificity of clinical trials is generally set to be 95%, based on the conventional significance threshold of P<0.05. Finally, an estimate of the prior probability is needed to interpret a subgroup analysis. Burke JF, Sussman JB, Kent DM, Hayward RA. Three simple rules to ensure reasonably credible subgroup analyses. BMJ. 2015 Nov 4;351:h5651. doi: 10.1136/bmj.h5651. PMID: 26537915; PMCID: PMC4632208 A sample calculation is required that includes subgroups for subgroup analysis On the other hand, an RRF subgroup analysis cannot be done as the absence of RRF is an exclusion criterion or not? Discusion Page 12 (lines 17-21) "Continuation of loop diuretics after hemodialysis initiation was associated with lower rates of hospitalization and intradialytic hypotension as well as lower interdialytic weight gain", "During first year o f dialysis" should be added. Discussion A discussion about complications about loop diuretic use should be included: Loop diuretics are generally the agents of choice in end-stage renal disease. They need to be used at higher doses because of pharmacokinetic changes in the context of diminishing renal clearance. Other classes of diuretics can still be used in end-stage renal disease, but usually in conjunction with loop diuretics or for benefits independent of diuresis. Complications can occur with the use of diuretics, but are avoidable with appropriate use. Dose-related ototoxicity, especially with concomitant use of other ototoxic medications, can occur. Hyperkalemia is possible with the use of

	potassium-sparing diuretics, but studies suggest that these agents can be safely administered with close monitoring. The major concern with the use of loop diuretics is the development of ototoxicity. In early studies, ototoxicity developed with furosemide given intravenously at 25 mg/minute in two-thirds of patients, but this risk decreased significantly at 15 mg/minute. Rates of less than 4 mg/minute are now recommended. Thus, using oral diuretics in conventional hemodialysis patients to decrease IDWG with consequent reduction in UF rates would be expected to be beneficial. Furthermore, lower UF rates may lead to fewer episodes of intradialytic hypotension, also known to predict mortality and cardiovascular events. Repeated episodes of intradialytic hypotension can cause serious adverse events such as cramping, myocardial, mesenteric or cerebral ischemia, inefficient dialysis and vascular access complications. Moreover, hypotensive episodes can lead to renal ischemia, with potentially faster loss of residual renal function. Patients on diuretictherapy retained more residual renal function after 1 year, had lower IDWG and had a 7% reduced mortality risk; they also had a decreased risk of hyperkalemia . However, these results may be confounded by the fact that patients receiving diuretics were more likely to have residual renal function. Impact of residual renal function (defined as renal urea clearance and renal creatinine clearance derived from 24-hour urinary volumes) on mortality over a 2-year period was 50 deaths occurred in 114 patients. The presence of residual renal function was protective against mortality (odds ratio for death, 0.44; 95% confidence interval, 0.24 to 0.81; P = 0.008), even after adjustment for duration of dialysis treatment, age, smoking, presence of diabetes, presence of cardiovascular disease, serum albumin level, and urea reduction rate. In conclusion, the presence of residual renal function, even at a low level, is associated with a lower mortality risk in HD patients. Possible reasons for discontinuation the use of loop diuretics include the assumption that dialysis treatment alone is sufficient for management of fluid overload, the misconception that diuretics may no longer be effective in advanced renal disease, the belief that they may hasten decline of residual renal function, and the fear of side effects such as ototoxicity. With regard to effectiveness, van Olden et al. showed that the use of a daily dose of furosemide of 250–1000 mg led to an increased urine volume by 60% in chronic hemodialysis patients, although the response declined over time. Furthermore, in the CHOICE study, 28% of patients still reported the urine output of >250 ml/day after 1 year. Therefore, when used at an appropriate dosage, diuretics may benefit many conventional hemodialysis patients with residual renal function, even after 1 year. In short, the overall level of the paper is good. This paper has a potential to be accepted, once the above questions have been answered.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Major comments

