PEER REVIEW HISTORY

ARTICLE DETAILS

Title (Provisional)

Effects of Canagliflozin on brain natriuretic peptide level in patients with type 2 diabetes on peritoneal dialysis: protocol for a multicenter, prospective, randomized controlled trial (CARD-PD trial)

Authors

Matsuoka, Naoko; Nakazawa, Daigo; Nishio, Saori; Cho, Kyu Yong; Maoka, Tomochika; Kaneshima, Nobuharu; Yamamoto, Rie; Yamamoto, Junya; Shimamoto, Mamiko; Makita, Minoru; Iriuda, Satoko; Igarashi, Kento; Ito, Yosuke; Kato, Akiko; Yoshikawa, Junpei; Kudo, Takashi; Nagashima, Takahiro; Ito, Yoichi M; Atsumi, Tatsuya

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Ushiogi, Yasuyuki**
Affiliation	**Fukui-ken Saiseikai Hospital, Internal medicine**
Date	**05-Jun-2024**
COI	**None**

This is an interesting study. However, there are minor concerns about the method.

First, it is written as “In principle, treatments that influence the outcome, including doses of antihypertensive drugs, anti-hyperglycemic agents, and peritoneal dialysis prescriptions, will not be adjusted during the study period. If necessary, diabetes or antihypertensive drugs will be properly adjusted to avoid hypoglycemia or to prevent uncontrolled hypertension.” This statement is vague and needs to be clarified. For example, “the target systolic blood pressure is 130-140 mmHg”.

Second, you mentioned “to avoid hypoglycemia” but what do you think the criteria for hypoglycemia are? Is it below 3.0 mmol/L, below 3.9 mmol/L or severe hypoglycemia? Since SGLT2 is a glucose-lowering agent, careful observation of hypoglycemia is required in patients with advanced chronic kidney disease who are prone to hypoglycemia. Hypoglycemia is a risk factor for cardiovascular disease. It is also important to be careful of nocturnal hypoglycemia.

Third, it is written as “to maintain fluid balance” What is the indicator for determining the appropriate range? In clinical practice, BNP itself is used as an indicator.

Reviewer	**2**
Name	**Artan, Ayse Serra**
Affiliation	**Bezmialem Vakif Universitesi**
Date	**21-Jun-2024**
COI	**None**

There are multiple minor typographical and grammatical errors throughout the manuscript that should be corrected.

Many laboratory tests and imaging techniques will be performed during the study. These tests seem to be intended for detecting hypervolemia and assessing cardiac status. However, further explanation is needed to clarify the purpose of these planned examinations. For example, what is the relevance of cervical echocardiography? The PET test is probably intended to provide information regarding peritoneal membrane function, but the intention behind this is absent from the text. Additionally, which cardiac echo parameters are specifically planned to be examined? Which markers of reactive oxygen species will be measured?

I suggest that the mentioned CT scan is a coronary CT angiography; this should be clarified in the methods section.

VERSION 1 - AUTHOR RESPONSE

Response to Reviewer’s comments

Reviewer: 1
Dr. Yasuyuki Ushiogi, Fukui-ken Saiseikai Hospital
Comments to the Author:

> This is an interesting study. However, there are minor concerns about the method. First, it is written as “In principle, treatments that influence the outcome, including doses of antihypertensive drugs, anti-hyperglycemic agents, and peritoneal dialysis prescriptions, will not be adjusted during the study period. If necessary, diabetes or antihypertensive drugs will be properly adjusted to avoid hypoglycemia or to prevent uncontrolled hypertension.” This statement is vague and needs to be clarified. For example, “the target systolic blood pressure is 130-140 mmHg”.

(Response) We appreciate the reviewer's suggestion to clarify the statement during the study period. We attempted to minimize the impact of antihypertensive drugs and peritoneal dialysis efficacy to evaluate the direct effect of SGLT2 inhibitors on hypertension and fluid volume. However, when patients are not controlled according to clinical guidelines (target BP is 130/80 mmHg, and euvolemic volume management, KDIGO; https://kdigo.org/wp-content/uploads/2017/05/KDIGO-BP-Volume-in-Dialysis-FINAL.pdf), they will be treated with antihypertensive drugs or have their peritoneal

dialysis prescription adjusted at the discretion of the attending physician. These descriptions have been added to the manuscript. （Line147-148）

Second, you mentioned “to avoid hypoglycemia” but what do you think the criteria for hypoglycemia are? Is it below 3.0 mmol/L, below 3.9 mmol/L or severe hypoglycemia? Since SGLT2 is a glucose-lowering agent, careful observation of hypoglycemia is required in patients with advanced chronic kidney disease who are prone to hypoglycemia. Hypoglycemia is a risk factor for cardiovascular disease. It is also important to be careful of nocturnal hypoglycemia.

(Response) We thank the reviewer for the comment. Although no specific protocols for hypoglycemia management were established in advance, adjustments to diabetes medications will be made to keep blood glucose levels above 70 mg/dL, where clinical symptoms are likely to appear. To prevent the occurrence of hypoglycemic symptoms, primary physicians will individually adjust treatments according to guideline recommendations (PMID 31862747).

Third, it is written as “to maintain fluid balance” What is the indicator for determining the appropriate range? In clinical practice, BNP itself is used as an indicator.

