PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Prognostic value of reduction in left atrial size during a follow-up of heart failure: an observational study
AUTHORS	Shiba, Masayuki; Kato, Takao; Morimoto, Takeshi; Yaku, Hidenori; Inuzuka, Yasutaka; Tamaki, Yodo; Ozasa, Neiko; Seko, Yuta; Yamamoto, Erika; Yoshikawa, Yusuke; Kitai, Takeshi; Yamashita, Yugo; Iguchi, Moritake; nagao, kazuya; Kawase, Yuichi; Morinaga, Takashi; Toyofuku, Mamoru; Furukawa, Yutaka; Ando, Kenji; Kadota, Kazushige; Sato, Yukihito; Kuwahara, Koichiro; Kimura, Takeshi

VERSION 1 – REVIEW

REVIEWER	Donal, Erwan CHU Rennes, Rennes, France
REVIEW RETURNED	02-Oct-2020

GENERAL COMMENTS	Reduction in Left Atrial Size Associates with Better Prognosis during a Follow-Up of Heart Failure This a nice study. It provides new data. Authors focused on LA diameters, it is a pity that they did not provide LA volumes! Still, there is a potential for reverse LA remodeling and it seems that it is associated with a relative risk of HF related events. The purpose and the results are valuable. The manuscript is nicely presented. Remarks: - “271 patients who died during index hospitalization”: this is huge, why is it so? - A multivariable analysis of the factors associated with a decrease in LAD should be provided - LA volume is recommended by Lang et (ASE/EACVI recommendation paper for chambers’quantification) - E’, E/E’, E-deceleration time, Output…there are parameters that are missing in the present manuscript. GLS as well! (Cho et al JACC…)

REVIEWER	Peter Riis Hansen Department of Cardiology Herlev and Gentofte Hospital DK-2900 Herlev Denmark
REVIEW RETURNED	03-Oct-2020

GENERAL COMMENTS	Major points Study primary outcome: Why was a composite of ‘all-cause death or

	HF hospitalization' selected instead of 'cardiovascular death or HF hospitalization' that is usually employed in heart failure studies? Use of the latter would have facilitated comparison of study outcome rates with those of other studies. Selection bias: This bias is briefly mentioned in relation to missing data on medications (P20, L27) but the authors are advised to dwell more on the matter, not least the fact that a substantial n=1516 of KCHF study participants (n=4056) were considered ineligible for the follow-up mandated by the present protocol (P8, L13). One reason was apparently that patients were 'unable to visit a hospital due to patients' conditions' (Figure 1). On the other hand, patients included in the present study were old (mean age around 75 years) and yet did not appear to display excessive mortality rates, i.e. 23 of 1246 (1.8%] died between time of discharge from index hospitalization to 6 month echocardiography (Figure 1) and 4.6-8.6% in the ensuing 180 days (Table 3). The authors may further explain considerations that led to ineligibility of patients for the follow-up study, provide information about outcomes of these patients, and discuss the mortality of enrolled patients in the present study compared to other studies. Minor points P5, L6: That 'observing the change in LAD helps us modify the intensity of treatment..' was not examined in this study. The statement should be modified accordingly. Unclear wordings on duration of follow-up: It is stated that 'clinical follow-up was performed at 1 year after enrollment and the data were censored at 210 after the 6-month echocardiography' (P7, L40), 'outcome measures were followed for 180 days from time zero [date of 6-month echocardiography'], and 'median (interquartile range) follow-up length was 302 (207-497) with a 96.3% follow-up rate at 180-day after 6 month echocardiography' (P14, L22). If outcome measures were followed for 180 days, it seems unclear why data were censored at 210 days (and not 180 days) after the 6-month echocardiography. Along this line, 'time zero' of follow-up, i.e. time of the 6-month echocardiography, is obfuscated by the statement about 'echocardiography at 6-months with allowance of 1-month' (P7, L33). The authors should clarify. L9, L30: Change 'enrolling patients were to have..' to 'enrolling patients who were to have..'. P16, L43: Change 'cardiac function by echocardiography' to 'cardiac structure and function by echocardiography'.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author
Reduction in Left Atrial Size Associates with Better Prognosis during a Follow-Up of Heart Failure
This a nice study. It provides new data. Authors focused on LA diameters, it is a pity that they did not provide LA volumes!

Still, there is a potential for reverse LA remodeling and it seems that it is associated with a relative risk of HF related events. The purpose and the results are valuable. The manuscript is nicely presented.

