PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Guideline-directed medical therapy in elderly patients with heart failure with reduced ejection fraction: a cohort study
AUTHORS	Seo, Won-Woo; Park, Jin Joo; Park, Hyun Ah; Cho, Hyun-Jai; Lee, Hae-Young; Kim, Kye Hun; Yoo, Byung-Su; Kang, Seok-Min; Baek, Sang Hong; Jeon, Eun-Seok; Kim, Jae-Joong; Cho, Myeong-Chan; Chae, Shung Chull; Oh, Byung-Hee; Choi, Dong-Ju

VERSION 1 – REVIEW

REVIEWER	Takehiro Sugiyama National Center for Global Health and Medicine, Japan
REVIEW RETURNED	01-Apr-2019

GENERAL COMMENTS	The author appreciates the authors for their work. The manuscript is overall well-written, well-organized, and concise. The reviewer's comment is as below: <Major points> 1. The reviewer agrees to the first limitation the authors described (possible confounding). The reviewer supposes that there can be a significant level of residual confounding from the controlled variables and confounding from the unmeasured variables. For example, CKD was adjusted as a binary variable. There can be a residual confounding; in this case, the authors may be able to examine the existence of confounding by summarizing the eGFR level among those who were categorized as CKD, by their treatment strategy. Including this example, the authors need to defend that these possible confounding is not so strong that it can change the observed significant association into insignificant one. Please evaluate the extent of confounding. 2. For the reason described in 1., the conclusion is too strong. 3. The reviewer understands that the novelty of this study was to show the efficacy of GDMT in very elderly patients with HFrEF. The author reviewed several similar articles, but it may not include a few important articles. Although the reviewer is not so familiar with this field, the reviewer found another article as below: Akita K, Kohno T, Kohsaka S, Shiraishi Y, Nagatomo Y, Izumi Y, Goda A, Mizuno A, Sawano M, Inohara T, Fukuda K, Yoshikawa T, West Tokyo Heart Failure Registry Investigators. Current use of guideline-based medical therapy in elderly patients admitted with acute heart failure with reduced ejection fraction and its impact on event-free survival. International journal of cardiology. 2017;235:162-168. Please add some important articles in the reference and reconstruct the discussion.

	4. The authors described that they tried to enroll all of the hospitalized patients with acute HF at each hospital to minimize selection bias. The reviewer would like to know how they made this effort and its result. What is the specific measure they took in order to enroll all the hospitalized patients? Among those who were eligible, what percentage of patients were included in the registry? <Minor points> 1. Page 8, Line 17: The eGFR was adjusted by body surface area/1.72m2? The reviewer thought that it should be 1.73. 2. Table 2: The reviewer supposes that the dependent variable in the model of Table 2 is a binary variable of GDMT vs. others (no GDMT, beta-blocker only, RAS inhibitor only). Is it correct? 3. Table 2: If possible, ORs and their 95% CIs may be converted into RRs because the prevalence is of GDMT was quite high. If not, please note that the ORs should not be taken as the approximation of RRs.

REVIEWER	Wouter Ouwerkerk National Heart Center Singapore, Singapore Amsterdam UMC, The Netherlands
REVIEW RETURNED	01-Apr-2019

GENERAL COMMENTS	In this manuscript the authors show a relation between guideline-directed medical treatment (GDMT) of beta-blockers (BB) and ACE-inhibitors (ACEi) and all cause mortality. They also show what patient characteristics play a role in getting GDMT or solely ACEi or BB or even nothing after hospital discharge. The manuscript is well written and the goal and results are clear. I do have some issues that need to be resolved. And some items that need to be clarified. The first question that immediately comes to mind when I read the introduction where the authors mention in the first paragraph that these patients are at high risk of re-hospitalization. What are the risks of re-hospitalization in the studied groups? If the risks are so high I expected that this would be studied as well in addition all-cause mortality. It is known that BB is especially beneficial to prevent mortality, but ACEis might be more important in preventing hospitalizations. I also had a question regarding the GDMT. Is GDMT considered given any dose of ACEi and BB? The dose given is a very important factor! If GDMT is the recommended dose according to the ESC-HF guidelines, and no GDMT is lower than that dose; then this should also be mentioned. There is a huge difference in dose-efficacy. Another major remark is estimating the effect of GDMT on outcome. Because this study is a cohort type study, you cannot directly estimate the GDMT on outcome. As is visible in table 1, the effect of GDMT could be attributed to other patient characteristics other than the treatment. E.g patients who do not get GDMT are older have more co-morbidities get less medication on initial hospital admission etc. In this type of analyses you have to correct for this treatment indication type of bias. There are

	multiple statistical methods well known that try to achieve this (e.g. by inverse probability weighting, or propensity score matching). I'm also very interested in the patients who were on BB at initial hospital admission but are not anymore at discharge, and the same for ACEi (table 1). What are the reasons to withhold BB/ACEi? And do these patient better/worse than the rest? Are the patients who are not on ACEi on MRAs? And what is the survival (and re-hospitalization) related to the other groups?

REVIEWER	George Divine Henry Ford Health System, United States
REVIEW RETURNED	22-Jun-2019

GENERAL COMMENTS	The description of the study and the results are generally clear and convincing. However, there several instances where improvement could be made. Page 7, line 58 The words "patient" and "provider" should be plural. Page 8, line 32 The word "numbers" is somewhat ambiguous. "counts" would work better. Page 8, line 41 The meaning of the term "post hoc" is not apparent. It should either be explained or omitted. Page 8, lines 53-55 A clearer, longer explanation is needed about what interactions were tested and how. Page 9, lines 46-50 The percentages presented would seem to pertain to Table 1, but they are not found directly in the table. This should be made clearer. Page 25 The Figure 1 removals between the registry and the analysis cohort are presented as if they all might be unique. If overlapping exclusions are present this should be acknowledged and the method used to handle this should be described. Since the analysis of observational data is intended to assess whether or not clinical trial results can be extended to older ages not studied in such trials, the authors might consider commenting upon why they have not used a causal inference method such as propensity analysis.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Takehiro Sugiyama

[Major comment #1]

The reviewer agrees to the first limitation the authors described (possible confounding). The reviewer supposes that there can be a significant level of residual confounding from the controlled variables and confounding from the unmeasured variables. For example, CKD was adjusted as a binary variable. There can be a residual confounding; in this case, the authors may be able to examine the

existence of confounding by summarizing the eGFR level among those who were categorized as CKD, by their treatment strategy. Including this example, the authors need to defend that these possible confounding is not so strong that it can change the observed significant association into insignificant one. Please evaluate the extent of confounding.

