## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | General Practitioners' use of absolute risk versus individual risk factors in cardiovascular disease prevention: An experimental study |
| **AUTHORS** | Jansen, Jesse; Bonner, Carissa; McKinn, Shannon; Irwig, Les; Glasziou, Paul; Doust, Jenny; Teixeira-Pinto, Armando; Hayen, Andrew; Turner, Robin; McCaffery, Kirsten |

## VERSION 1 - REVIEW

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| **REVIEWER** | Tom Marshall<br>University of Birmingham<br>UK |
| **REVIEW RETURNED** | 24-Feb-2014 |

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| **GENERAL COMMENTS** | An interesting paper on an important aspect of clinical decision making. This is an under-researched area and the study adds usefully to knowledge of this area.<br><br>Introduction<br>There is a reasonable introduction however a few additional points could be made. The first Framingham risk equation was published in 1976. Health economists proposed using multivariable risk factors to identify patients most likely to benefit from antihypertensives in 1978. The idea of using absolute risk to identify which patients to treat first became part of guidelines in New Zealand in 1993. This is therefore not an entirely new idea.<br><br>The aim of the study appears to be to evaluate the influences of risk factors and CVD risk on GP decision making. But it is unclear if there was a prior hypothesis that was being investigated.<br><br>Method<br>I found the presentation of the Methods confusing.<br><br>The method should explain more clearly how the GPs were selected for participation in the experiment. Were all delegates at the conferences eligible for participation? Is it possible that non GPs or non-Australian GPs could have completed the questionnaires?<br><br>How was randomisation carried out?<br><br>It would be clearer to use consistent terminology throughout (“paper based vignettes” or “cases” and in the Results section “patients” but not all three types of terminilogy). It would be clearer to state in the |

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| | following order:<br><br>The target participants (GPs at conferences)<br>The general format of the experiment (asked treatment decisions about paper based vignettes representing clinical cases – explain what the treatment decisions were)<br>The number of paper based vignettes presented to each GP<br>A more detailed description of the construction of the paper based vignettes<br><br>Results<br>It was unclear how missing data were dealt with or whether the analysis was confined to participants who answered all questions. If so how many partially completed questionnaires were discarded?<br><br>I was not entirely clear which findings were univariable analyses and which were multivariable analyses e.g. “years of practice” and “age of GP” are clearly likely to be correlated.<br><br>No information is provided on the final GEE model – how much variation in prescribing decisions could be explained by the statistical model? (Pseudo r squared)<br><br>Discussion<br>It was not always clear which in paper based vignettes represented patients who were eligible for BP treatment / statins under Australian guidelines and which did not.<br><br>As the guidelines referred to were written in 2012 and the experiment took place in 2012 it might be useful to know what the previous guidelines said as GPs might be more influenced by the previous than the more recent guidelines.<br><br>Vignettes invariably are hypothetical decisions but there is also evidence from GPs real decisions in patient records, which can be used to investigate whether real decisions follow the same pattern as those shown in case vignettes. Other studies looking at this could be referred to in the Discussion.<br><br>Others have looked at the pattern of prescribing statins and antihypertensives to patients in relation to their individual risk factors and their absolute risk in UK primary care. UK general practices that are high prescribers of statins to high risk patients appear also to be high prescribers of statins to low risk patients. This echoes the findings among Australian GPs who reported using absolute risk in the paper based vignettes. Some individual risk factors appear to correlate more strongly with statin prescribing than absolute risk in UK primary care. |

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| **REVIEWER** | Professor Zeljko Reiner, MD, PhD, FRCP, FESC, FACC<br>University Hospital Center Zagreb, School of Medicine, University of Zagreb, Zagreb, Croatia |
| **REVIEW RETURNED** | 15-Mar-2014 |

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| **GENERAL COMMENTS** | This is a very interesting article. I have just several minor comments and suggestions.<br><br>In the "Introduction" the authors, of course, refer to the Australian guidelines. However, I think that they should also at least mention several other most important and recently published guidelines such as: 1) ESC/EAS Guidelines for the management of dyslipidaemias: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011; 32:1769-1818.<br>2) European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). Europ Heart J 2012:33;1635–1701<br>and<br>3) 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults, Circulation, 2013<br><br>In "Introduction" in the sentence: "Past research includes studies exploring barriers to GP's use of absolute risk[13-16] and studies quantifying treatment gaps using clinical databases[6,10,11,17..." after "17" one more reference should be added: Reiner Z, Sonicki Z, Tedeschi-Reiner E. Physicians' perception, knowledge and awareness of cardiovascular risk factors and adherence to prevention guidelines: The PERCRO-DOC survey. Atherosclerosis. 2010;213:598:603.<br><br>In the "Discussion" I am not sure that "The strengths of this study include its sample size..." since the number of GPs was sufficient but not very big. Therefore I would suggest to omit this part of the sentence.<br>Also in the "Discussion" after the sentence "proposals such as the use of the "polypill" based solely on an age cut off.[22]" another sentence should follow. It might be something like: However, it has to be mentioned that the "polypill" concept has been heavily criticized exactly because of danger of medicalization a major part of population without physicians' control (ref. Reiner Z. Polypill is not a "Vaccine-like" solution for primary cardiovascular disease prevention in all parts of the world. J Epidemiol Community Health 2013; 67:981-982.) |

