PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of the low e' and high E/e' with long-term outcomes in patients with normal ejection fraction: A hospital population-based observational cohort study
AUTHORS	Seko, Yuta; Kato, Takao; Shiba, Masayuki; Morita, Yusuke; Yamaji, Yuhei; Haruna, Yoshizumi; Nakane, Eisaku; Hayashi, Hideyuki; Haruna, Tetsuya; Inoko, Moriaki

VERSION 1 – REVIEW

REVIEWER	Sean Zheng Imperial College London, King's College London
REVIEW RETURNED	04-Aug-2019

GENERAL COMMENTS	Many thanks for being given the opportunity to review this article by Seko and colleagues. They have used routinely collected echocardiographic and clinical data, with medium-term clinical follow-up to show that patients with low e' have worse outcomes compared with those with normal e'. Those with raised E/e' have additionally poorer outcomes compared with those with preserved E/e'. Please could the authors provide additional echocardiographic information. This should include whether e' is calculated using septal, lateral or an average of the two. It would be interesting for analysis to be undertaken using septal or lateral e' seperately, and then using mean. Please could authors also provide information on aortic gradients and prevalence of mild aortic stenosis given that this can affect loading conditions. Please could the authors also provide information regarding respiratory co-morbidities where available, including COPD, OSA and smoking status, where reported. This should be included in multivariate adjustment.

REVIEWER	Prof. H. von Bibra Technical University Munich, retired Germany
REVIEW RETURNED	05-Aug-2019

GENERAL COMMENTS	The authors studied the association of the severity of left ventricular diastolic dysfunction with long-term outcomes in patients with normal ejection fraction. They found that this severity measured as pulsed tissue Doppler e' and presence or absence of relaxation abnormalities or high E/e' was incrementally associated with higher risk for primary outcomes (MACE).

	The authors are to be congratulated for assessing the prognostic value of diastolic dysfunction for all cause death and major cardiac events thereby omitting the limited focus on just one cardiac abnormality like ischemic heart disease or hypertension. They used a fair number of participants and a fair time period for follow-up. There is a major problem though – and this may be accomplished - with the definition of normal myocardial diastolic function as low e' versus dysfunction as high e' by using the traditional recommendations e' smaller or higher than 7 cm/s. There has been considerable concern to this and similar recommendations (W.T.Emmery et al, Eur J Echocardiogr. 2008, S.H.Wan et al, J Am Coll Cardiol 2014 and H von Bibra et al, IJC 2015). The major concern is the age dependence of e' and other measures of diastolic myocardial function that is well known for many decades. Recently, the age dependence of e' has been quantified. Age in years determines at least 80% of the velocity e' in healthy and normal individuals. This dependence physiologically decreases e' by 1% per year of age. The ages of the study participants ranged at least between 41 and 82 years so that normal e' in the 82 year old individuals is more than 40% lower than in the young ones. Accordingly, a mathematically more correct definition of normal e' needs to be introduced that refers to the age of the respective individual. The authors' observation that the association of low e' and high E/e' with outcomes was directionally week in patients over 70 years supports the above problem.

VERSION 1 – AUTHOR RESPONSE

Reviewer1

Please leave your comments for the authors below

Many thanks for being given the opportunity to review this article by Seko and colleagues. They have used routinely collected echocardiographic and clinical data, with medium-term clinical follow-up to show that patients with low e' have worse outcomes compared with those with normal e'. Those with raised E/e' have additionally poorer outcomes compared with those with preserved E/e'.

Response:

We thank the reviewer for the careful assessment and positive comments.

Please could the authors provide additional echocardiographic information. This should include whether e' is calculated using septal, lateral or an average of the two.

Response

We thank the reviewer for the careful assessment. We used septal e' in the current study. We have clarified it in the method section as follows:

"The septal e' was measured on the apical 4-chamber view and the E/e' ratio was calculated at the interventricular septum."(Page 7 line 16)

We have also added the word "septal" in the Abstract. (Page 2 line 9)

"we categorized them into 3 groups: septal normal tissue Doppler early diastolic mitral annular velocity (e')"

It would be interesting for analysis to be undertaken using septal or lateral e' seperately, and then using mean.

Response

We thank the reviewer for the valuable suggestions. Unfortunately, we did not collect the data of lateral e' in this study. We have included the lack of data regarding lateral e' in the Limitations.