Response

We thank the reviewer for the positive comments, the careful assessment, and the valuable suggestion. Unfortunately, we did not collect the data on LA volume and indicated it in the Limitation.

Remarks:

- "271 patients who died during index hospitalization": this is huge, why is it so?

Response

We appreciate your comment. As your comment, In-hospital mortality of KCHF registry (6.7%, 271/4056) was not low because of advanced age of study population. However, the mortality rate is comparable to that of EHFS II (Nieminen MS, et al. Eur Heart J. 2006;27:2725-36.) and ATTEND registry (Sato N, et al. Circ J. 2013;77:944-51.) (6.7% and 6.4%, respectively), thus we think that the mortality rate is not especially high.

- A multivariable analysis of the factors associated with a decrease in LAD should be provided

Response

We thank for your valuable suggestion. We analyzed factors associated with reduction in LAD by using univariate and multivariate logistic regression models (Page 12, line 12-18). The following variables were significantly associated with reduction in LAD in univariate logistic regression analysis: age ≥80 years, LAD ≥40 mm, change in LVDd >0 mm, LVEF <40%, change in LVEF >0%, TRPG >31.4 mmHg and change in TRPG >0 mmHg (Supplementary Table 4). In multivariate logistic regression analysis, LAD ≥40 mm, TRPG >31.4 mmHg and change in TRPG >0 mmHg were significantly associated with the reduction in LAD (Supplementary Table 4) (Page 17, line 5-11).

- LA volume is recommended by Lang et (ASE/EACVI recommendation paper for chambers'quantification)
- E', E/E', E-deceleration time, Output…there are parameters that are missing in the present manuscript. GLS as well! (Cho et al JACC…)

Response

We fully agree on your comments. LA volume is recommended by the American Society of Echocardiography and the European Association of Cardiovascular Imaging. And LA volume is more useful for prediction of clinical outcomes of patients with heart failure than LAD. Change in LA volume may be a more sensitive marker than that in LAD. Lack of data on LA volume is our weak point. In addition, we did not analyze data on cardiac output, diastolic

function (E', E/E' and E-deceleration time) and GLS. These weak points are described in the section of Limitations (Page 21, line 12-15 and Page 22, line 2-8).

Reviewer: 2

Response

We thank the reviewer for the careful assessment and the valuable suggestion.

Comments to the Author
Major points
Study primary outcome: Why was a composite of 'all-cause death or HF hospitalization' selected instead of 'cardiovascular death or HF hospitalization' that is usually employed in heart failure studies? Use of the latter would have facilitated comparison of study outcome rates with those of other studies.

Response
We appreciate your comment and suggestion. In the protocol of KCHF study (Yamamoto E, et al. ESC Heart Fail. 2017;4:216-23.), we defined a composite of all-cause death or hospitalization for HF as the primary outcome measure because the differentiation between cardiac and non-cardiac deaths are sometimes difficult in the heart failure settings. We defined cardiovascular death as follows "Death was regarded as cardiovascular in origin unless obvious non-cardiovascular causes could be identified. Cardiovascular death included death related to HF, sudden death, death related to stroke, and death from other cardiovascular causes. Sudden death was an unexplained death in a previously stable patient." Now, we have added a composite of cardiovascular death or hospitalization for HF into the secondary outcome measures.

The cumulative 180-day incidence of a composite of cardiovascular death or hospitalization for HF were significantly lower in the reduction in LAD group than in the no-reduction in LAD group (11.8% versus 19.2%, P =0.007, Figure 2D). However, after adjusting for confounders, the lower risk of the reduction in LAD group relative to the no-reduction in LAD group for a composite of cardiovascular death or hospitalization for HF were no longer significant (HR: 0.73, 95% CI: 0.43-1.24, P =0.24) (Table 3) (Page 15, line 18-Page 16, line 8).

Selection bias: This bias is briefly mentioned in relation to missing data on medications (P20, L27) but the authors are advised to dwell more on the matter, not least the fact that a substantial n=1516 of KCHF study participants (n=4056) were considered ineligible for the follow-up mandated by the present protocol (P8, L13). One reason was apparently that patients were 'unable to visit a hospital due to patients' conditions' (Figure 1). On the other hand, patients included in the present study were old (mean age around 75 years) and yet did not appear to display excessive mortality rates, i.e. 23 of 1246 (1.8%] died between time of discharge from index hospitalization to 6 month echocardiography (Figure 1) and 4.6-8.6% in the ensuing 180 days (Table 3). The authors may further explain considerations that led to ineligibility of patients for the follow-up study, provide information about outcomes of these patients, and discuss the mortality of enrolled patients in the present study compared to other studies.