Response:

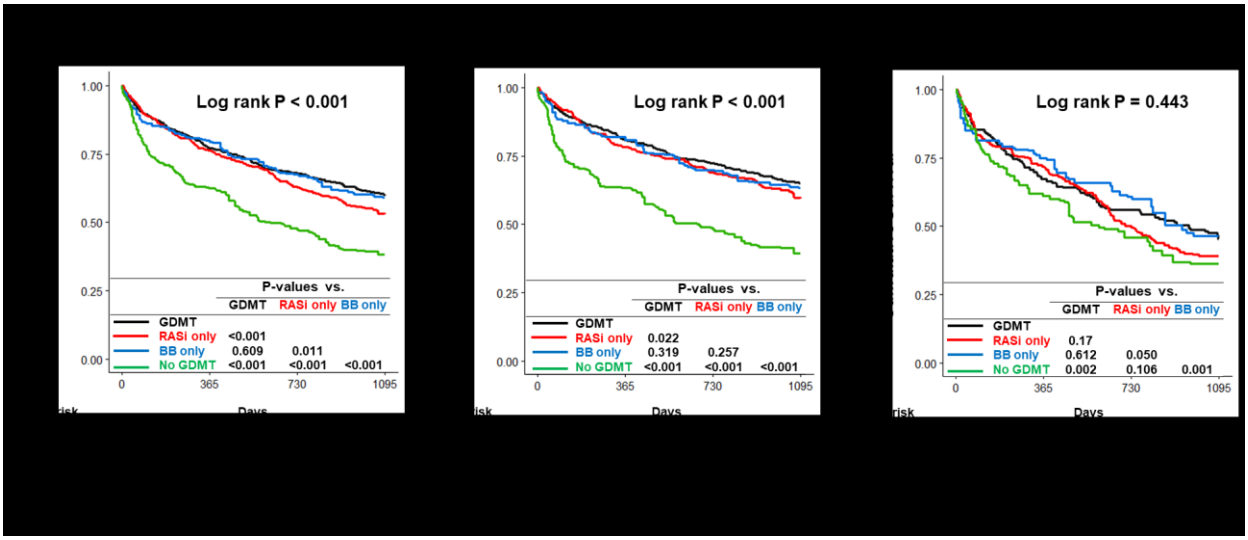
We agree with you that because this is not randomized clinical trials, the results may have been biased even after extensive adjustment for significant covariates. Therefore, we performed inverse-probability of treatment weight (IPTW) analysis. As shown below, the results were similar; patients with GDMT had the best prognosis, and those without no GDMT had the worst prognosis.

Online supplementary table 3. Patients characteristics in inverse probability treatment weight adjusted population

	GDMT (n=1813)	Beta blocker only (n=1298)	RAS inhibitor only (n=1709)	No GDMT (n=1132)	Std. Diff.	P value
Age, years	75.5 ± 6.7	75.6 ± 6.8	76.1 ± 7.0	76.7 ± 6.8	0.17	0.07
Men, n (%)	964 (53.2)	757 (58.3)	963 (56.3)	622 (54.9)	0.10	0.26
BMI, kg/m^2	22.7 ± 3.4	22.6 ± 3.5	22.4 ± 3.3	22.4 ± 3.2	0.08	0.34
Medical history						
Previous heart failure, n (%)	905 (49.9)	687 (52.9)	901 (52.8)	656 (58.0)	0.16	0.05
Hypertension, n (%)	1233 (68.0)	870 (67.0)	1108 (64.9)	732 (64.6)	0.07	0.24
Diabetes, n (%)	774 (42.7)	481 (37.0)	650 (38.0)	472 (41.7)	0.11	0.09
Chronic kidney disease, n (%)	933 (51.5)	769 (59.2)	877 (51.3)	674 (59.6)	0.16	0.05
Atrial fibrillation, n (%)	566 (31.2)	448 (34.5)	515 (30.2)	380 (33.6)	0.09	0.32
COPD, n (%)	211 (11.6)	168 (12.9)	247 (14.5)	162 (14.3)	0.08	0.12
Myocardial infarction, n (%)	395 (21.8)	330 (25.4)	384 (22.5)	292 (25.8)	0.10	0.34
Cause of heart failure						
Ischemic, n (%)	920 (50.8)	752 (57.9)	837 (49.0)	615 (54.4)	0.18	0.06
Dilated, n (%)	434 (23.9)	250 (19.2)	387 (22.6)	213 (18.8)	0.12	0.15
Medication on admission						
Beta-blocker, n (%)	561 (31.0)	442 (34.0)	439 (25.7)	259 (22.9)	0.24	0.03

RAS inhibitor, n (%)	727 (40.1)	459 (35.4)	762 (44.6)	409 (36.2)	0.19	0.06
MRA, n (%)	301 (16.6)	277 (21.3)	296 (17.3)	224 (19.8)	0.12	0.15
Medication on discharge						
MRA, n (%)	936 (51.6)	643 (49.6)	839 (49.1)	486 (42.9)	0.17	0.03
Loop diuretics, n (%)	1427 (78.7)	977 (75.2)	1305 (76.4)	794 (70.2)	0.21	0.01
Digoxin, n (%)	547 (30.2)	358 (27.6)	488 (28.5)	361 (31.9)	0.09	0.39
Systolic BP on discharge, mm Hg	114.7 ± 16.8	113.8 ± 16.8	115.0 ± 16.5	112.5 ± 15.4	0.15	0.39
Diastolic BP on discharge, mm Hg	66.1 ± 10.8	66.1 ± 10.1	66.1 ± 10.9	65.0 ± 9.9	0.10	0.20
Heart rate on discharge, beats/min	76.3 ± 13.6	77.8 ± 12.3	77.2 ± 14.2	77.4 ± 13.5	0.10	0.21
NYHA functional class on discharge					0.10	0.23
I or II, n (%)	1598 (88.1)	1148 (88.4)	1496 (87.5)	1028 (90.8)		
III or IV, n (%)	215 (11.9)	150 (11.6)	213 (12.5)	105 (9.2)		
Echocardiographic parameters						
LVEDD, mm	60.2 ± 8.8	59.6 ± 8.7	60.3 ± 8.7	59.3 ± 8.7	0.11	0.40
LVESD, mm	50.3 ± 9.3	49.9 ± 9.3	50.0 ± 9.5	49.4 ± 9.5	0.09	0.26
LVEF, %	28.7 ± 7.3	28.2 ± 7.7	28.9 ± 7.3	29.0 ± 7.2	0.11	0.57
Laboratory data on admission						
Hemoglobin, g/dL	12.3 ± 2.0	12.3 ± 1.9	12.3 ± 2.1	12.1 ± 2.1	0.08	0.49
eGFR, ml/min/1.73m^2	61.6 ± 32.6	58.6 ± 30.1	62.3 ± 30.1	56.5 ± 28.1	0.18	0.07