"Third, we use only septal e' and E/e' because only septal information was available for most patients." (Page 21 line 4-5)

Please could authors also provide information on aortic gradients and prevalence of mild aortic stenosis given that this can affect loading conditions.

Response:

We fully agree on the reviewer. We have added the information regarding the mild aortic stenosis in the Supplementary Table 1.

	Total (n=3,255)	**Normal e' (e'≥7) (n=1,384)**	**Low e' and normal E/e' (e'<7, E/e'≤14) (n=1,295)**	**Low e' and high E/e' (e'<7, E/e'>14) (n=578)**	**P value**	**Cochran-Armitage trend test**
The prevalence of mild AS, (%)	58 (1.8)	5 (0.4)	23 (1.8)	30 (5.2)	＜0.001	＜0.001
Mean PG, mmHg, mean (SD)	15.8 (2.4)	NA	17.6 (1.1)	14.6 (2.3)	0.032	

Although mild AS can affect the loading condition, we could not perform subgroup analyses due to the very limited number of patients and the lacking data of mean pressure gradients because of excluding the moderate-severe AS.

We have included following sentences in the Discussion.

"Although mild aortic stenosis can affect the loading condition, we could not perform subgroup analyses because of the very limited number of patients with mild aortic stenosis after excluding moderate to severe aortic stenosis, as presented in Supplemental Table 1." (Page 20 line 14-16)

Please could the authors also provide information regarding respiratory co-morbidities where available, including COPD, OSA and smoking status, where reported. This should be included in multivariate adjustment.

Response:

We have acknowledged the importance of COPD, OSA, and smoking status. However, we had no data regarding respiratory co-morbidities because we **extracted specific comorbidities from their electronic medical records*****. Thus, we have included the lack of data regarding respiratory co-morbidities in the Limitations.***

"Thus, we had no data regarding the proportion of heart failure with preserved ejection fraction [18-20] nor the respiratory comorbidities, such as chronic obstructive lung diseases, obstructive sleep apnea, and smoking status." (Page 21 line 1-3)

Reviewer2

The authors studied the association of the severity of left ventricular diastolic dysfunction with long-term outcomes in patients with normal ejection fraction. They found that this severity measured as pulsed tissue Doppler e' and presence or absence of relaxation abnormalities or high E/e' was incrementally associated with higher risk for primary outcomes (MACE).

The authors are to be congratulated for assessing the prognostic value of diastolic dysfunction for all cause death and major cardiac events thereby omitting the limited focus on just one cardiac abnormality like ischemic heart disease or hypertension. They used a fair number of participants and a fair time period for follow-up.

Response:

We thank the reviewer for the careful assessment and positive comments.

There is a major problem though – and this may be accomplished - with the definition of normal myocardial diastolic function as low e' versus dysfunction as high e' by using the traditional recommendations e' smaller or higher than 7 cm/s. There has been considerable concern to this and similar recommendations (W.T.Emmery et al, Eur J Echocardiogr. 2008, S.H.Wan et al, J Am Coll Cardiol 2014 and H von Bibra et al, IJC 2015). The major concern is the age dependence of e' and other measures of diastolic myocardial function that is well known for many decades. Recently, the age dependence of e' has been quantified. Age in years determines at least 80% of the velocity e' in healthy and normal individuals. This dependence physiologically decreases e' by 1% per year of age.

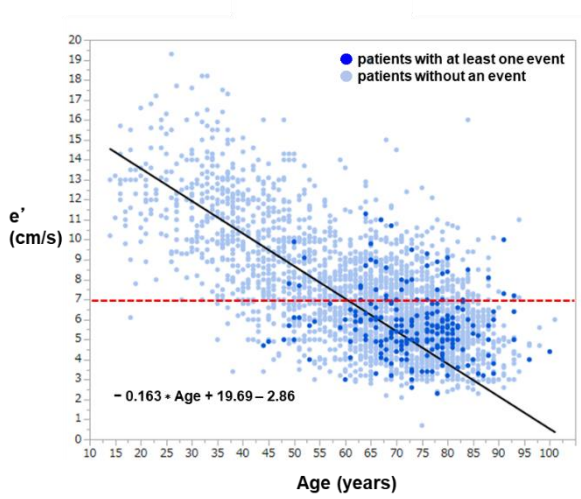
The ages of the study participants ranged at least between 41 and 82 years so that normal e' in the 82 year old individuals is more than 40% lower than in the young ones. Accordingly, a mathematically more correct definition of normal e' needs to be introduced that refers to the age of the respective individual.