Response

We thank for your essential comment and suggestion. Many patients ineligible for the protocol mandated follow-up were excluded from KCHF registry participants (N=4,056). In short, many patients who were disabled and expected to have short life expectancy was excluded and patients in stable conditions may be included. Actually, the mortality during 6 months after index hospitalization (1.8%) (Figure 1) and in the ensuing 180-day after 6-month follow-up echocardiography (4.6-8.6%) (Table 3) were much lower than 180-day mortality of the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) and trial-eligible GWTG-HF (Get With The Guidelines–Heart Failure) cohorts (18.6% and 21.2%) (32). 180-day mortality of 1,516 patients ineligible for the protocol mandated follow-up (15.0%) (data not shown) was comparative to that of the previous trials. (Page 22, line 12-Page 23, line 4).

Minor points
P5, L6: That 'observing the change in LAD helps us modify the intensity of treatment..' was not examined in this study. The statement should be modified accordingly.

Response

We agree on your comment. We have modified the sentence (Page 5, line 3-4).

Unclear wordings on duration of follow-up: It is stated that 'clinical follow-up was performed at 1 year after enrollment and the data were censored at 210 after the 6-month echocardiography' (P7, L40), 'outcome measures were followed for 180 days from time zero [date of 6-month echocardiography'], and 'median (interquartile range) follow-up length was 302 (207-497) with a 96.3% follow-up rate at 180-day after 6 month echocardiography' (P14, L22). If outcome measures were followed for 180 days, it seems unclear why data were censored at 210 days (and not 180 days) after the 6-month echocardiography. Along this line, 'time zero' of follow-up, i.e. time of the 6-month echocardiography, is obfuscated by the statement about 'echocardiography at 6-months with allowance of 1-month' (P7, L33). The authors should clarify.

Response
We thank for your comments. We apologize to the reviewer for confusing expressions. We have changed expressions about baseline, follow-up echocardiography and clinical follow-up and highlighted changes in red characters in the revised manuscript. To understand the time course of this study at a glance, we have added Figure 1B. We designed a 6-month index visit and echocardiography with allowance of 1-month and clinical follow-up at 1 year after enrollment with 1-month allowance. Therefore, the data were censored at 210 days after the follow-up echocardiography at 6-month after index hospitalization (Page 9, line 8-12). Some cases were followed more longer, but we censored 210 days in the anlaysis; thus, we deleted the median value of follow-up.

L9, L30: Change 'enrolling patients were to have..' to 'enrolling patients who were to have..'.
P16, L43: Change 'cardiac function by echocardiography' to 'cardiac structure and function by echocardiography'.

Response
We appreciate your comments. We have modified the sentences (Page 7, line 9 and Page 18, line 15).

VERSION 2 – REVIEW

REVIEWER	Donal, Erwan CHU Rennes, Rennes, France
REVIEW RETURNED	21-Nov-2020

GENERAL COMMENTS	This is a rather large study. It pushes forward the look at LA size during the follow-up of patients diagnosed for heart failure. The authors did their best to provide answers to the previous round of review. The authors acknowledged the important limits of their analysis: no corelab, no respect of the recommendations (LA volume)… This is a really pity that the analyses are so "macro" and did not provide more about the determinants of LA size changes according to co-factors, treatments and clinical status. Getting more precise data on the initial echocardiography at least could have been nice: mitral regurgitation, shape of heart cavities, RV involvement in the heart failure, cause of the heart failure… Except these granularity that we're eager to get the manuscript is rather nice.