## VERSION 1 – AUTHOR RESPONSE

REVIEWER 1

An interesting paper on an important aspect of clinical decision making. This is an under-researched area and the study adds usefully to knowledge of this area.

We thank the reviewer for acknowledging the importance of this study and topic, and their helpful suggestions for improving the paper. We have addressed specific concerns as follows:

Reviewer comment = C
Our response = R

Changes made in text = T

Introduction

C1. There is a reasonable introduction however a few additional points could be made. The first Framingham risk equation was published in 1976. [1] Health economists proposed using multivariable risk factors to identify patients most likely to benefit from antihypertensives in 1978. [2] The idea of using absolute risk to identify which patients to treat first became part of guidelines in New Zealand in 1993. [3] This is therefore not an entirely new idea.

[1] Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham study. American Journal of Cardiology 1976;38:46-51.
[2] Weinstein MC, Stason WB. Economic considerations in the management of mild hypertension Annals of the New York Academy of Science 1978; 304:424-38.
[3] Jackson R, Barham P, Maling T, MacMahon S, Bills J, Birch B, et al. The management of raised blood pressure in New Zealand. British Medical Journal 1993;307: 107-10.

R1. We agree with the reviewer that the idea of absolute risk to prioritize preventive treatment for CVD is not new, and have added this point to the introduction with earlier references:

T1. The first Framingham risk equation was published in 1976[14] and New Zealand was the first country to introduce an absolute risk approach in 1993.[15] More than twenty years have passed since then and the absolute risk approach has been shown to reduce short-term CVD risk without causing clinical harms.[14] However, research suggests that General Practitioners (GPs) often do not use absolute risk to guide their decision making about CVD prevention.[15-19]

C2. The aim of the study appears to be to evaluate the influences of risk factors and CVD risk on GP decision making. But it is unclear if there was a prior hypothesis that was being investigated.

R2. We did have prior hypotheses and have added them to the introduction and discussion:

T2. Introduction:
In line with the literature suggesting that GPs tend to use an individual risk factor approach, we hypothesized that:
(1) GPs are more likely to treat lower absolute risk with medication when individual risk factors (blood pressure, cholesterol) are high than when individual risk factors are lower; and conversely
(2) GPs are less likely to treat high absolute risk with medication when individual risk factors (blood pressure, cholesterol) are lower than when individual risk factors are high.

T2. Discussion:
The results suggest that, inconsistent with the Australian guidelines,[10-11] GPs are likely to prescribe blood pressure and cholesterol lowering medication to lower risk patients (5 year risk of CVD event < 15% ) if these risk factors are elevated, even when an absolute risk assessment is specifically provided to GPs. Conversely, GPs did not always prescribe medication to higher risk cases when blood pressure or cholesterol were not elevated. These results are in line with our hypotheses, and previous studies of patient records showing overtreatment of low risk patients and undertreatment of high risk patients, and that individual risk factors influence prescribing.[26-28, 31-33]

Method

C3. I found the presentation of the Methods confusing. The method should explain more clearly how the GPs were selected for participation in the experiment. Were all delegates at the conferences

eligible for participation? Is it possible that non GPs or non-Australian GPs could have completed the questionnaires?

R3. Only GP delegates were eligible for participation, but there were also nurses and students attending the conferences. All participants were asked when they became a GP and whether they were currently practicing in Australia through survey questions, and eligibility of all returned questionnaires was verified before the data were analyzed. We have clarified this in the method section:

T3. GPs currently practicing in Australia were recruited between May and November 2012 at four general practice conferences in New South Wales, Victoria and Queensland. All participants were asked when they became a GP and whether they were currently practicing in Australia through survey questions, and the eligibility of returned questionnaires was verified before data analysis.

C4. How was randomisation carried out?