The authors' observation that the association of low e' and high E/e' with outcomes was directionally week in patients over 70 years supports the above problem.

Response:

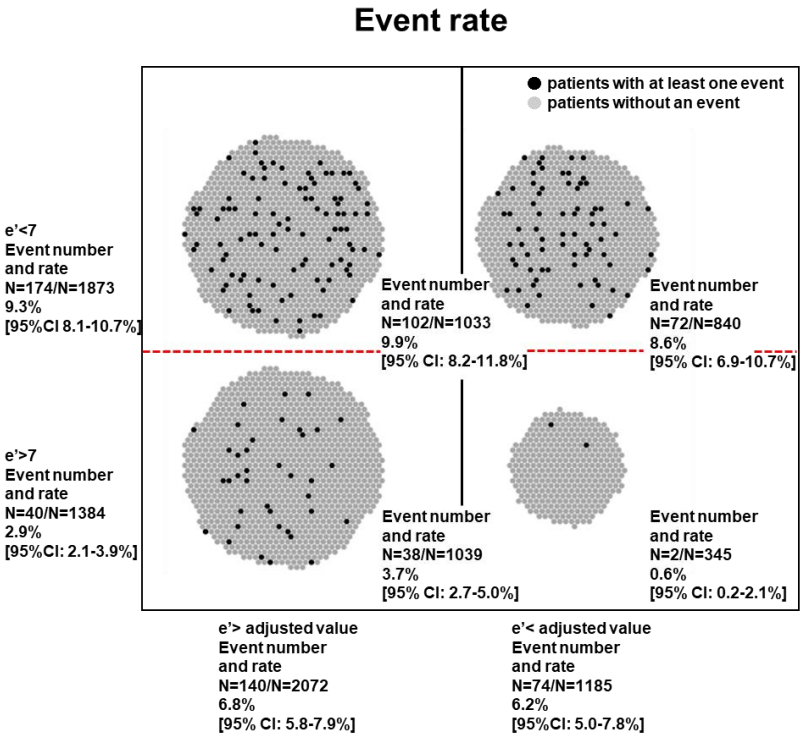
We thank the reviewer for the important question. We created figures about scatter plot and event rate in the conventional classification and new recommendation [H von Bibra et al. Int J Cardiol. 2015 Mar 1;182:368-74.] (Fig. 1 and 2 in the letter).

Figure 1 Scattered plots of e' and age. Calculation formula was according to Dr. H von Bibra's paper.



The event rate is higher in the low e' group (new recommendation) than that in in the e'<7 group than in the low e' group (new recommendation) [Figure 2].

Figure 2



Thus, we want to keep our manuscript in the current form but we have acknowledged the importance of age-dependent decline in e'. We have added the discussion as follows:

"In addition, the age dependence of e' has been quantified recently [25,26,27]. Age in years determines at least 80% of the velocity e' in healthy and normal individuals. This dependence physiologically decreases e' by 1% per year of age [27]. The observation that the association of low e' and high E/e' with outcomes was directionally week in patients over 70 years supports the above problem." (Page 19 line 19-Page 20 line 4)

VERSION 2 – REVIEW

REVIEWER	Helene von Bibra Technical university Munich Germany
REVIEW RETURNED	18-Sep-2019

GENERAL COMMENTS	The authors had been recommended to produce a major revision of their paper/data based on the more recent scientific information, that a physiologically normal value of e' depends so much on age (normal e' decreases by 1% each year of life), that one single cut-off value for normality like 7cm/s (as proposed by the American guidelines) is not at all a valid method to investigate the prognostic potential of e' in a population between 40 and 80 years of age. Instead of applying this age dependence methodology for the calculation of data, comparison, evaluation and discussion, the authors have kept their data and methods completely unchanged. The have just added the citations into the list of references and

	added some phrases into the discussion but kept the interpretation of their data and conclusion practically unchanged. In order to avoid further misunderstanding: the authors are required to incorporate the information that e' depends to more than 80% on the individual age into the calculation and interpretation of their data when evaluating the prognostic value of a e' for longterm outcomes in patients with normal ejection fraction.