REVIEWER	Peter Riis Hansen Department of Cardiology Herlev and Gentofte Hospital DK-2900 Gentofte, Denmark
REVIEW RETURNED	22-Nov-2020

GENERAL COMMENTS	Study limitations: In response to the prior inquiry about the large number of patients (n=1516) excluded because 'they were unable to visit a hospital due to patient's conditions' (Figure 1), the authors have expanded on the subject of excluded patients, including that 'In short, many patients who were disabled and expected to have short life expectancy was excluded and patients in stable conditions may be included' (P22 L13-15) and they also found that the n=1516 had a considerably higher mortality than patients included in the present study. However, the n=1516 were not part of those excluded because of, e.g. end stage renal disease or severe comorbidity (Figure 1), and a 'stable condition' would arguably seem to apply for all patients discharged after an admission for ADHF (indeed, 'stable condition' was not mentioned among inclusion criteria cited in the text. These apparent uncertainties may question the external validity of the findings. Regarding time frames of echocardiography at 6 months and follow-up for 6 months hereafter, both are said to have had a '...one-month allowance...' (e.g. P7 L10) or '…allowance of 1-month…' (e.g. P9 L8-9). This wording appears incorrect and it seems unclear if respective assessments were made at 6 +/- one month or at 6-7 months. P4 L15: That 'The present study demonstrated the effect of the reduction in left atrial diameter (LAD) during 6 months on clinical outcomes…' seems misguided as it was an observational study that examined associations, not causal relationships. The sentence should be revised accordingly, e.g. to 'The present study

	demonstrated a link between reduction in left atrial diameter (LAD) and favorable outcomes after 6 months on clinical outcomes…'. P5 L3: The statement that 'Observing the change in LAD helps us to access conditions of patients with HF' is imprecise and may be deleted. P7 L9-10 etc.: The term 'index' has been introduced here ('…patients who were to have a 6-month index visit and echocardiography…') and elsewhere hereafter, likely to highlight that the 6-month visit and the attending echocardiography at that time represented the starting point for subsequent monitoring of patients prognosis in the ensuing 6 months. Indeed, an 'index' event is usually seen as the starting point of a subsequent observation period. However, elsewhere in the text, 'index' is also used for the ADHF hospitalization that was the admission point for entering the original KCHF study (P8 L8), i.e. 6 months before the 'index' 6-month echocardiography. Also, it is confusing that the 'index' hospital contact is both denoted as a 'visit' (e.g. P8 L4) and a 'hospitalization' (e.g. P12 L16; P22 L15-16), since this contact was likely (always?) an out-patient visit that was planned to take place 6 months after admission in the KCHF study that started out with a hospitalization for ADHF. The authors should refine their use of 'index' to make these matters crystal clear. P19 L15-16: The sentence 'After adjusting for these findings, improved congestive status was significantly associated with the reduction in LAD group' does not make sense as 'congestive status' was not directly assessed. P20 L15: I suggest to change 'prosperous' to 'favorable'.

VERSION 2 – AUTHOR RESPONSE

Response

We appreciate the careful evaluation and valuable comments. We have modified our manuscript and given additional explanation along the reviewer's comments.

Comments from the Editor:

The reviewer(s) have recommended revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript. Please note that we normally allow a maximum of two manuscript revisions. As such, we urge you to make all the necessary revisions at this stage in an effort to convince the reviewers that your work is suitable for publication in BMJ Open.

Response

We thank the editor for the second chance to revise our manuscript. We tried to consider better response in order to persuade the reviewers.

Reviewer: 1

Dr. Erwan Donal, Univ Hosp Rennes

Comments to the Author:

This is a rather large study. It pushes forward the look at LA size during the follow-up of patients diagnosed for heart failure.

The authors did their best to provide answers to the previous round of review.

The authors acknowledged the important limits of their analysis: no corelab, no respect of the recommendations (LA volume)…

This is a really pity that the analyses are so “macro” and did not provide more about the determinants of LA size changes according to co-factors, treatments and clinical status. Getting more precise data on the initial echocardiography at least could have been nice: mitral regurgitation, shape of heart cavities, RV involvement in the heart failure, cause of the heart failure…

Except these granularity that we’re eager to get the manuscript is rather nice.

Response

We thank the reviewer for the suggestion to improve this manuscript and positive comments.

Reviewer: 2

Response

We appreciate your reasonable assessment and suggestion.

Comments to the Author:

Study limitations: In response to the prior inquiry about the large number of patients (n=1516) excluded because ‘they were unable to visit a hospital due to patient’s conditions’ (Figure 1), the authors have expanded on the subject of excluded patients, including that ‘In short, many patients who were disabled and expected to have short life expectancy was excluded and patients in stable conditions may be included’ (P22 L13-15) and they also found that the n=1516 had a considerably higher mortality than patients included in the present study. However, the n=1516 were not part of those excluded because of, e.g. end stage renal disease or severe comorbidity (Figure 1), and a ‘stable condition’ would arguably seem to apply for all patients discharged after an admission for ADHF (indeed, ‘stable condition’ was not mentioned among inclusion criteria cited in the text. These apparent uncertainties may question the external validity of the findings.