Sodium, mEq/L	137.8 ± 4.5	138.0 ± 4.2	137.6 ± 4.5	137.4 ± 4.5	0.11	0.78
Potassium, mEq/L	4.4 ± 0.7	4.4 ± 0.7	4.4 ± 0.7	4.5 ± 0.7	0.14	0.46
BNP, pg/mL	1692.2 ± 1528.3	1703.7 ± 1403.4	1731.0 ± 1389.8	1732.8 ± 1858.4	0.03	0.81
NT-pro-BNP, pg/mL	11650.7 ± 11236.4	10810.0 ± 10121.4	10549.1 ± 10321.2	12307.0 ± 10979.5	0.16	0.10



We added the results of IPTW analysis as supplementary table3 and supplementary figure 2. We thank you very much for your kind comment.

Before revision

All statistical analyses were performed using SPSS 24.0 for Windows (IBM Corp., Armonk, NY, USA), and a P value of <0.05 was considered statistically significant.

After revision (page 8 - 9)

To mitigate the impact of potential confounding factors in a registry data, we additional performed the inverse probability of treatment weighting (IPTW). The inferences regarding the rate of all-cause death were conducted with robust standard errors after examining covariate balances among the treatment groups. We used the “Twang” package for R programming for IPTW analysis. Success of IPTW analyses was assessed by calculating standardized differences in the baseline characteristics. All statistical analyses were performed using SPSS 24.0 for Windows (IBM Corp., Armonk, NY, USA) and R v3.1.0 (The R Foundation for Statistical Computing, Vienna, Austria), and a P value of <0.05 was considered statistically significant.

Before revision

blockers only and RAS inhibitors only groups (**figure 3**). Upon further stratification of the patients according to age above or below 80 years, the GDMT group had the lowest mortality in patients aged above and below 80 years, consistently. In the Cox model after adjustment for significant covariates,

After revision (page 15)

blockers only and RAS inhibitors only groups (**figure 3**). Upon further stratification of the patients according to age above or below 80 years, the GDMT group had the lowest mortality in patients aged above and below 80 years, consistently. In IPTW adjusted population patients in the GDMT group had lower mortality than those in the no GDMT group among the overall patients, patients aged between 65-69 years, and the patients aged 80 years or older (**online supplementary table 3, online supplementary figure 2**). In the Cox model after adjustment for significant covariates,

[Major comment #2]

For the reason described in 1., the conclusion is too strong.

Response:

We thank you for this constructive comment. We understand you concern that because of the nature of study design the conclusion may be too strong. We were also aware of this when we first wrote our draft and tried to tone the conclusion as much as possible. But as shown in the additional analysis including IPTW analysis, the results were the same, so that we may preserve the current conclusions. If you believe that the conclusions should be toned down more, please let us know.

[Major comment #3]

The reviewer understands that the novelty of this study was to show the efficacy of GDMT in very elderly patients with HFrEF. The author reviewed several similar articles, but it may not include a few important articles. Although the reviewer is not so familiar with this field, the reviewer found another article as below:

Akita K, Kohno T, Kohsaka S, Shiraishi Y, Nagatomo Y, Izumi Y, Goda A, Mizuno A, Sawano M, Inohara T, Fukuda K, Yoshikawa T, West Tokyo Heart Failure Registry Investigators. Current use of guideline-based medical therapy in elderly patients admitted with acute heart failure with reduced ejection fraction and its impact on event-free survival. International journal of cardiology.

2017;235:162-168.
Please add some important articles in the reference and reconstruct the discussion.

Response:

We thank you for your meticulous review. We read the important literature you recommended and included in the discussion section. However, we omitted the appropriate citation by mistake. We apologize for the inattentiveness and in the revised manuscript we included the appropriate reference.

After revision (page 17)

Recently, in a subgroup of 237 elderly patients aged ≥80 years in the WET-HF registry, GDMT with beta-blockers and RAS inhibitors did not reduce rates of cardiac death or HF readmission[22]. By contrast, the present study showed that GDMT was associated with all-cause mortality in elderly HFrEF patients, defined by age ≥65 years.

22 Akita K, Kohno T, Kohsaka S, et al. Current use of guideline-based medical therapy in elderly patients admitted with acute heart failure with reduced ejection fraction and its impact on event-free survival. *Int J Cardiol* 2017;**235**:162-8.

[Major comment #4]
The authors described that they tried to enroll all of the hospitalized patients with acute HF at each hospital to minimize selection bias. The reviewer would like to know how they made this effort and its result. What is the specific measure they took in order to enroll all the hospitalized patients? Among those who were eligible, what percentage of patients were included in the registry?

Response:

The KorAHF registry was a prospective multicenter cohort study and it was supported by Korea Centers for Disease Control and Prevention. Ten high-volume tertiary (university affiliated) hospitals participated in this study. Per protocol *all* patients who met the inclusion criteria were consecutively enrolled. These were patients who had signs or symptoms of HF and one of the following criteria 1) lung congestion or 2) objective finding of LV systolic dysfunction or structural heart disease, and there were no exclusion criteria. It was indeed an all-comer HF registry.

In addition, investigators of each participating center were encouraged to enroll all patients through regular investigator-meetings or e-mail correspondences. However, we do not know how many of all eligible patients have been enrolled. We fully understand the concern of the reviewer that this could be a limitation which we now acknowledge in the revised manuscript.

Before revision (page 19)

have influenced the results. Second, the registry could not capture all comorbidities including functional or cognitive impairment, an important prognostic factor for elderly patients.[27] Finally, we do not know whether the patients actually took the prescribed drugs

After revision

have influenced the results. Second, the registry could not capture all comorbidities including functional or cognitive impairment, an important prognostic factor for elderly patients.[27] Third, although the KorAHF registry was designed to enroll all hospitalized HF patients, there exists possibility that some of the patients may not have been enrolled. Fourth, we did not consider dose when defining the GDMT. Although there exists controversy on the relationship between drug dose and outcomes, it should also be investigated in elderly patients.[28] Finally, we do not know whether the patients actually took the prescribed drugs

[Minor comment #1]

Page 8, Line 17: The eGFR was adjusted by body surface area/1.72m2? The reviewer thought that it should be 1.73.

