PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between subjective risk perception and objective risk estimation in atrial fibrillation patients: a cross-sectional study.
AUTHORS	Zweiker, David; Zweiker, Robert; Winkler, Elisabeth; Roesch, Konstantina; Schumacher, Martin; Stepan, Vinzenz; Krippl, Peter; Bauer, Norbert; Heine, Martin; Reicht, Gerhard; Zweiker, Gudrun; Sprenger, Martin; Watzinger, Norbert

VERSION 1 – REVIEW

REVIEWER	JM Rivera-Caravaca Department of Hematology and Clinical Oncology, Hospital General Universitario Morales Meseguer (Murcia, Spain)
REVIEW RETURNED	08-Jul-2017

GENERAL COMMENTS	In the manuscript entitled “Mind the gap - atrial fibrillation patients and their physicians perceive risk and benefits of stroke prevention differently”, the authors showed that patients with higher knowledge of AF estimated more accurately their stroke risk according to the CHA2DS2-VASc score, but not the bleeding risk according to HAS-BLED. In my opinion, this is a very interesting article but there are some limitations to note. There are no doubts that the main limitation is the small sample size. Despite that 9 centers were involved in the enrolling process, only 91 patients were included. Moreover, the recruitment was not performed in a consecutive manner, which is of important interest in this type of articles. If the sample was obtained by convenience as the authors recognize, more details are needed in the Methods section about how were the patients included. Another important limitation is the absence of follow-up. Without follow-up, we cannot observe how many adverse events occurred, and if those were significantly higher in patients with lower knowledge about AF. Discontinuations rates would be also interesting to investigate in relation to knowledge about AF and lower subjective stroke risk/higher subjective bleeding risk. Other comments to considerate: In Table 1, the authors must show how many patients had CHA2DS2-VASc ≥2 and HAS-BLED ≥3. Also, hypertension for CHA2DS2-VASc is in 82% of patients whereas hypertension for HAS-BLED is only in 46% of patients. For HAS-BLED, they give 1 point if systolic blood pressure was >160 mmHg: For CHA2DS2-VASc I suppose that they give 1 point if systolic blood pressure was

	>140 mmHg but this is not clear in the paper. I think this must be clarified in methods. Only 1 patient had labile INR, but when this was measured? If all patients were naïve (i.e., no previous information of VKA treatment existed) and no follow-up is available, it is a little odd that 1 patient had labile INR. The authors might add to Table 1 the time in therapeutic range (TTR) of VKA patients and when TTR was assessed. Also, this might be included in methods. Minor comments: 1. There are no supplemental figures so this sentence “After informed consent was signed, a standardized questionnaire was handed out to all patients (supplemental figure S1)” might be changed to “After informed consent was signed, a standardized questionnaire was handed out to all patients (supplemental Table S1)”. 2. I am not sure why the authors named “Univariate analysis” to the type of statistical analyses they performed. 3. In page 16, line 21, the authors stated that 41% of patients interpreted the bleeding risk accurately. I think this is a mistake since in Results is 37%. 4. In my opinion, it is not necessary to recognize the use of HAS-BLED as limitation. This is probably the most widely use bleeding risk score in AF and, despite that not be endorsed in the recent ESC guidelines, is still in the NICE and the 2017 Asian guidelines (see Chern-En Chiang et al. 2017 consensus of the Asia Pacific Heart Rhythm Society on stroke prevention in atrial fibrillation).

REVIEWER	Federico Guerra Cardiology and Arrhythmology Clinic, Department of Biomedical Sciences and Public Health, Marche Polytechnic University
REVIEW RETURNED	20-Jul-2017

GENERAL COMMENTS	The paper by Zweiker and colleagues deals with an interesting issue, is methodologically sound, and delivers clear messages. I have only a couple of comments: - As the authors correctly pointed out, the small sample size is the main limitation of the present study. As nine hospitals and one general practitioner have been involved, it is unclear to me how only 91 patients have been enrolled. The size of the studied sample is even more baffling if one considers that the inclusion and exclusion criteria are not so difficult to meet in clinical practice and the questionnaire was easy to administer. While I understand that the sample size calculation was properly performed and demonstrates an acceptable statistical power, I still think the paper could have gained more impact at least twice the number of patients, and a power of 90%. Moreover, as the patients have not been consecutively enrolled, the authors should also state how the patients were selected, how many failed the screening phase, and for what reason. - Had the authors tried to test the correlation between the survey and the new ATRIA and ORBIT bleeding scores? They have shown as better predictors of bleeding events. - Results, patient population: low-molecular weight heparin was prescribed to two patients, despite not being in the current guidelines and not present in the references used by the authors to