VERSION 2 – AUTHOR RESPONSE

Reviewer2
Please leave your comments for the authors below
The authors had been recommended to produce a major revision of their paper/data based on the more recent scientific information, that a physiologically normal value of e' depends so much on age (normal e' decreases by 1% each year of life), that one single cut-off value for normality like 7cm/s (as proposed by the American guidelines) is not at all a valid method to investigate the prognostic potential of e' in a population between 40 and 80 years of age. Instead of applying this age dependence methodology for the calculation of data, comparison, evaluation and discussion, the authors have kept their data and methods completely unchanged. The have just added the citations into the list of references and added some phrases into the discussion but kept the interpretation of their data and conclusion practically unchanged. In order to avoid further misunderstanding: the authors are required to incorporate the information that e' depends to more than 80% on the individual age into the calculation and interpretation of their data when evaluating the prognostic value of a e' for longterm outcomes in patients with normal ejection fraction

Response:
We thank the reviewer for the careful assessment. We have re-analyzed the data according to the comments in this round and the previous round of review.
Additional analysis 1) We constructed a multivariable cox hazard model using age as a continuous variable (model 2).
The trend was generally consistent with the original model; however, the trend of the risk was generally consistent, but it was hampered by the model construction.

Additional analysis 2)
First, we created figures about scatter plot in the conventional classification and age adjusted e' classification by sex [H von Bibra et al. Int J Cardiol. 2015 Mar 1;182:368-74.] (Supplementary Fig 1).
Next, we analyzed the outcome data using the age- and sex- adjusted e' values (Supplementary Fig 2). Finally, we have performed integrated discrimination improvement (IDI) and net reclassification improvement (NRI) analysis to investigate which classification would be more predictive (Supplementary Table 4).
The KM curves and the IDI and NRI analysis suggested that conventional classification showed a better prognosis prediction accuracy.

Our study population is a hospital-based population who underwent scheduled echocardiography. The results may differ from those found in the general population, but no studies have actually examined the long-term prognosis of the abnormality of the e' value in the general population. In addition, there might be a difference between the age- and sex-adjusted normal values and the age- and sex- adjusted cutoff values to predict prognosis. Thus, after mentioned the age dependence of e', we discuss the meaning of conventional cutoff value of e' (<7) to predict outcome in the real-world clinical setting. We also paid special attention to overstatement that e' >7 was normal, but it was a conventional cutoff, throughout the manuscript.

We have added the results as follows:
“In the model 2 where we included age as a continuous variable, the e’<7 and E/e’>14 group (HR: 1.24, 95% CI 1.01 to 1.53, p=0.041) relative to that in the e’ ≥7 group remained significant, whereas the excess risk of primary outcome measures in the e’<7 and E/e’ ≤14 group (HR: 1.04, 95% CI 0.86 to 1.27, p=0.69) relative to that in the e’ ≥7 group was not significant. The severity of grades was incrementally associated with higher risk for primary outcome measure (HR per 1 grade increase:1.13; 95% CI, 1.03-1.25; p= 0.012).”. (Page 15, lines 7-12)

“Additional analysis using age- and sex-adjusted value of e’
The baseline characteristics of the three groups based on the age- and sex-adjusted value of e’ are presented in Supplementary Table 3. The cumulative 3-year incidence of the primary outcome measures were significantly lower in the low e’ and E/e’ ≤14 group (Supplementary Fig 2). According to integrated discrimination improvement and net reclassification improvement analysis, staging using conventional e’ and E/e’ showed a better prognosis prediction accuracy than the staging using age- and sex-adjusted value of e’ (Supplementary Table 4).” (Page 18, lines 11-18)

We have added the discussion as follows:
“In addition, when we included age as a continuous variable into the adjusting model (the model 2), the trend of the risk was consistent, but it was hampered by the model construction. However, we could not find the superiority of the classification using the age- and sex-adjusted criteria of e’ compared to that using the conventional criteria of e’ in the risk prediction. Our study population is a hospital-based population who underwent scheduled echocardiography. The results may differ from those found in the general population, but no studies have actually examined the long-term prognosis in the general population. In addition, there might be a difference between the age- and sex-adjusted normal values and the age- and sex- adjusted cutoff values to predict prognosis. Regarding E/e’, Yoshida et al. reported an increase in E/e’ with age, in which mean E/e’ is from 6.5 in 20s to 10.0 in 70s and 80s in healthy participants [Yoshida Y et al. J Am Coll Cardiol. 2019;74(14):1789-800.]. Although the cutoff value of e’<7 and E/e’>14 had a prognostic impact in clinical settings in a hospital-based population, further study is needed to confirm the link between the age- and sex-adjusted criteria of e’ or E/e’ and the long-term prognosis in general population.” (Page 21, lines 4-18).