Response

We thank the reviewer for this reasonable assessment. We are sorry and think that “In short, many patients who were disabled and expected to have short life expectancy was excluded and patients in stable conditions may be included.” is an irrelevant, unclear expression. The participating physicians judged that it was difficult for the patients to visit 19 participating hospitals and undergo laboratory tests and echocardiography at 6 +/- one month because of poor compliance with follow-up and HF management, cognitive dysfunction, frailty or functional disability and because they discharged to and were mainly followed by primary-level hospitals and clinics, nursing care facilities, and facilities offering long-term medical care or treatment unconnected with the participating hospitals or moved in a distant area. Dementia, frailty and functional disability are associated with clinical outcomes. Other matters may be associated with loss of opportunity for appropriate HF management/treatment.

The mortality during 6 months after index hospitalization (1.8%) and in the ensuing 180-day after 6-month follow-up echocardiography (4.6-8.6%) were much lower than that of patients ineligible for the protocol mandated follow-up and previous studies.

In the section of Limitation

It is possible that absent data can alter the study results (i.e. selection bias); many patients ineligible for the protocol mandated follow-up were excluded from KCHF registry participants (N=4,056). The participating physicians judged that it was difficult for the patients to visit 19 participating hospitals and undergo laboratory tests and echocardiography at 6 +/- one month because of poor compliance with follow-up and HF management, cognitive dysfunction, frailty or functional disability and because they discharged to and were mainly followed by primary-level hospitals and clinics, nursing care facilities, and facilities offering long-term medical care or treatment unconnected with the participating hospitals or moved in a distant area. The mortality during 6 months after index hospitalization (1.8%) (Figure 1) and in the ensuing 180-day after 6-month follow-up echocardiography (4.6-8.6%) (Table 3) were much lower than 180-day mortality of the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) and trial-eligible GWTG-HF (Get With The Guidelines–Heart Failure) cohorts (18.6% and 21.2%) (32). The 180-day mortality of 1,516 patients ineligible for the protocol mandated follow-up (15.0%) (data not shown) was comparative to that of the previous trials. (Page 22, line 9-Page 23, line 6).

Regarding time frames of echocardiography at 6 months and follow-up for 6 months hereafter, both are said to have had a '...one-month allowance...' (e.g. P7 L10) or '…allowance of 1-month…' (e.g. P9 L8-9). This wording appears incorrect and it seems unclear if respective assessments were made at 6 +/- one month or at 6-7 months.

Response

We appreciate your comment and suggestion. We have changed from "with allowance of 1-month" to "6 +/- one month" according to your suggestion (Page 7, line 10 and Page 9, line 6).

P4 L15: That 'The present study demonstrated the effect of the reduction in left atrial diameter (LAD) during 6 months on clinical outcomes…' seems misguided as it was an observational study that examined associations, not causal relationships. The sentence should be revised accordingly, e.g. to 'The present study demonstrated a link between reduction in left atrial diameter (LAD) and favorable outcomes after 6 months on clinical outcomes…'.

Response

We thank the reviewer for the valuable suggestion. We have modified the statement (Page 4, line 15-18).

P5 L3: The statement that 'Observing the change in LAD helps us to access conditions of patients with HF' is imprecise and may be deleted.

Response

We agree on your recommendation. We have eliminated the statement.

P7 L9-10 etc.: The term 'index' has been introduced here ('…patients who were to have a 6-month index visit and echocardiography…') and elsewhere hereafter, likely to highlight that the 6-month visit and the attending echocardiography at that time represented the starting point for subsequent monitoring of patients prognosis in the ensuing 6 months. Indeed, an 'index' event is usually seen as the starting point of a subsequent observation period. However, elsewhere in the text, 'index' is also used for the ADHF hospitalization that was the admission point for entering the original KCHF study (P8 L8), i.e. 6 months before the 'index' 6-month echocardiography. Also, it is confusing that the 'index' hospital contact is both denoted as a 'visit' (e.g. P8 L4) and a 'hospitalization' (e.g. P12 L16; P22 L15-16), since this contact was likely (always?) an out-patient visit that was planned to take place

6 months after admission in the KCHF study that started out with a hospitalization for ADHF. The authors should refine their use of 'index' to make these matters crystal clear.