1) I have some doubts about the planned dose of furosemide. I see the safety reason for choosing a low dose of furosemide, however, some papers demonstrated that a higher dose of furosemide

means more urine output.
[Response]
Thanks so much for your comments. We also expected more benefits from higher dose of furosemide. The limited evidence supporting the effect of higher dose of furosemide for hemodialysis and the accompanying ototoxicity and other side effects remained a barriers to obtain permission from the biomedical research ethics committee. Although previous study reported the use of a daily dose of furosemide of 250–1000 mg led to an increased urine volume by 60% in chronic hemodialysis patients, more than 20% patients had side effects. The dosing is variable in clinical practice. While European centers use doses of up to 500 mg, daily furosemide doses of 80-160 mg for reported in hemodialysis patients in China. Based on the previous experience, we chose the initial dose of 80 mg and increased to 160 mg after two weeks. In addition, we add some suggestions on the Discussion part.
In ´Discussion´ section, Page12, Line 11-13.
“Since we adopted a relatively low and safe dose of furosemide, more prospective studies investigating the ideal does, especially dose based on the residual kidney function of individual are need.”

2) Did the Authors plan a cut-off point of urine output to stop furosemide in the treated group? In other words, when the urine output decrease below a determined value, will be the furosemide stopped?
[Response]
Thank you and we have added the cut-off point of 200 ml urine output per day to stop furosemide in the treated group. This value was consistent with the criteria for residual renal function of included participants.
In ´Method´ section, Page7, Line3-4:
“Once the patient's daily urine output is less than 200 ml, the use of furosemide is discontinued”.

3) Among parameters to be recorded the trial should include: Charlson comorbidity index score, the type of vascular access (AV fistula, CVC), episode of frank (or suspected) sepsis.
[Response]
Thank you for this important comment. We have added these key parameters to our data collection form as well as in the Method section. Information about Charlson comorbidity index score and the type of vascular access will be collected at baseline, and episode of frank (or suspected) sepsis will be evaluated during the treatment period.
Details are summarized in Table 1, Method section, Page8, Line 1-2.

Minor comments
1) I think that “intradialytic weight gain” stands for “interdialytic weight gain”.
[Response]
Thank you. As suggested, we used“interdialytic weight gain” instead and we have carefully checked the entire text to make sure we did not mix these two terms.

Reviewer: 2
Specific comments

Abstract
1) At the end of the introduction, the objective of the study should be included.
[Response]
Thank you for this comment. As suggested, we have added our aim to this part.
In ´Abstract´ section, Page 2, Line 10-12:
“The purpose of this study was to assess the efficacy of furosemide for reducing intradialytic hypotension in hemodialysis patients with residual renal function.”

Introduction
2) Page 5 (line 34)
“No other effective pharmacological approach are recommended to addressing IDH excepting adjusting antihypertensive drugs”.
It should be” “No other effective pharmacological approach is...”
[Response]
Thank you so much for your careful review. We have corrected these errors and we have carefully checked the entire text and correct any spelling and grammar errors we identified.
In ´Introduction´ section, Page 3, Line 27-28:
“No other effective pharmacological approach is are recommended to addressing IDH excepting adjusting antihypertensive drugs.”

3) Page 6 (lines 41-42)
“We plan to recruit participants at each HD units from March 2021 to December 2021 by the nephrologist”.
According to the Trial registration record the study begins in January 2021, being the last update on November 6, 2020.
[Response]
Thank you. This trial has been postponed several times due to the COVID-19 epidemic. We planned to recruit participants from June 2021. We also update the information in the Method section.
In ´Method´ section, Page 5, Line3-5:
“We plan to recruit participants at each HD units from June 2021 by the nephrologist and expect to end in March 2022.”