Response: We changed it according to your instruction.

[Minor comment #2]

Table 2: The reviewer supposes that the dependent variable in the model of Table 2 is a binary variable of GDMT vs. others (no GDMT, beta-blocker only, RAS inhibitor only). Is it correct?

Response: It is correct. The dependent variable was GDMT vs. others. To be more precise, we revised the manuscript as follows:

After revision (page 13)

The predictors of GDMT prescription compared to the other groups included age 65-79 years, hypertension, diabetes, de-novo onset of heart failure, and concomitant MRA prescription (**table 2**).

After revision (page 14)

Table 2. Predictor of prescription of guideline-directed medical therapy compared to the other groups

[Minor comment #3]

Table 2: If possible, ORs and their 95% CIs may be converted into RRs because the prevalence is of GDMT was quite high. If not, please note that the ORs should not be taken as the approximation of RRs.

Response: We agree with you. We hope that the readers will be aware of that because of the high prevalence of GDMT, the ORs should not be taken as the approximation of RRs. We thank you for this comment.

Reviewer: 2
Reviewer Name: Wouter Ouwerkerk

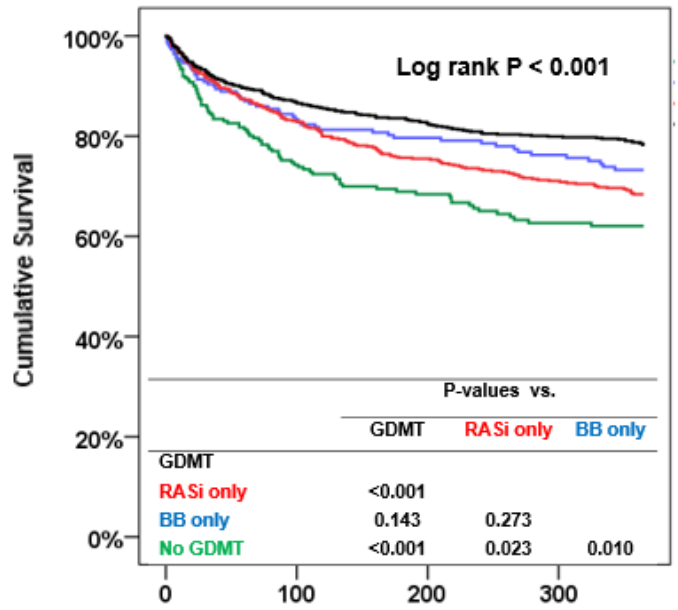
[Comment #1]
The first question that immediately comes to mind when I read the introduction where the authors mention in the first paragraph that these patients are at high risk of re-hospitalization. What are the risks of re-hospitalization in the studied groups? If the risks are so high I expected that this would be studied as well in addition all-cause mortality. It is known that BB is especially beneficial to prevent mortality, but ACEis might be more important in preventing hospitalizations.

Response:

We appreciated the careful review and this insightful comment. We also agree that hospitalization for HF (HHF) is an important outcome in HF study. The KorAHF registry also gathered information on HHF. However, unfortunately HHF events until 1 year after index admission have been adjudicated, so that we do not have 3-year HHF data. Regarding 1-year HHF, the GDMT group had the lowest and those in the no GDMT group had the highest HHF rate which is similar to 3-year all-cause mortality. Regarding the effect of beta-blockers and RAS-inhibitors, patients with beta-blockers seem to benefit more than those with RAS-inhibitors in terms of HHF.

Because we do not have 3-year HHF data, we would like to withhold to present the HHF outcomes, unless you insist to show these results. We thank you again for this sophisticated comment.

Kaplan-Meier analysis for re-hospitalization of heart failure during 1-year follow-up



No at risk				
GDMT	892	683	616	561
RASi only	642	460	396	355
BB only	228	160	143	130
No GDMT	283	162	127	102

[Comment #2]

I also had a question regarding the GDMT. Is GDMT considered given any dose of ACEi and BB? The dose given is a very important factor! If GDMT is the recommended dose according to the ESC-HF guidelines, and no GDMT is lower than that dose; then this should also be mentioned. There is a huge difference in dose-efficacy.

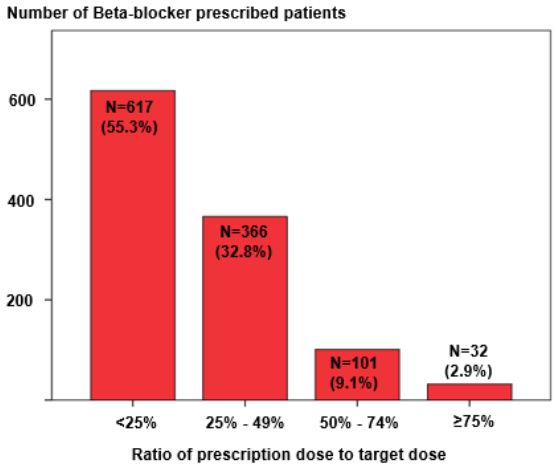
Response:

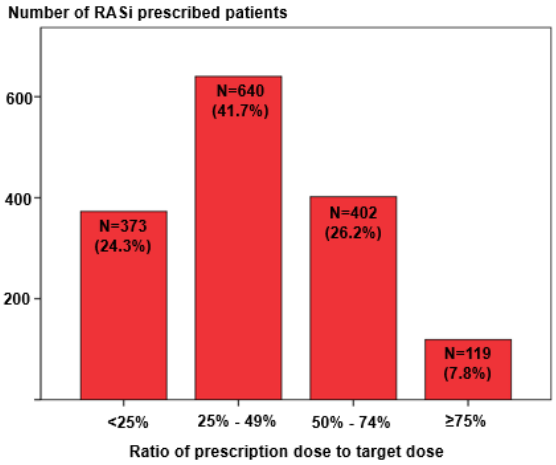
We thank you for this sophisticated comment. We agree with that the dose is important. However, in this study we did not take the dose of each drug into account, and GDMT was defined as the use of drug regardless of prescribed dose. Because it was not a randomized controlled study most patients did not receive the target dose of each drug.

