Author's response to reviews

Title: Prevalence of peripheral arterial disease in subjects with moderate cardiovascular risk: Italian results from the PANDORA study

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Author's response to reviews: see over
Dear Professor Norton,

Re: MS: 2120219544542481

Thank you for your letter dated 19th July, 2011, regarding the above manuscript entitled “Prevalence of peripheral arterial disease in subjects with moderate cardiovascular risk: Italian results from the PANDORA study”.

We would like to thank the editor and reviewers for their critical reading of the manuscript and their helpful comments. Our point-by-point response to these comments is listed below. Also attached is the revised manuscript. Each change made to the manuscript is detailed in the response. We believe the manuscript has improved because of the opportunity to revise it as suggested. We hope that as an effect of the changes made and of the explanations provided, our paper may now merit publication. If you, or the reviewers, require further elaboration on any points, we would be happy to provide this.

The manuscript, or part of it, neither has been published nor is currently under consideration for publication by any other journal. I declare that the co-authors and I have read the manuscript and approved its publication in *BMC Cardiovascular Disorders*.

Thank you again for considering this revised manuscript. I look forward to hearing from you.

Yours sincerely,

Dr Guido Sanna
We thank the reviewers for their thorough assessment of our manuscript, and for the appreciative remarks. We answer the various comments as follows:

Response to Reviewer #1 (Dr Ken-ichi Aihara)

Sanna et al. demonstrated that Italian subjects with cardiovascular risk factors manifest high prevalence of asymptomatic PAD diagnosed by low ABI. In addition, they also found that statin treatment is an independent preventive factor for the development of PAD.

Although their study seems to have some clinical significance for promoting public health in Italia, there are some concerns to confirm the results.

1. **The authors should explain why they excluded diabetes subjects in this study.**
   Patients with diabetes were excluded as this condition was deemed to be a secondary prevention risk. The exclusion of patients with diabetes from the study population reduced the category of patients with ABI >1.40, which is known to be associated with increased CV risk [1, 2].

2. **Table 1 is needed to add several clinical values such as prevalence of hypertension, dyslipidemia, cigarette smoking, family history of early CHD, statin treatment and serum lipids profile.**
   The reviewer makes a pertinent point. These additional clinical parameters have now been added into Table 1. Furthermore, all statistically significant differences are indicated and highlighted in the results section (page 8, paragraph 2, lines 4-12).

3. **Figure 1 indicated the odds ratio of prevalence of PAD in European countries, including Italy, Greece, France, Switzerland, Belgium and Netherland. The authors need to demonstrate a brief summary table of clinical characteristics of the each country.**
   This is a valid point, however all clinical characteristics for the different countries involved in the PANDORA study [3] have been previously described in a recent publication. We prefer to avoid repeating these data due to potential copyright and plagiarism infringement.

4. **Additional discussion is needed to speculate the reason why marital status influenced on the prevalence of PAD.**
   Additional discussion has now been provided that specifically addresses this aspect (page 13, lines 6-14).
Response to Reviewer #2 (Dr David P Brasil)

Comments, questions, and considerations:

1) Discretionary suggestion: The “abstract” mentions “A range of cardiovascular risk factors were significantly associated with asymptomatic PAD (p<0.0001)”.
This sentence may be rephrased as: Suggested version: “A range of risk factors comprising smoking, hypertension, low HDL-C, family history of CHD, and habit of moderate-high alcohol intake were significantly associated with asymptomatic PAD”. This will help readers who did not have access to the entire publication to get to know the specific risk factors positively associated with asymptomatic PAD”. We agree with the observation made the reviewer and feel that this modification will also improve clarity for the reader. We have modified the text accordingly (page 2, results, line 3-15).

2) Comment: The chi-square test was used to compare frequency of different groups of independent categorical variables. The authors tested the relationship of three variables: the ABI, lifestyle habits, and CV risk factors. In order to test whether two of the variables were independent of each other the Cochran-Mantel-Haenszel hypothesis test was performed. Finally, logistic regression was proposed to assess relationship between PAD and other categorical variables. The statistical analysis sounds consistently planned. The co-authors and I appreciate these supportive comments.