4) Page 6 (lines 19-23)
“In this study, we aim to conduct a prospective multicenter randomized controlled trial to primarily examine if furosemide can reduce IDH and improve prognosis in HD patients”.
The aim of the study should include: “HD patients with residual renal function (RRF)”, since only those patients in HD with RRF of more than 200 ml urine output per day are included in the study.
Diuretics commonly are prescribed only to patients who have some urine output, and previous studies showed an association between improved clinical status and quality of life in HD patients and the presence of RRF. The association between lower mortality and diuretic use shown in this analysis may simply reflect the known survival benefit conferred by RRF. It is possible that diuretic use helps preserve RRF by minimizing hypotensive episodes during dialysis, and the resultant preserved RRF improves survival. In addition, hypotension during dialysis is the most common complication of HD and is associated consistently with greater morbidity and mortality. Volume managed gradually with diuretics instead of intermittently when confined to HD treatments could help minimize hypotension during HD and thus improve survival. Similarly, use of a diuretic in an HD patient may improve volume management by removing fluid between dialysis treatments and minimizing IDWG. Greater IDWG was associated with lower survival. In this analysis, both lower IDWG and higher survival were associated with diuretic use.
[Response]
Thanks so much for your insightful comment. As mentioned in the comments above, diuretic use can improve the prognosis through possible multiple pathways, such as preserved RRF, better volume management and minimizing IDWG, not only by reducing IDH, and the association and interaction between them is beyond our study. Therefore, we revised our description about the study purpose and concentrated on the efficacy of prevention of intradialytic hypotension.
In ´Introduction´ section, Page 4, Line 21-23:
“In this study, we aim to conduct a prospective multicenter randomized controlled trial to primarily examine if furosemide can reduce IDH in HD patients with residual renal function (RRF).”

Methods and analysis

5) Page 7 (lines 8-13)
The inclusion criteria are as follows: participants who have been treated with HD three times a week for more than 3 months, with residual renal function (RRF) of more than 200 ml urine output per day, and consent to participate in the study.
RRF is defined by a yes/no answer to the question at study entry: “Did the patient have RRF (ie, urine output>200 mL/d or 1 cup/d) on or before the enrollment date?” RRF also was collected every 4 months afterward (which asked about the most recent month). What is the temporary reference of the RRF? Was RRF based on a 24-hour urine collection?
[Response]
Thank you. The RRF was based on a 24-hour urine collection, measured by a 200 ml measuring cup. We have add the description and reference in the methods section.
In ´Method´ section, Page 5, Line 16-20:
“The inclusion criteria are as follows: participants who have been treated with HD three times a week for more than 3 months, with residual renal function (RRF) of more than 200 ml urine output per day (based on a 24-hour urine collection, measured by a 200 ml measuring cup), and consent to participate in the study14.”

6) Page 8 (lines 41-47):
“The definition of IDH is systolic blood pressure (BP) <90 mmHg (among patients with predialysis systolic BP<160 mmHg) or systolic BP <100 mmHg (among patients with predialysis BP>160 mmHg)” Flythe JE et al. J Am Soc Nephrol 2015; 26(3):724-34. In the same referenced article says: BP ≥ 160 mmHg.
[Response]
Thank you. We have corrected definition according to the reference and carefully checked the entire text to keep the consistency.
In ´Method´ section, Page 7, Line 9-12:
“The definition of IDH is systolic blood pressure (BP) <90 mmHg (among patients with pre-dialysis systolic BP<160 mmHg) or systolic BP <100 mmHg (among patients with pre-dialysis BP≥160 mmHg)3.”

7) Page 9 (lines 56-60):
Why hospitalization, all cause mortality, cardiac mortality, cardiovascular events are collected in the basal period? If they presented any of these events they would not be included in the study
[Response]
Thank you for this comment. We have removed the outcome measurement at the baseline.
Please see details in the Table 1, in Method part, Page 8, Line 1-2.