Guidelines also recommend that GDMT should be started with a low dose and titrated to a maximal tolerating dose during follow-up. However, it is difficult to achieve and maintain the target dose due to adverse effects, and a recent RCT study showed that most patients achieved 50% of beta-blockers target dose and 50% of RAS inhibitor target dose during 1-year follow-up [JAMA 2017;318:713-720]. In addition, there exists controversy regarding the dose-effect relationship

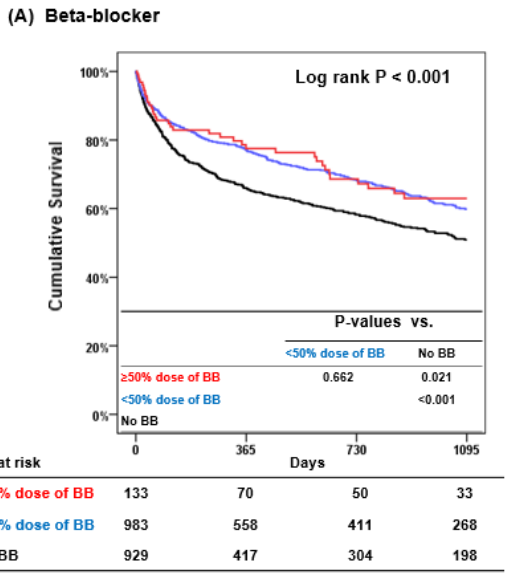
between beta-blockers, RAS inhibitor and outcomes [Eur J Heart Fail 2012; PLoS ONE 14(2): e0212907].

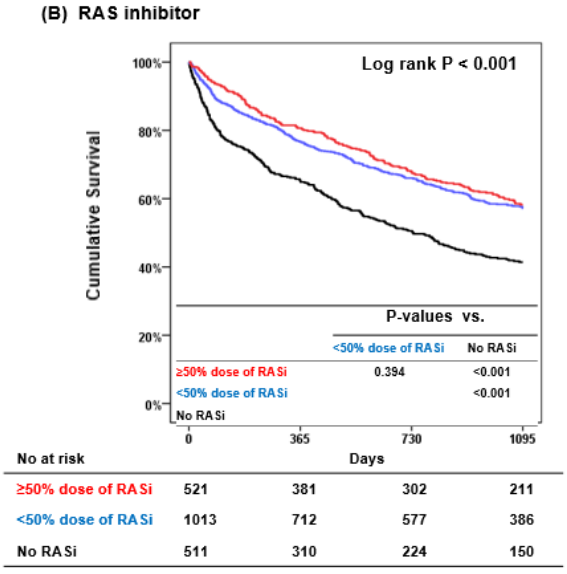
In this study with elderly patients with HFrEF, 55% and 33% received <25% and 25-49% beta-blocker target dose, respectively; whereas 24% and 42% received <25% and 25-49% RAS-inhibitor target dose, respectively, as shown below.





Regarding the survival, there was no difference between patients above and below the 50% beta-blocker target dose. Similar finding was observed for RAS-inhibitor dose.





Because the outcome according to dose is a very important issue, we are currently preparing a separate manuscript on the dose-outcome relationship in elderly HFrEF patients, which we hope to present in the near future. Therefore, in the current manuscript we would like to note the necessity of clinical studies on dose-outcome relationship in the elderly HF patients. We thank you very much for this constructive comment.

Before revision

have influenced the results. Second, the registry could not capture all comorbidities including functional or cognitive impairment, an important prognostic factor for elderly patients.[27] Finally, we do not know whether the patients actually took the prescribed drugs

After revision (page 19)

have influenced the results. Second, the registry could not capture all comorbidities including functional or cognitive impairment, an important prognostic factor for elderly patients.[27] Third, although the KorAHF registry was designed to enroll all hospitalized HF patients, there exists possibility that some of the patients may not have been enrolled. Fourth, we did not consider dose when defining the GDMT. Although there exists controversy on the relationship between drug dose and outcomes, it should also be investigated in elderly patients.[28] Finally, we do not know whether the patients actually took the prescribed drugs

After revision [Reference]

28 Turgeon RD, Kolber MR, Loewen P, et al. Higher versus lower doses of ACE inhibitors, angiotensin-2 receptor blockers and beta-blockers in heart failure with reduced ejection fraction: Systematic review and meta-analysis. *PLoS One* 2019;**14**:e0212907.

[Comment #3]

Another major remark is estimating the effect of GDMT on outcome. Because this study is a cohort type study, you cannot directly estimate the GDMT on outcome. As is visible in table 1, the effect of GDMT could be attributed to other patient characteristics other than the treatment. E.g patients who do not get GDMT are older have more co-morbidities get less medication on initial hospital admission etc. In this type of analyses you have to correct for this treatment indication type of bias. There are multiple statistical methods well known that try to achieve this (e.g. by inverse probability weighting, or propensity score matching).

Response:

We thank you very much for this sophisticated comment. Similar concern was raised by reviewer #1. We agree with you that due to differences in baseline characteristics of the population, Cox proportional hazard regression analysis may not suffice. Thus, we performed IPTW. In IPTW analysis, the results were similar. We added the results of IPTW analysis as supplementary table 3 and supplementary figure 2. We thank you very much for your kind comment.

Online supplementary table 3. Patients characteristics in inverse probability treatment weight adjusted population