Response

We appreciate your comment. We have eliminated "index" from "index visit" in text, Table 2 and Figure 1B.

P19 L15-16: The sentence 'After adjusting for these findings, improved congestive status was significantly associated with the reduction in LAD group' does not make sense as 'congestive status' was not directly assessed.

Response

We agree on your assessment. We have eliminated the statement.

P20 L15: I suggest to change 'prosperous' to 'favorable'.

Response

We thank the reviewer for the suggestion. We have changed the word (Page 20, line 13).

VERSION 3 – REVIEW

REVIEWER	Donal, Erwan CHU Rennes, Rennes, France
REVIEW RETURNED	18-Jan-2021

GENERAL COMMENTS	this is interesting the answer to previsous comments are a bit disappointing and authors should underscore more clearly that diameter is not the right thing to measure in HF patients. They should have measure indexed LA volume and they should aknowledge that it is a strong limitation of their work correlation between changes and change in filling pressure could also be highlighted better

REVIEWER	Peter Riis Hansen Department of Cardiology Herlev and Gentofte Hospital DK-2900 Hellerup Denmark
REVIEW RETURNED	19-Jan-2021

GENERAL COMMENTS	The authors have responded to the new round of inquiries in a reasonable manner, not least by explaining that n=1516 KCHF registry patients were excluded from the present study because they were considered unable to undergo the mandated echocardiography at 6±1 month due to reasons spanning from cognitive dysfunction and frailty, to patients moving to distant areas. These patients had considerably higher mortality than individuals examined in the present study. This information has been added to the study limitations section (P22, L9-). Importantly, as also stated in the text (P7, L12-18) and in Figure 1 study flowchart, this large number of excluded patient come on top of patients excluded for non-consent (n=238), infection (n=297), acute coronary syndrome (n=157), renal failure (218), and severe comorbidity (n=112), death during the

	index admission (n=271), patients that in the period before the 6-month echocardiography either died (n=23), were lost (n=14) or were unavailable (n=461), and patients where the 6-month echocardiography did not allow for measurement of change in left atrial diameter (n=75). At the end of the day, the study population only comprised 673 patients of the 4056 patients enrolled in the KCHF registry or of the 1246 patients scheduled for a 6-month echocardiography. This very significant selection of patients remains a major limitation to the present study that questions the external validity of findings. Minor comments Quite a few imprecisions of wordings may be need to be fixed, e.g.: P3, L14: Change '..for HF after 6-month follow-up..' to '..for HF during 180 days after the 6-month follow-up..' P6, L6: Change '..deteriorate, finally leading..' to '..deteriorate, with HF finally leading..' P6, L7: Change '..there were.. to '..there are..' P6, L11: Change '..and death in general population' to '..and death in the general population' P7, L10: Change 'At a 6 month visit..' to 'At the 6-month visit..' P12, L12: Change '..variables consist on.. to '..variables consisted of…' P18, L16: Change '..the fundamental.. to '..a fundamental..' P18, L17: Change '..thus we can easily evaluate the changes of left atrial size' to '..thus changes of LAD can easily be evaluated' P19, L3: Change '..and no reduction groups..' to '..and no reduction in LAD groups..' P19, L15: Change '..a reduction in LAD, namely..' to '..a reduction in LAD suggestive of..' P20, L 7: Change '..similar in types of heart failures, the effect of reduction in LAD was.. to '..similar in different types of heart failure etiologies, improved outcome associated with reduction in LAD was.. P20, L13: Change '..favorable result..' to 'improved outcome..' P22, L7: That very advanced age of the study population 'might be a reason for us to obtain the detailed data including follow-up echocardiography..' doesn't really make sense. P22, L15: Change '..and because they discharged to..' to '..or because they were discharged to..' P22, L17: Change '..or moved in a distant area.' to '..or moved to a distant area, respectively' P23, L5: Change 'The 180-day mortality of 1,526 patients..' to 'Indeed, the 180-day mortality of the 1,526 patients..' P23, L6: Change 'comparative' to 'comparable'

VERSION 3 – AUTHOR RESPONSE

Reviewer: 1
Dr. Erwan Donal, Univ Hosp Rennes
Comments to the Author:
this is interesting
the answer to previous comments are a bit disappointing and authors should underscore more clearly that diameter is not the right thing to measure in HF patients. They should have measure indexed LA volume and they should aknowledge that it is a strong limitation of their work

Response
We appreciate your comment. We have given additional explanation and emphasized this limitation.