3) Discretionary suggestion: In the section “results” (top of page 8) the sentence below may be rephrased, targeting a more clear approach of the paragraph: “The most recurrent exclusion criteria were: less than 80% of CRF fields completed (2.45%), unmeasurable ABI (2.36%) and the lack of fatty serum (?) data collected within the previous 12 months (0.68%)”. This sentence has now been modified accordingly (page 8, lines 3-5).

4) Discretionary suggestion: In the section “results” (middle of page 8) the sentence may be rephrased. Suggested version: “Among the 6 participating countries of the previous PANDORA study, a higher prevalence of PAD was observed in Greece (28.0%) and Italy (22.9%), rather than in France (12.2%), Belgium (7.0%), the Netherlands (8.1%) or Switzerland (12.2%). Multiple logistic regression analysis confirmed that following Greek subjects, Italians had a greater risk of PAD. (Figure 1).” This sentence has now been modified accordingly (page 8, final paragraph).

5) Discretionary suggestion: In the section “results” (top of page 9) the sentence may be rephrased. Suggested version: “Multiple logistic regression did not yield any difference regarding gender, race, physical activity, elevated waist circumference, dyslipidemia, high LDL-C levels or BMI. Variables significantly associated with PAD are shown in Figure 3”. This sentence has now been modified accordingly (page 9, paragraph 2, lines 5-8).

6) Discretionary suggestion: In the section “results” (top of page 9) the sentence may be rephrased. Suggested version: “In addition to age, most subjects (with or without PAD) presented 2 or 3 CVD risk factors (Figure 4A). Whenever subjects were evaluated for the presence of #2 or >2 risk factors, frequency of PAD was higher above 2 risk factors (Figure 4A, inset).” This sentence has now been modified accordingly (page 9, paragraph 3, lines 8-11).
7) Discretionary suggestion: In the section “results” (bottom of page 9) the sentence may be rephrased. Suggested version: “However, statin therapy was significantly associated with absence of PAD (Figure 3).
This sentence has now been modified accordingly (page 10, last 2 lines).

8) Revision: In the section “discussion” (first paragraph of page 10). Please elaborate and explain the sentence: “The present study is in agreement with findings from the original PANDORA study in that (in which?) it (is?) confirms (confirmed?) that the prevalence of a low ABI is not eligible (??) in patients who would otherwise be classified as intermediate and even low risk.”
This sentence has now been modified accordingly (page 11, lines 4-7)

9) Discretionary suggestion: In the section “discussion” (page 10). Long sentence - consider shortening it as it follows. Suggested version: “Limited use of statins in the total cohort of Italian subjects (10.5%) was also confirmed within the subgroup of dyslipidemia (24%). Other participant countries had higher percents of patients on statins.”
This sentence has now been modified accordingly (page 11, lines 8-10).

10) Revision: In the section “discussion” (page 10). Needs correction. “Subjects without symptoms of the lower limbs and overt CV diseases, who are defined by current guidelines as at risk of PAD, include (including?) those less than 50 years old with diabetes and one (additional?) atherosclerosis risk factor (smoking, dyslipidemia, hypertension, or hyperhomocysteinemia) or subjects aged 50 to 69 years with a history of smoking or diabetes, or subjects aged 70 years and older.”
This sentence has now been modified accordingly (page 11, final paragraph, lines 2 and 3).

11) Discretionary suggestion: In the section “discussion” (page 11). Long sentence - consider breaking it up in two sentences as it follows. Suggested version: “This frequency is in agreement with results of the present study, even though in the Get ABI study 2.8% of the subjects with low ABI had PAD symptoms. In addition, risk profile in the Get ABI population showed differences from that of PANDORA, which was due to fewer previous cardiovascular events or diabetes”.
This sentence has now been modified accordingly (page 12, lines 4-7).

12) Discretionary suggestion: In the section “discussion” (page 11) sentence maybe rephrased as it follows. Suggested version: “Nevertheless, as evidenced by PANDORA, the Get ABI also confirmed the usefulness of expanding measurement of ABI over to other risk categories beyond those indicated by guidelines”.
This sentence has now been modified accordingly (page 12, lines 7-9).