	GDMT (n=1813)	Beta blocker only (n=1298)	RAS inhibitor only (n=1709)	No GDMT (n=1132)	Std. Diff.	P value
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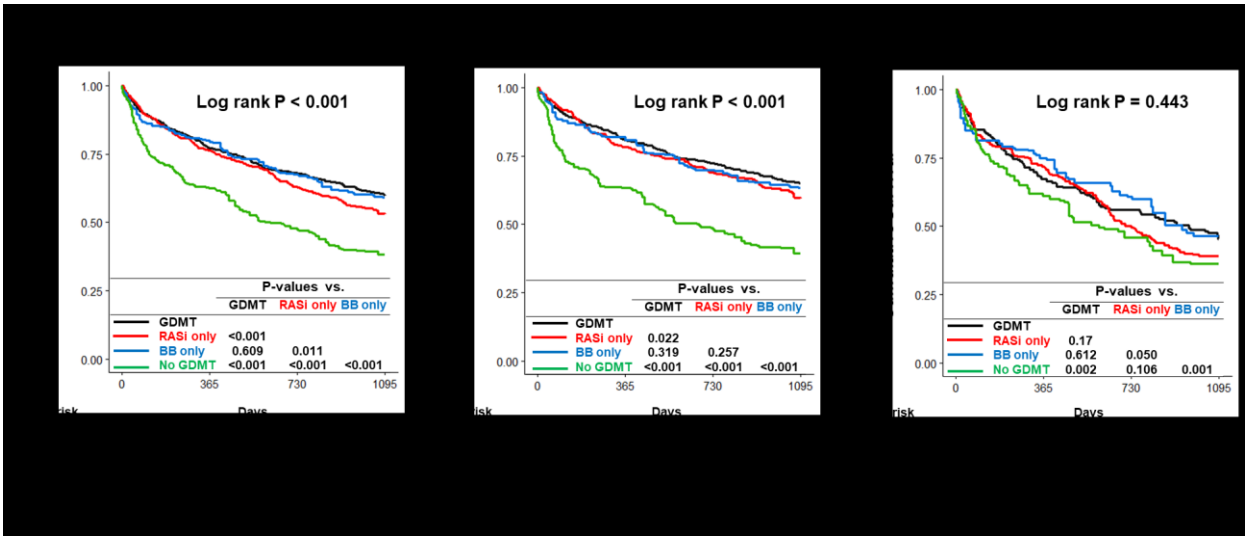
MRA, n (%)	301 (16.6)	277 (21.3)	296 (17.3)	224 (19.8)	0.12	0.15
Medication on discharge						
MRA, n (%)	936 (51.6)	643 (49.6)	839 (49.1)	486 (42.9)	0.17	0.03
Loop diuretics, n (%)	1427 (78.7)	977 (75.2)	1305 (76.4)	794 (70.2)	0.21	0.01
Digoxin, n (%)	547 (30.2)	358 (27.6)	488 (28.5)	361 (31.9)	0.09	0.39
Systolic BP on discharge, mm Hg	114.7 ± 16.8	113.8 ± 16.8	115.0 ± 16.5	112.5 ± 15.4	0.15	0.39
Diastolic BP on discharge, mm Hg	66.1 ± 10.8	66.1 ± 10.1	66.1 ± 10.9	65.0 ± 9.9	0.10	0.20
Heart rate on discharge, beats/min	76.3 ± 13.6	77.8 ± 12.3	77.2 ± 14.2	77.4 ± 13.5	0.10	0.21
NYHA functional class on discharge					0.10	0.23
I or II, n (%)	1598 (88.1)	1148 (88.4)	1496 (87.5)	1028 (90.8)		
III or IV, n (%)	215 (11.9)	150 (11.6)	213 (12.5)	105 (9.2)		
Echocardiographic parameters						
LVEDD, mm	60.2 ± 8.8	59.6 ± 8.7	60.3 ± 8.7	59.3 ± 8.7	0.11	0.40
LVESD, mm	50.3 ± 9.3	49.9 ± 9.3	50.0 ± 9.5	49.4 ± 9.5	0.09	0.26
LVEF, %	28.7 ± 7.3	28.2 ± 7.7	28.9 ± 7.3	29.0 ± 7.2	0.11	0.57
Laboratory data on admission						
Hemoglobin, g/dL	12.3 ± 2.0	12.3 ± 1.9	12.3 ± 2.1	12.1 ± 2.1	0.08	0.49
eGFR, ml/min/1.73m^2	61.6 ± 32.6	58.6 ± 30.1	62.3 ± 30.1	56.5 ± 28.1	0.18	0.07

Sodium, mEq/L	137.8 ± 4.5	138.0 ± 4.2	137.6 ± 4.5	137.4 ± 4.5	0.11	0.78
Potassium, mEq/L	4.4 ± 0.7	4.4 ± 0.7	4.4 ± 0.7	4.5 ± 0.7	0.14	0.46
BNP, pg/mL	1692.2 ± 1528.3	1703.7 ± 1403.4	1731.0 ± 1389.8	1732.8 ± 1858.4	0.03	0.81
NT-pro-BNP, pg/mL	11650.7 ± 11236.4	10810.0 ± 10121.4	10549.1 ± 10321.2	12307.0 ± 10979.5	0.16	0.10



Before revision

All statistical analyses were performed using SPSS 24.0 for Windows (IBM Corp., Armonk, NY, USA), and a P value of <0.05 was considered statistically significant.

After revision (page 8 – 9)

To mitigate the impact of potential confounding factors in a registry data, we additional performed the inverse probability of treatment weighting (IPTW). The inferences regarding the rate of all-cause death were conducted with robust standard errors after examining covariate balances among the treatment groups. We used the “Twang” package for R programming for IPTW analysis. Success of IPTW analyses was assessed by calculating standardized differences in the baseline characteristics.

All statistical analyses were performed using SPSS 24.0 for Windows (IBM Corp., Armonk, NY, USA) and R v3.1.0 (The R Foundation for Statistical Computing, Vienna, Austria), and a P value of <0.05 was considered statistically significant.

Before revision blockers only and RAS inhibitors only groups (**figure 3**). Upon further stratification of the patients according to age above or below 80 years, the GDMT group had the lowest mortality in patients aged above and below 80 years, consistently. In the Cox model after adjustment for significant covariates,
After revision (page 15) blockers only and RAS inhibitors only groups (**figure 3**). Upon further stratification of the patients according to age above or below 80 years, the GDMT group had the lowest mortality in patients aged above and below 80 years, consistently. In IPTW adjusted population patients in the GDMT group had lower mortality than those in the no GDMT group among the overall patients, patients aged between 65-69 years, and the patients aged 80 years or older (**online supplementary table 3, online supplemetary figure 2**). In the Cox model after adjustment for significant covariates,

VERSION 2 – REVIEW

REVIEWER	Takehiro Sugiyama National Center for Global Health and Medicine, Japan
REVIEW RETURNED	01-Aug-2019

GENERAL COMMENTS	Thank you very much for responding to the reviewer's comment. Although the authors added the IPTW analysis, the IPTW method is able to produce comparable groups only when the variables included in the model are sufficiently categorized and the model for the IPTW calculation is appropriate. The reviewer doubts that the categorization is sufficient. Unless the author defends that the model is sufficiently appropriate, the reviewer recommends that the authors should mention the possibility of residual confounding and that the authors should weaken the tone of conclusions. In the minor comment #3, although the authors agree with the reviewer, the authors did not take action. Please convert the ORs into RRs or the authors should mention it in the limitation section.