8) Page 10 (lines 33-37):
According to the previous study, the rate of intradialytic hypotension was 0.25, compared to the control group, the OR that furosemide could reduce the rate of IHD was 0.55 (DOPPS report)
It should be noted that the greater reduction in hypotensive events observed in the DOPPS report could be the result of the effects of other classes of diuretics as well as differences in international prescription patterns, such as usage of higher doses, or international HD treatment practices. Furthermore and offering perhaps the most likely explanation for the discrepancy, the studies used different definitions of intradialytic hypotension, with the present study using a more strict, nadir-based definition.(Hypertensive episodes were defined at study entry as a change in predialysis to postdialysis systolic blood pressure (SBP) greater than 30 mm Hg and a postdialysis SBP less than 100 mm Hg.)
[Response]
Thank you. Considering the greater reduction in the hypotensive events observed in the DOPPS study, we have set the expected OR of 0.6 to recalculate the sample size.
In ´Method´ section, Page 9, Line10-14:

“Sample size calculations was conducted using G-Power V.3.1, with an α value of 0.05, power of 80%, relative risk of IHD for treatment group relative to controls is 0.6, a sample size 250 patients per arm is required. The dropout rate of furosemide treatment during the study is estimated to be 10%, so a minimum sample size of 560 patients will be needed in each group.”

9) Page 11 (lines 19-20):
Subgroup analyses will be conducted according to the level of pre-dialysis systolic BP (<160 vs >160 mmHg), years of dialysis (<3 years vs 3-5years vs >5 years) and residual renal function (yes vs no).
The limitations of subgroup analyses are well established—false positives due to multiple comparisons, false negatives due to inadequate power, and limited ability to inform individual treatment decisions because patients have multiple characteristics that vary simultaneously.
Trialists, reviewers, and editors should carefully consider such issues when making the essential scientific distinction between primary (that is, hypothesis testing) and secondary (that is, hypothesis generating) subgroup analyses. A positive, hypothesis testing analysis can directly influence patient care whereas a positive hypothesis generating analysis only calls for confirmatory research.
The sensitivity of a subgroup analysis is its statistical power: the probability of finding a true difference between groups if one exists. Most large clinical trials are powered to find a clinically meaningful difference between treatment and control groups around 80-90% of the time. Compared with the power for the trial’s main effect, most subgroup analyses have much less statistical power to identify subgroup effects. Power might often be closer to 20-30% for subgroup effect sizes similar in magnitude to the main treatment effect sizes (that is, a relative odds ratio for a subgroup treatment that is equal to the odds ratio for the overall treatment). Thus, the sample size needed to adequately contrast treatment effects measured in two different subgroups is much larger than the sample needed to distinguish an overall treatment effect from the null. Just as statistical power can be thought of as the sensitivity of a trial, the specificity of clinical trials is generally set to be 95%, based on the conventional significance threshold of P<0.05.
Finally, an estimate of the prior probability is needed to interpret a subgroup analysis.
Burke JF, Sussman JB, Kent DM, Hayward RA. Three simple rules to ensure reasonably credible subgroup analyses. BMJ. 2015 Nov 4;351:h5651. doi: 10.1136/bmj.h5651. PMID: 26537915; PMCID: PMC4632208
A sample calculation is required that includes subgroups for subgroup analysis
On the other hand, an RRF subgroup analysis cannot be done as the absence of RRF is an exclusion criterion or not?
[Response]
Thank you. We have learn the theory in the above-mentioned study about subgroup analysis. Considering the difficulty to recruiting participants and management during the COVID-19, it is risky to increase the sample size to ensure the statistics power for the prespecified subgroup analysis. On the other hand, prespecified subgroup analysis is aimed to determine which patients most benefit from the treatment, based on specific risk factors, and furosemide is such a cheap drug and is expected to reduce the IDH in all HD patients with RRF. We therefore have removed these subgroup analyses at this stage.

10) Discussion: Page 12 (lines 17-21):
“Continuation of loop diuretics after hemodialysis initiation was associated with lower rates of hospitalization and intradialytic hypotension as well as lower interdialytic weight gain”,
“During first year of dialysis” should be added.
[Response]
Thank you. As suggested, we have added this information.
In ´Discussion´ section, Page 10-11, Line 28-1:
“Continuation of loop diuretics after hemodialysis initiation was associated with lower rates of hospitalization and intradialytic hypotension as well as lower interdialytic weight gain during the first year of dialysis13.”