In the section of Limitations

LAD is not enough to measure left atrial size in HF patients. This is a strong limitation of the present study.

correlation between changes and change in filling pressure could also be highlighted better

Response
We appreciate your suggestion. We have given an additional sentence in the section of Discussion.

In the Discussion

In particular, LA size is closely linked to LV filling pressure, indicating the change in LA size would be correlated to the change in LV filling pressure (24-26).

Response
We thank the editor for detailed comments.

Reviewer: 2
Dr. Peter Hansen, University of Copenhagen
Comments to the Author:
The authors have responded to the new round of inquiries in a reasonable manner, not least by explaining that n=1516 KCHF registry patients were excluded from the present study because they were considered unable to undergo the mandated echocardiography at 6±1 month due to reasons spanning from cognitive dysfunction and frailty, to patients moving to distant areas. These patients had considerably higher mortality than individuals examined in the present study. This information has been added to the study limitations section (P22, L9-). Importantly, as also stated in the text (P7, L12-18) and in Figure 1 study flowchart, this large number of excluded patient come on top of patients excluded for non-consent (n=238), infection (n=297), acute coronary syndrome (n=157), renal failure (218), and severe comorbidity (n=112), death during the index admission (n=271), patients that in the period before the 6-month echocardiography either died (n=23), were lost (n=14) or were unavailable (n=461), and patients where the 6-month echocardiography did not allow for measurement of change in left atrial diameter (n=75). At the end of the day, the study population only comprised 673 patients of the 4056 patients enrolled in the KCHF registry or of the 1246 patients scheduled for a 6-month echocardiography. This very significant selection of patients remains a major limitation to the present study that questions the external validity of findings.

Response
We appreciate your valuable comments. We have changed the order of exclusion criteria in Figure 1 and added the description of many excluded patients at each stage and that this

selection remains a major limitation. We have emphasized it in the section of Strengths and Limitations.

See in Figure 1.

In the section of Strengths and Limitations

- ***The study results were derived from very selected patients from KCHF registry participants.***
- ***Further studies are needed to generalize our study results.***

In the section of Limitations

In addition, many other patients were excluded at each stage (See in Figure 1). This study population only comprised 673 patients of the 4056 patients enrolled in the KCHF registry or of the 1246 patients scheduled for a 6-month echocardiography. This very significant selection of patients remains a major limitation to the present study. Further studies are needed to generalize our study results.

Minor comments
Quite a few imprecisions of wordings may be need to be fixed, e.g.:
P3, L14: Change '..for HF after 6-month follow-up..' to '..for HF during 180 days after the 6-month follow-up..'
P6, L6: Change '..deteriorate, finally leading..' to '..deteriorate, with HF finally leading..'
P6, L7: Change '..there were.. to '..there are..'
P6, L11: Change '..and death in general population' to '..and death in the general population'
P7, L10: Change 'At a 6 month visit..' to 'At the 6-month visit..'
P12, L12: Change '..variables consist on.. to '..variables consisted of…'
P18, L16: Change '..the fundamental.. to '..a fundamental..'
P18, L17: Change '..thus we can easily evaluate the changes of left atrial size' to '..thus changes of LAD can easily be evaluated'
P19, L3: Change '..and no reduction groups..' to '..and no reduction in LAD groups..'
P19, L15: Change '..a reduction in LAD, namely..' to '..a reduction in LAD suggestive of..'
P20, L 7: Change '..similar in types of heart failures, the effect of reduction in LAD was.. to '..similar in different types of heart failure etiologies, improved outcome associated with reduction in LAD was..
P20, L13: Change '..favorable result..' to 'improved outcome..'
P22, L7: That very advanced age of the study population 'might be a reason for us to obtain the detailed data including follow-up echocardiography..' doesn't really make sense.
P22, L15: Change '..and because they discharged to..' to '..or because they were discharged to..'
P22, L17: Change '..or moved in a distant area.' to '..or moved to a distant area, respectively'
P23, L5: Change 'The 180-day mortality of 1,526 patients..' to 'Indeed, the 180-day mortality of the 1,526 patients..'
P23, L6: Change 'comparative' to 'comparable'

Response

We are sorry for imprecisions of wordings and wrong grammar and grateful for detailed comments. We have corrected words along with your comments.