REVIEWER	George Divine Henry Ford Health System
REVIEW RETURNED	13-Aug-2019

GENERAL COMMENTS	The authors have made numerous very good improvements to the paper in response to the first review. However, some issues remain. On page 49, lines 56-58 and page 50, lines 4-14 the new text describing the analysis for interaction is confusing and it does not match Figure 4 as clearly as it might. For instance, I suspect (but

	am not certain) that a more accurate description of the interaction analysis might say something like: "We evaluated whether there was an interaction between GDMT treatment [GDMT vs all other treatment groups (beta-blockers only, RAS inhibitors only and no GDMT combined)] and each subgroup on survival. For calculation of interaction p-values, Cox regression models were used, which included the indicator variables for: GDMT, the subgrouping variable of interest (age, CKD, COPD, HF etiology or HF onset), GDMT, and GDMT-by-subgroup interaction, as independent variables. The following covariates were also included in the interaction models: sex, hypertension, diabetes, atrial fibrillation, and prescription of MRA, digitalis and diuretics. Separate estimates of the GDMT hazard ratios in each subgroup category were computed, along with their 95% confidence intervals and plotted in a figure for comparison." Relatedly, figure 4, which shows the interaction testing results, should have a much more detailed legend that tells the reader what the quantities shown represent, and mentioning the covariates, etc. On page 54, lines 48-50 and page 44, lines 4-6, the revised wording “compared to other groups” is still a bit unclear. Better might be something like “compared to any of the other three treatment groups”.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Takehiro Sugiyama

[Comment #1]

Thank you very much for responding to the reviewer's comment. Although the authors added the IPTW analysis, the IPTW method is able to produce comparable groups only when the variables included in the model are sufficiently categorized and the model for the IPTW calculation is appropriate. The reviewer doubts that the categorization is sufficient. Unless the author defends that the model is sufficiently appropriate, the reviewer recommends that the authors should mention the possibility of residual confounding and that the authors should weaken the tone of conclusions.

Response:

We thank you very much for this sophisticated and highly valuable comment. We agree with you that some of the variables could not be sufficiently categorized. For example, number of previous heart failure admission, the severity of coronary artery disease of patients with ischemic cardiomyopathy and others may have affected the results. In addition, we could not gather the information on the

functional or cognitive capacity which are important prognostic factors for the elderly patients. As the reviewer suggested, we have revised the limitation section; we mentioned the possibility of residual confounding and toned down the conclusions.

Before revision

First, owing to the observational nature of the study design, confounding factors may have influenced the study results, despite adjustment for significant covariates. Furthermore, there exists a possibility that unmeasured variables may have influenced the results. Second, the registry could not capture all comorbidities including functional or cognitive impairment, an important prognostic factor for elderly patients.[27] Third, although the KorAHF registry was designed to enroll all hospitalized HF patients, there exists the possibility that some of the patients may not have been enrolled

After revision (page 19)

First, owing to the observational nature of the study design, confounding factors may have influenced the study results, despite adjustment for significant covariates. Furthermore, there exists a possibility that unmeasured variables may have influenced the results. Second, the registry could not capture all comorbidities including functional or cognitive impairments, which are an important prognostic factor for elderly patients.[28] Third, we performed the IPTW analysis to mitigate the impact of compounding factors but there exists the possibility that variables included in the IPTW analysis had not been sufficiently categorized for producing balanced groups. Fourth, although the KorAHF registry was designed to enroll all hospitalized HF patients, there exists the possibility that some of the

Before revision

Heart failure is common among the elderly, but elderly patients with HF receive less GDMT. Since elderly and very elderly patients with HFrEF appear to benefit from GDMT, physicians should make an effort to prescribe GDMT to these high-risk patients.

After revision (page 20)

Heart failure is common among the elderly, but elderly patients with HF receive less GDMT. The present study suggests that GDMT may be effective in elderly and very elderly patients with HFrEF and physicians should make an effort to prescribe GDMT to these high-risk patients.

[Comment #2]

In the minor comment #3, although the authors agree with the reviewer, the authors did not take action. Please convert the ORs into RRs or the authors should mention it in the limitation section.

Response:

We apologize that we did not adequately address the reviewer's comment in the previous revision. According to reviewer's instruction, we have converted the ORs into RRs in the revised manuscript. We revised the statistical analysis section in the method section and modified Table 2 as follows.

Before revision

Logistic regression analysis was used to determine the predictors of GDMT prescription. The cumulative event rate was assessed using the Kaplan-Meier method with

After revision (page 8)

Logistic regression analysis was used to determine the predictors of GDMT prescription. We converted the odds ratios from logistic regression analysis into relative risks because of the high prevalence of GDMT.[17] The cumulative event rate was assessed using the Kaplan-Meier method with

17 Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998;280:1690-1.

Before revision

Table 2. Predictor of prescription of guideline-directed medical therapy compared to other groups

Variable	Odds ratio	95% CI	P value
Age 65-79 (vs. age ≥80 years)	1.52	1.24 – 1.87	<0.001
Male	0.90	0.75 – 1.08	0.240
Hypertension	1.24	1.01 – 1.51	0.036
Diabetes	1.27	1.05 – 1.54	0.014
De novo heart failure (vs. previous heart failure)	1.55	1.29 – 1.86	<0.001
Atrial fibrillation	1.01	0.82 – 1.25	0.911
Chronic kidney disease	0.76	0.63 – 0.92	0.004
Ischemic CMP (vs. non-ischemic)	0.94	0.78 – 1.14	0.546
COPD	0.67	0.50 – 0.88	0.004
Discharge MRA	1.30	1.08 – 1.56	0.007
Discharge digoxin	0.95	0.77 – 1.18	0.634
Discharge loop diuretics	0.76	0.61 – 0.96	0.018

CI, confidence interval; CMP, cardiomyopathy; COPD, chronic obstructive pulmonary disease;

MRA, mineralocorticoid receptor antagonist

After revision (page 14)

Table 2. Predictors of prescription of guideline-directed medical therapy compared to any of the other three treatment groups

Variable	Relative risk	95% CI	P value
Age 65-79 (vs. age ≥80 years)	1.28	1.14 – 1.43	<0.001
Male	0.94	0.85 – 1.04	0.240
Hypertension	1.13	1.01 – 1.25	0.036
Diabetes	1.14	1.03 – 1.26	0.014

De novo heart failure (vs. previous heart failure)	1.28	1.16 – 1.40	<0.001
Atrial fibrillation	1.01	0.89 – 1.13	0.911
Chronic kidney disease	0.86	0.77 – 0.96	0.004
Ischemic CMP (vs. non-ischemic)	0.97	0.86 – 1.07	0.546
COPD	0.79	0.65 – 0.93	0.004
Discharge MRA	1.16	1.05 – 1.28	0.007
Discharge digoxin	0.97	0.86 – 1.09	0.634
Discharge loop diuretics	0.84	0.72 – 0.98	0.018

CI, confidence interval; CMP, cardiomyopathy; COPD, chronic obstructive pulmonary disease; MRA, mineralocorticoid receptor antagonist

Reviewer: 3

Reviewer Name: George Divine

[Comment #1]

The authors have made numerous very good improvements to the paper in response to the first review. However, some issues remain.