13) Discretionary suggestion: In the section “discussion” (middle of page 11), instead of using e.g. (exempli gratia, or “for instance”) perhaps a better fit would be i.e. (id est, meaning “that is”). Suggested version: “Furthermore, demographic and clinical characteristics of this Turkish population were similar to the Italian cohort (i.e., age, gender ratio, associated risk factors, etc.), suggesting that a relatively high prevalence of PAD can be observed in other Mediterranean-like lifestyles”.
This sentence has now been modified accordingly (page 12, line 12).
14) Revision: In the section “discussion” (page 11). Difficult understanding of sentence. Please consider rewrite it. “The marked differences between these results and those of the PANDORA study results where, even in countries with minimal prevalence of low ABI, reported frequencies of over 3%, thus emphasizing the need to apply this issue in many risk-groups that should be submitted to the periodical measurement of ABI”.
This sentence has now been modified to improve clarity (page 12, lines 16-19).

15) Revision: In the section “discussion” (bottom of page 11). “This finding showed the uncertain role of cholesterol in the pathogenesis of dyslipidemia, as a relevant risk factor as also reported in other studies.”... uncertain role of cholesterol in the pathogenesis of dyslipidemia? What does this mean? Please elaborate on this sentence.
This sentence has now been modified to improve clarity (page 12, final paragraph).

16) Revision: In the section “discussion” (page 12). “It is also worth highlighting the association between marital status and the presence of low ABI, with unmarried or widowed subjects more likely affected by low ABI than married subjects”. This data is presented as demographics for no PAD versus PAD: unmarried 4.9 vs 4.5; married 79.7 vs 68; widowed 11.4 vs 13.5. The PANDORA is an exploratory observational (cross sectional) study, whose aim is to predict systematically the relationship among two or more variables. The marital status data above does not infer that unmarried subjects are more likely affected by low ABI, but otherwise presumes a “real world” inclusion of subjects, which is typical of observational studies. Indeed, it looks like marital status may be a confounding variable in this case. Confounders are imbalances between groups that can affect real estimation of results. Thus, some statistical methods are required to adjust the imbalance and control for observed confounders. Two examples of statistical methods to control for possible confounders are the logistic regression (for categorical data) and a propensity matching analysis (AKA as propensity score). In the case of the present study the methods section on page 5 describes that “the relationship between PAD … and the features of patients admitted … was assessed by multivariate logistic regression …”
The reviewer makes a good observation. Logistic regression analysis was performed in the present study and it was incorrectly described as "multivariate logistic regression" in the methods section. The methods section has now been corrected to describe the analysis that was performed (page 7, Sample size and statistical analysis).

17) Revision: In the section “conclusion” (page 13). “Moreover, the finding of a relatively high prevalence of asymptomatic PAD among Italian subjects was paradoxical, given the recognised lipid-lowering benefits of the so-called “Mediterranean diet”. There is no evidence that the present study tested the specific benefits of the “Mediterranean diet” on asymptomatic PAD patients so data does not support this conclusion. This is a mere speculation rather than a confirmed fact and should not be part of the conclusion.
We agree with the reviewer and have omitted this section from the Conclusions section of the Discussion (page 15).

18) Revision: In the section “conclusion” (page 13). “Although compared to other countries (from the original PANDORA study) this Italian population showed a restricted statin medical prescription and treatment, although it is unlikely that this
effect may alone account for this increased prevalence”. The use of “although” twice in the sentence is confuse. Consider rephrase it.
We agree with the reviewer and this section has now been revised (page 15, paragraph 1).

19) Tables and figures miss the legends that can help readers navigate through the results.
In accordance with the journal requirements, we have included a page describing figure legends for figures 1-4 (page 31). Titles imbedded directly in the figures are not normally requested since the figure legend and table captions will be placed directly next (flanking or beneath) the figures presented in the proof and final version of the published manuscript.

20) In conclusion, the data presented in the manuscript may be largely interesting, but would benefit from a more consistent “discussion” and “conclusions” to support the authors’ hypothesis.
We appreciate the reviewers’ comments and substantial changes have now been made to the Discussion section.

References