11) Discussion
A discussion about complications about loop diuretic use should be included:
Loop diuretics are generally the agents of choice in end-stage renal disease. They need to be used at higher doses because of pharmacokinetic changes in the context of diminishing renal clearance. Other classes of diuretics can still be used in end-stage renal disease, but usually in conjunction with loop diuretics or for benefits independent of diuresis. Complications can occur with the use of diuretics, but are avoidable with appropriate use. Dose-related ototoxicity, especially with concomitant use of other ototoxic medications, can occur. Hyperkalemia is possible with the use of potassium-sparing diuretics, but studies suggest that these agents can be safely administered with close monitoring.
The major concern with the use of loop diuretics is the development of ototoxicity. In early studies, ototoxicity developed with furosemide given intravenously at 25 mg/minute in two-thirds of patients, but this risk decreased significantly at 15 mg/minute. Rates of less than 4 mg/minute are now recommended.
Thus, using oral diuretics in conventional hemodialysis patients to decrease IDWG with consequent reduction in UF rates would be expected to be beneficial. Furthermore, lower UF rates may lead to fewer episodes of intradialytic hypotension, also known to predict mortality and cardiovascular events. Repeated episodes of intradialytic hypotension can cause serious adverse events such as cramping, myocardial, mesenteric or cerebral ischemia, inefficient dialysis and vascular access complications. Moreover, hypotensive episodes can lead to renal ischemia, with potentially faster loss of residual renal function.
Patients on diuretic therapy retained more residual renal function after 1 year, had lower IDWG and had a 7% reduced mortality risk; they also had a decreased risk of hyperkalemia. However, these results may be confounded by the fact that patients receiving diuretics were more likely to have residual renal function. Impact of residual renal function (defined as renal urea clearance and renal creatinine clearance derived from 24-hour urinary volumes) on mortality over a 2-year period was 50 deaths occurred in 114 patients. The presence of residual renal function was protective against mortality (odds ratio for death, 0.44; 95% confidence interval, 0.24 to 0.81; P = 0.008), even after adjustment for duration of dialysis treatment, age, smoking, presence of diabetes, presence of cardiovascular disease, serum albumin level, and urea reduction rate. In conclusion, the presence of residual renal function, even at a low level, is associated with a lower mortality risk in HD patients.
Possible reasons for discontinuation the use of loop diuretics include the assumption that dialysis treatment alone is sufficient for management of fluid overload, the misconception that diuretics may no longer be effective in advanced renal disease, the belief that they may hasten decline of residual renal function, and the fear of side effects such as ototoxicity. With regard to effectiveness, van Olden et al. showed that the use of a daily dose of furosemide of 250–1000 mg led to an increased urine volume by 60% in chronic hemodialysis patients, although the response declined over time. Furthermore, in the CHOICE study, 28% of patients still reported the urine output of >250 ml/day after 1 year. Therefore, when used at an appropriate dosage, diuretics may benefit many conventional hemodialysis patients with residual renal function, even after 1 year.
[Response]
Thanks so much for your insightful suggestions. It is helpful for us to improve the quality of our study. We carefully made some modifications and supplementations about complications and benefit of furosemide in accordance with suggestions in the part Discussion. Now it reads as below.
In ´Discussion´ section, Page 11, Line 10-19:
“The major concern about the development of ototoxicity and other side effect of loop diuretics in dialysis patients hindered its use in HD12. Another possible reasons for discontinuation the use of loop diuretics include the assumption that dialysis treatment alone is sufficient for management of fluid overload and underestimate of its benefit for hemodialysis patients. A recent systematic review has found that loop diuretics might may benefit hemodialysis patients by reducing the incidence rate of IDH, all-cause mortality and CV mortality for HD patients23. However, evidence about its safety is

still limited. The present prospective study will confirm the efficacy and gain evidence about the and safety of furosemide in hemodialysis and further guide the clinical practices."