(Response) We appreciate the reviewer's comments.
In this trial, fluid management will be conducted using volume assessment parameters including physical examination, blood pressure, chest x-ray, and BNP based on clinical guidelines (PMID: 32278617). Our hypothesis is that SGLT2 inhibitors reduce BNP levels and contribute to effective fluid management. As reviewer 1 indicated BNP is also an indicator of volume assessment. Therefore, we attempt to avoid the change of peritoneal dialysis prescription within the allowable range to evaluate the direct effect of SGLT2 inhibitor. These explanations have been rephrased.

Reviewer: 2
Dr. Ayse Serra Artan, Bezmialem Vakif Universites. I
Comments to the Author:
There are multiple minor typographical and grammatical errors throughout the manuscript that should be corrected
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(Response) We thank the reviewer for the critical comments. We will carefully review the manuscript and correct all identified errors to improve the overall quality and readability of our manuscript.

Many laboratory tests and imaging techniques will be performed during the study. These tests seem to be intended for detecting hypervolemia and assessing cardiac status. However, further explanation is needed to clarify the purpose of these planned examinations. For example, what is the relevance of cervical echocardiography? The PET test is probably intended to provide information regarding peritoneal membrane function, but the intention behind this is absent from the text. Additionally, which cardiac echo parameters are specifically planned to be examined? Which markers of reactive oxygen species will be measured?

I suggest that the mentioned CT scan is a coronary CT angiography; this should be clarified in the methods section.

(Response) We appreciate the reviewer's detailed feedback and for pointing out the areas that require further clarification. Patients with end-stage CKD have multiple clinical problems, including cardiovascular disease, fluid imbalance, mineral and bone disorders,

inflammation, oxidative stress, etc. SGLT2 inhibitors are reported to contribute to addressing these issues in diabetes, heart failure, and chronic kidney disease. Thus, we aim to assess these significant findings in patients with end-stage CKD for the first time in this trial. As suggested by reviewer 2, the intention of each examination has been described in manuscript as follows（Line94-104）;

*Cervical echo assesses the progression of arteriosclerosis to examine its association with the risk of cardiovascular disease.
*PET provides detailed information regarding peritoneal membrane function and assesses any changes in its permeability.
*CT is performed to evaluate coronary artery disease. Its definition has been added in text.
*Cardiac echo assesses cardiac function and structure, crucial for detecting heart diseases. Its specific parameters that will be examined include left ventricular ejection fraction, left atrial enlargement, and ventricular filling pressure.
*Holter Electrocardiograph monitors heart rhythms over 24 hours, detecting arrhythmias.
*Chest X-ray provides information about heart size and lung condition.
*Bone Mineral Density Measurement evaluates the presence of bone mineral disorders common in patients with chronic kidney disease (CKD).

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Ushiogi, Yasuyuki**
Affiliation	**Fukui-ken Saiseikai Hospital, Internal medicine**
Date	**03-Sep-2024**
COI	**None**

This is an interesting study. Patients with end-stage renal failure are prone to changes in blood pressure, plasma glucose levels, and body fluid volume. And thus, it is difficult to treat patients with end-stage renal disease for 6 to 12 months without changing their antihypertensive and antihyperglycemic medications or peritoneal dialysis prescriptions. However, if they can observe them under stable conditions, they are likely to gain a lot of insight into the possible cardioprotective effects of SGLT2.

Reviewer	**2**
Name	**Artan, Ayse Serra**
Affiliation	**Bezmialem Vakif Universitesi**
Date	**07-Sep-2024**
COI	**None**

The authors have responded to the concerns regarding the manuscript appropriately, and I have no further recommendations

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VERSION 2 - AUTHOR RESPONSE

Reviewer: 1
Dr. Yasuyuki Ushiogi, Fukui-ken Saiseikai Hospital
Comments to the Author:
This is an interesting study. Patients with end-stage renal failure are prone to changes in blood pressure, plasma glucose levels, and body fluid volume. And thus, it is difficult to treat patients with end-stage renal disease for 6 to 12 months without changing their antihypertensive and antihyperglycemic medications or peritoneal dialysis prescriptions. However, if they can observe them under stable conditions, they are likely to gain a lot of insight into the possible cardioprotective effects of SGLT2.

(Response)Thank you for the insightful comments. We fully acknowledge that patients with end-stage renal failure are prone to fluctuations in blood pressure, plasma glucose levels, and body fluid volume, which indeed makes it challenging to maintain a stable condition over a prolonged period. In response to your concern, we would like to clarify that, throughout the study, antihypertensive medications, blood glucose-lowering drugs, and peritoneal dialysis prescriptions will be adjusted as necessary at the discretion of the attending physician to address any changes in blood pressure, fluid retention, or blood glucose levels in accordance with relevant guidelines. These adjustments will be documented and accounted for in our analysis to ensure the stability of patient conditions as much as possible while also allowing us to capture the potential cardioprotective effects of SGLT2 inhibitors. We have included this description as a limitation of the study (in line with editor's comment).

Reviewer: 2
Dr. Ayse Serra Artan, Bezmialem Vakif Universitesi
Comments to the Author:
The authors have responded to the concerns regarding the manuscript appropriately, and I have no further recommendations

Reviewer: 1
If you have selected 'Yes' above, please provide details of any competing interests.:
None

Reviewer: 2

If you have selected ‘Yes’ above, please provide details of any competing interests.:
None