	assess thromboembolic and bleeding risk. Can the authors explain that? Also, from Figure 1 two patients had a CHA2DS2-VASc of 0, were they treated anyway? - Discussion, page 16: the authors state that the reported perception gap "...hinders not only shared decision making, but it also influences treatment compliance and adherence." Please provide a suitable reference for this statement.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: JM Rivera-Caravaca
Institution and Country: Department of Hematology and Clinical Oncology, Hospital General Universitario Morales Meseguer (Murcia, Spain)
Please state any competing interests or state 'None declared': None declared
Please leave your comments for the authors below
In the manuscript entitled "Mind the gap - atrial fibrillation patients and their physicians perceive risk and benefits of stroke prevention differently", the authors showed that patients with higher knowledge of AF estimated more accurately their stroke risk according to the CHA2DS2-VASc score, but not the bleeding risk according to HAS-BLED. In my opinion, this is a very interesting article but there are some limitations to note.
There are no doubts that the main limitation is the small sample size. Despite that 9 centers were involved in the enrolling process, only 91 patients were included. Moreover, the recruitment was not performed in a consecutive manner, which is of important interest in this type of articles. If the sample was obtained by convenience as the authors recognize, more details are needed in the Methods section about how were the patients included.
- Answer: We thank the reviewer for this comment. Please acknowledge the fact that sample size calculations were performed before the initiation of the study. The sample size achieved provides a power of 80% to prove a correlation ($|\rho|<0.3$) with type I error (α) of 0.05.
- However, our findings need further confirmation from larger numbers of randomly sampled cases to facilitate generalizability.
- All centres were asked to recruit all eligible patients. However, we did not use a screening log and patients could have been admitted during absence of the study team. Therefore, our study population constitutes a convenience sample. We added details about the recruitment in the "Methods" section and adapted the paragraph "Limitations" of the "Discussion" section.
Another important limitation is the absence of follow-up. Without follow-up, we cannot observe how many adverse events occurred, and if those were significantly higher in patients with lower knowledge about AF. Discontinuations rates would be also interesting to investigate in relation to knowledge about AF and lower subjective stroke risk/higher subjective bleeding risk.
- Answer: We performed a follow up via telephone and observed a OAC discontinuation rate despite clear indication of 3%. During follow up, we experienced five deaths, two strokes and one bleeding. Our study was not powered for an assessment of association between baseline characteristics and adherence to OAC or cardiovascular events during the follow up period. We updated the abstract and added details to the "Strenghts and limitations" section.

We added new paragraphs "Follow Up" in the "Methods" and "Results" sections and added details of follow up in the first paragraph as well as the paragraphs "No correlation between subjective assessment and objective risk", "Stroke is topping bleeding risk" and "Limitations" of the "Discussion" section.
- We added Elisabeth Winkler to the authors' list because of her efforts in obtaining follow up data.
Other comments to considerate:
In Table 1, the authors must show how many patients had CHA2DS2-VASc ≥2 and HAS-BLED ≥3. Also, hypertension for CHA2DS2-VASc is in 82% of patients whereas hypertension for HAS-BLED is

only in 46% of patients. For HAS-BLED, they give 1 point if systolic blood pressure was >160 mmHg: For CHA2DS2-VASc I suppose that they give 1 point if systolic blood pressure was >140 mmHg but this is not clear in the paper. I think this must be clarified in methods.
- Answer: We added the corresponding data of patients with CHA2DS2-VASc VASc ≥2 and HAS-BLED ≥3 to Table 1.
- We agree that there is an inconsistent definition of hypertension in CHA2DS2-VASc and HAS-BLED scores. We used the original definitions based on original publications:
- “Hypertension” as parameter of the HAS-BLED score is defined as “systolic blood pressure > 160 mmHg” (according to Pisters et al., Chest 138(5): 1093-1100).
- “Hypertension” in CHA2DS2-VASc score is defined as “diagnosis of arterial hypertension” with or without treatment (based on the definition of arterial hypertension in CHADS2 score, according to Gage et al., JAMA 285(22): 2864-2870). We added this definition to Table 1.
Only 1 patient had labile INR, but when this was measured? If all patients were naïve (i.e., no previous information of VKA treatment existed) and no follow-up is available, it is a little odd that 1 patient had labile INR. The authors might add to Table 1 the time in therapeutic range (TTR) of VKA patients and when TTR was assessed. Also, this might be included in methods.
- Answer: This patient already had a history of OAC of short duration with labile INRs. Unfortunately, we have no TTR of this patient available as OAC had been started and stopped by the general practitioner some time before enrolment into this study. All other patients had no history of OAC before enrolment into this study. Therefore, there is no TTR of those patients available.
Minor comments:
1. There are no supplemental figures so this sentence “After informed consent was signed, a standardized questionnaire was handed out to all patients (supplemental figure S1)” might be changed to “After informed consent was signed, a standardized questionnaire was handed out to all patients (supplemental Table S1)”.
- Answer: Thank you for this comment, we changed the paragraph accordingly.
2. I am not sure why the authors named “Univariate analysis” to the type of statistical analyses they performed.
- Answer: Thank you for pointing out this misconception. For clarification, we removed the titles of the paragraphs “Sample size calculation” and “Univariate analysis”.
3. In page 16, line 21, the authors stated that 41% of patients interpreted the bleeding risk accurately. I think this is a mistake since in Results is 37%.
- Answer: We accidently mixed up the proportion and the total count in the “Results” section. We corrected the numbers accordingly.
4. In my opinion, it is not necessary to recognize the use of HAS-BLED as limitation. This is probably the most widely use bleeding risk score in AF and, despite that not be endorsed in the recent ESC guidelines, is still in the NICE and the 2017 Asian guidelines (see Chern-En Chiang et al. 2017 consensus of the Asia Pacific Heart Rhythm Society on stroke prevention in atrial fibrillation).
- We adapted the “Limitations” section accordingly.
Reviewer: 2
Reviewer Name: Federico Guerra
Institution and Country: Cardiology and Arrhythmology Clinic, Department of Biomedical Sciences and Public Health, Marche Polytechnic University