VERSION 2 – REVIEW

REVIEWER	Mariano, Filippo University of Turin, Department of Medical Sciences
REVIEW RETURNED	16-May-2021

GENERAL COMMENTS	No further comments.

REVIEWER	Mata, J Son Llàtzer Hospital, Anaesthesia
REVIEW RETURNED	24-May-2021

GENERAL COMMENTS	This is a two-arm, parallel, prospective, multicenter randomized controlled trial, which is intent to primarily examine if furosemide can reduce IDH and improve prognosis in HD patients. The research subject is interesting: Intradialytic hypotension (IDH) is a common and serious complication of hemodialysis patients (HD), with an incidence of up to 20%-30% of all dialysis sessions. The frequent occurrence of IDH increases the risk of thrombosis in vascular access, inadequate dialysis, cardiovascular disease and mortality. A number of strategies had been built to reduce the frequency and severity of IDH, including the modulation of ultrafiltration, qualitative changes in dialysate composition and lowering of dialysate temperature, while all of those reached a limited effect. No other effective pharmacological approach is recommended to addressing IDH excepting adjusting antihypertensive The effect of furosemide in dialysis has been investigated in several observational studies, unfortunately, prospective randomized studies evaluating furosemide therapy for IDH are lacking. I would like to congratulate the authors on their work. This was a very interesting manuscript. The questions have been satisfactorily responded at all to several points raised in the review and the paper has been modified. This paper has a potential to be accepted, although there is a minor recommendation should be taken into account before: The trial registration number must display the date that the trial record was last updated. All the changes in the study protocol must be included in the last version (participants' recruitment, sample size…) with the date that the trial record was last updated. Clinical trial registration is the practice of documenting clinical trials before they are performed in a clinical trials registry so as to combat publication bias and selective reporting. Trial registration number ChiCTR2000039724 (last updated: Version 1.4 (2021/2/13).

VERSION 2 – AUTHOR RESPONSE

Comments from Reviewers
Reviewer: 2

This is a two-arm, parallel, prospective, multicenter randomized controlled trial, which is intent to primarily examine if furosemide can reduce IDH and improve prognosis in HD patients.
The research subject is interesting: Intradialytic hypotension (IDH) is a common and serious complication of hemodialysis patients (HD), with an incidence of up to 20%-30% of all dialysis sessions. The frequent occurrence of IDH increases the risk of thrombosis in vascular access, inadequate dialysis, cardiovascular disease and mortality. A number of strategies had been built to reduce the frequency and severity of IDH, including the modulation of ultrafiltration, qualitative changes in dialysate composition and lowering of dialysate temperature, while all of those reached a limited effect. No other effective pharmacological approach is recommended to addressing IDH excepting adjusting antihypertensive. The effect of furosemide in dialysis has been investigated in several observational studies, unfortunately, prospective randomized studies evaluating furosemide therapy for IDH are lacking.
I would like to congratulate the authors on their work. This was a very interesting manuscript. The questions have been satisfactorily responded at all to several points raised in the review and the paper has been modified. This paper has a potential to be accepted, although there is a minor recommendation should be taken into account before:
The trial registration number must display the date that the trial record was last updated. All the changes in the study protocol must be included in the last version (participants' recruitment, sample size…) with the date that the trial record was last updated.
Clinical trial registration is the practice of documenting clinical trials before they are performed in a clinical trials registry so as to combat publication bias and selective reporting.
Trial registration number ChiCTR2000039724 (last updated: Version 1.4 (2021/2/13).

[Response]
Thanks so much for your insightful suggestions. It is really helpful for us to improve the quality of our study. We have updated the protocol on the clinical trial registration website. The main changes in the study protocol include: 1) participants' recruitment is expected to start from June 2021 and end in March 2022; 2) the sample size is 580; 3) plan a cut-off point of urine output to stop furosemide in the treated group. Please refer the clinical trial registration website for further information.