On page 49, lines 56-58 and page 50, lines 4-14 the new text describing the analysis for interaction is confusing and it does not match Figure 4 as clearly as it might. For instance, I suspect (but am not certain) that a more accurate description of the interaction analysis might say something like:

"We evaluated whether there was an interaction between GDMT treatment [GDMT vs all other treatment groups (beta-blockers only, RAS inhibitors only and no GDMT combined)] and each subgroup on survival. For calculation of interaction p-values, Cox regression models were used, which included the indicator variables for: GDMT, the subgrouping variable of interest (age, CKD, COPD, HF etiology or HF onset), GDMT, and GDMT-by-subgroup interaction, as independent variables. The following covariates were also included in the interaction models: sex, hypertension, diabetes, atrial fibrillation, and prescription of MRA, digitalis and diuretics. Separate estimates of the

GDMT hazard ratios in each subgroup category were computed, along with their 95% confidence intervals and plotted in a figure for comparison."

Relatedly, figure 4, which shows the interaction testing results, should have a much more detailed legend that tells the reader what the quantities shown represent, and mentioning the covariates, etc.

Response:

We thank you for this valuable comment and also apologize for the confusion. We produced hazard ratios of no GDMT vs any medical therapy (i.e. GDMT, beta-blockers only, RAS inhibitors only) from multivariable Cox regression analysis in various subgroups and **figure 4** demonstrated only hazard ratio of no GDMT vs GDMT among them. Accordingly, P for interaction indicates whether each subgroup interacts with the treatment strategy. According to review's instruction, we revised manuscript and reinforced legend of **figure 4**.

Before revision
Multivariable Cox regression analysis was used to evaluate the adjusted relative risk of the variables. Multivariable models including age, sex, hypertension, diabetes, previous heart failure history, atrial fibrillation, CKD, cause of heart failure, COPD, and prescription of RAS inhibitors, beta-blockers, mineralocorticoid receptor antagonists (MRA), digitalis, and diuretics were chosen according to their clinical relevance and based on the results of previous trials.[3, 11] We evaluated whether there was an interaction between the treatment groups (no GDMT, beta-blockers only, RAS inhibitors only and GDMT) and subgroups on outcomes. For calculation of P for interaction, we performed Cox regression model and included all variables for defining subgroups (age, CKD, COPD, HF etiology, HF onset), treatment group, and interaction term of each subgroup variables by treatment group as independent variables, in addition to the following covariates: sex, hypertension, diabetes, atrial fibrillation, and prescription of MRA, digitalis and diuretics.
After revision (page 8-9)
Multivariable Cox regression analysis was used to evaluate the adjusted relative risk of the variables. Multivariable models including age, sex, hypertension, diabetes, previous heart failure history, atrial fibrillation, CKD, cause of heart failure, COPD, treatment strategy (no GDMT, beta-blockers only, RAS inhibitors only and GDMT), and prescription of mineralocorticoid receptor antagonists (MRA), digitalis, and diuretics were chosen according to their clinical relevance and based on the results of previous trials.[3, 11] Furthermore, we performed a pre-specified subgroup

analysis including age, CKD, COPD, HF etiology, and HF onset, and produced forest plots of the hazard ratio of medical therapy (i.e. GDMT, beta-blockers only, RAS inhibitors only) compared with no GDMT. We evaluated whether there was an interaction between treatment strategy and the subgroups on all-cause mortality. For the calculation of P for interaction, Cox regression models were used which included the indicator variables for treatment strategy, subgrouping variables, and interaction term of the treatment strategy-by-subgrouping variable of interest (age, CKD, COPD, HF etiology or HF onset), as independent variables. The following covariates were also included in the interaction models: sex, hypertension, diabetes, atrial fibrillation, and prescription of MRA, digitalis and diuretics.

Before revision

Figure 4. Subgroup analysis.

There was no interaction between the effect of GDMT and diverse subgroups, and GDMT was associated with lower morality across subgroups.

After revision (page 26-27)

Figure 4. Subgroup analysis.

The hazard ratios (HRs) of medical therapy (i.e. GDMT, beta-blockers only, RAS inhibitors only) compared with no GDMT for all-cause mortality in subgroups were calculated using multivariate Cox regression analysis. The forest plots demonstrate the HRs of GDMT vs. no GDMT from the results. There was no significant interaction between the treatment strategy (no GDMT, beta-blockers only, RAS inhibitors only and GDMT) and diverse subgroups, and GDMT was associated with lower morality across subgroups.

HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; GDMT, guideline-directed medical therapy

*The P for interaction indicates whether treatment strategy interacts with the subgrouping variable. It was calculated from multivariable Cox regression analysis which included the variables for treatment strategy, subgrouping variables, interaction term of the treatment strategy-by-subgrouping variable, sex, hypertension, diabetes, atrial fibrillation, and prescription of mineralocorticoid receptor antagonists, digitalis and diuretics.

[Comment #2]

On page 54, lines 48-50 and page 44, lines 4-6, the revised wording “compared to other groups” is still a bit unclear. Better might be something like “compared to any of the other three treatment groups”.

Response]

We agree with the reviewer’s comment, and we replaced “compared to other groups” with “compared to any of the other three treatment groups”

VERSION 3 – REVIEW

REVIEWER	Takehiro Sugiyama National Center for Global Health and Medicine, Japan
REVIEW RETURNED	29-Oct-2019

GENERAL COMMENTS	The authors sufficiently responded to the comments. The reviewer recommends that the authors should use the word "risk ratio" instead of "relative risk" to prevent confusion. The reviewer thinks that some readers may imagine "odds ratio" from the word "relative risk" when looking at Table 2.

REVIEWER	George Divine Henry Ford Hospital, USA
REVIEW RETURNED	11-Nov-2019

GENERAL COMMENTS	The authors have addressed all of my comments and concerns made for the previous review.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Takehiro Sugiyama

[Comment #1]
The authors sufficiently responded to the comments.
The reviewer recommends that the authors should use the word "risk ratio" instead of "relative risk" to prevent confusion. The reviewer thinks that some readers may imagine "odds ratio" from the word "relative risk" when looking at Table 2.

Response:

We thank you very much for this valuable comment. We agree with the reviewer's comment, and we replaced "relative risk" with "risk ratio" at Table 2.