Please state any competing interests or state ‘None declared’: None declared
Please leave your comments for the authors below
The paper by Zweiker and colleagues deals with an interesting issue, is methodologically sound, and delivers clear messages. I have only a couple of comments:
As the authors correctly pointed out, the small sample size is the main limitation of the present study. As nine hospitals and one general practitioner have been involved, it is unclear to me how only 91 patients have been enrolled. The size of the studied sample is even more baffling if one considers that the inclusion and exclusion criteria are not so difficult to meet in clinical practice and the

questionnaire was easy to administer. While I understand that the sample size calculation was properly performed and demonstrates an acceptable statistical power, I still think the paper could have gained more impact at least twice the number of patients, and a power of 90%. Moreover, as the patients have not been consecutively enrolled, the authors should also state how the patients were selected, how many failed the screening phase, and for what reason.

- Answer: The authors thank the reviewer for his valuable comment. However, sample size calculations were performed before the initiation of the study to answer our research question. The sample size achieved provides a power of 80% to prove a correlation ($|\rho|<0.3$) with a type I error (α) of 0.05. We agree that a higher number of patients would have increased the impact of this study.
- Unfortunately, this study did not run a screening log. Therefore, we can only assume that patients might be missed during off-hours of the study team members. However, all investigators put considerable effort into a high enrolment rate of suitable patients. We added details about the recruitment in the “Methods” section and adapted the paragraph “Limitations” of the “Discussion” section.

Had the authors tried to test the correlation between the survey and the new ATRIA and ORBIT bleeding scores? They have shown as better predictors of bleeding events.

- Answer: We primarily did not intend to include those bleeding risk scores into our analysis because at the time of recruitment to our study the impact of the ATRIA score was questionable (Roldan, V., et al. 2013, Chest 143(1): 179-184). Its increasing importance has been shown after our study has been conducted. The publication of the ORBIT score also happened after the recruitment of our first study patients (O'Brien et al. 2015, Eur Heart J 36(46): 3258-3264). Unfortunately, due to limited time until the revision deadline, we were not able to gather lab data of all patients to calculate the ATRIA and ORBIT bleeding scores in a post-hoc analysis. We added this limitation to the “Limitations” section.

Results, patient population: low-molecular weight heparin was prescribed to two patients, despite not being in the current guidelines and not present in the references used by the authors to assess thromboembolic and bleeding risk. Can the authors explain that? Also, from Figure 1 two patients had a CHA2DS2-VASc of 0, were they treated anyway?

- Answer: Two patients were on low-molecular weight heparin at time of enrolment into this study. However, OAC with non-VKA oral anticoagulants was started upon discharge from hospital in both patients.
- As correctly pointed out, two patients were enrolled despite a CHA2DS2-VASc score of 0. Both of them received pulmonary vein isolation as rhythm control therapy for AF. After the procedure, individual risk analysis was performed, taking additional risk factors into account, which are not included in the CHA2DS2-VASc score (according to ESC guidelines, Eur Heart J 37(38): 2893-2962). Based on shared decision making, both patients were prescribed chronic OAC. They were still on OAC at time of follow up.

Discussion, page 16: the authors state that the reported perception gap "...hinders not only shared decision making, but it also influences treatment compliance and adherence." Please provide a suitable reference for this statement.

- Answer: We added the following reference to this statement: Berkman, N. D., et al. (2011). "Low health literacy and health outcomes: an updated systematic review." Ann Intern Med 155(2): 97-107. In this systematic review, Berkman et al. found out that low health literacy was consistently associated with poorer health outcomes. The authors reported “poorer ability to demonstrate taking medications appropriately”.

VERSION 2 – REVIEW

REVIEWER	JM Rivera-Caravaca Hospital General Universitario Morales Meseguer (Murcia, Spain)
REVIEW RETURNED	19-Aug-2017

GENERAL COMMENTS	I want to congratulate authors for this revised version of the manuscript. They have fulfilled all my requirements and clarified some minor issues of the manuscript. I have no additional comments.

REVIEWER	Federico Guerra Marche Polytechnic University, Ancona, Italy
REVIEW RETURNED	20-Aug-2017

GENERAL COMMENTS	The paper by Zweiker and colleagues has been completely edited according to the reviewers' suggestions. The methods have been clarified, especially regarding the enrollment strategy. Moreover, a new section regarding follow-up via phone call was added to the paper. This new section offers interesting insights but was also a good opportunity in order to gather the data for the ORBIT and ATRIA risk scores, which would have added some more info on these patients overall risk. A new author has been added, and was probably responsible for the follow-up calls. Overall, I have no further comments.