R4. This is explained in the methods section, and has been clarified in the revised version of the manuscript:

T4. There were 25 core cases with systematically varied levels of absolute risk, cholesterol, blood pressure, and age. Each case had between one and three versions to enable male/female and smoking/non-smoking comparisons, depending on clinical plausibility. 11 of the core cases were randomly selected for each survey to reduce response burden, and only one version of the selected case was used (e.g. only the female, non-smoking version). The 11 selected cases were presented in random order. This process generated a total of 43 clinically possible cases (see Appendix for details of each case).

C5. It would be clearer to use consistent terminology throughout (“paper based vignettes” or “cases” and in the Results section “patients” but not all three types of terminology).

R5. We agree and now use ’cases’ throughout the paper, apart from the introduction and have added information to the introduction to clarify:

T5. In the current study we used patient cases (from here on referred to as cases) in which the levels of absolute risk and three individual risk factors (systolic blood pressure, cholesterol (TC/HDL ratio) and age) were systematically varied

C6. It would be clearer to state in the following order: The target participants (GPs at conferences) The general format of the experiment (asked treatment decisions about paper based vignettes representing clinical cases – explain what the treatment decisions were) The number of paper based vignettes presented to each GP A more detailed description of the construction of the paper based vignettes

R6. We have changed the order as suggested:
(a) Description of participants (subheading: recruitment)
(b) General format experiment (subheading: data collection and measurement)
(c) The number and types of cases presented (subheading: different sets of cases)
(d) Detailed information about cases (subheading: levels of absolute risk and individual risk factor levels)
(e) Randomization.

Results

C7. It was unclear how missing data were dealt with or whether the analysis was confined to participants who answered all questions. If so how many partially completed questionnaires were discarded?

R7. Missing data was limited; we now explain missing data handling in more detail in the method section:

T7. Missing data handling
Five participants completed only half of the survey (1 out of 2 pages). For those participants, only the completed part of the survey was included in the analysis. Additionally, there was an average of 5 missing responses per case. In most instances the missing values occurred in questionnaires where only positive responses were marked (i.e. GP only gave a response for cases where he/she would prescribe) and it was therefore assumed that the missing values were negative responses (i.e. GP would not prescribe for that case). A sensitivity analysis was conducted to check this assumption by excluding the surveys with missing values. The pattern of results did not change.

C8. I was not entirely clear which findings were univariable analyses and which were multivariable analyses e.g. “years of practice” and “age of GP” are clearly likely to be correlated.

R8. Given that the study was randomized we did not perform any adjustment for the main comparison. We analyzed how the chances of prescribing medication changed according to the risk profiles of the cases (i.e. levels of absolute risk and individual risk factors) using Generalized Estimation Equations (GEEs), but this procedure was chosen only to take into account clustering of cases per GP. We also performed an exploratory subgroup analysis to see if the effects were different across patients and physicians characteristics but instead of stratifying by each characteristic, we tested the interaction of each characteristic with the four sets of patient cases with different risk profiles: (A) high individual risk/lower absolute risk, B) high individual risk/high absolute risk, C) lower individual risk/high absolute risk, and D) lower individual risk/lower absolute risk) using logistic regression models (one model for each characteristic). Please note that each characteristic is analyzed separately so the correlation between the characteristics is not critical.

We have revised the manuscript to clarify this point:

T8. We performed exploratory analyses to examine 1) how risk management changed according to GP characteristics (i.e. age, gender, years in practice, practice size, and self-reported use of absolute risk in practice and in the cases); and 2) how risk management changed according to specific characteristics of the cases presented (i.e. age, gender, and smoking status). This was achieved by testing the interaction between each characteristic and the four sets of cases with different risk profiles in separate GEEs (one for each characteristic). The statistical analysis was performed with the software SPSS version 21.

C9. No information is provided on the final GEE model – how much variation in prescribing decisions could be explained by the statistical model? (Pseudo r squared)

R9. This question is related to the previous comment (#8). As mentioned in the response to the previous comment, the aim of the multivariable models was not prediction but to test the interactions between the four sets of cases/risk profiles and patient and physician characteristics, taking into account the clustering of cases per GP. Thus we don't think it is relevant to provide the prediction ability of the different regressions, as this was not a prospective study.

Discussion

C10. It was not always clear which paper based vignettes represented patients who were eligible for BP treatment/statins under Australian guidelines and which did not.

R10. The Australian guidelines classify patients with a 5 year risk of > 15% as high risk and recommend that they should be simultaneously treated with cholesterol and blood pressure lowering medication in addition to lifestyle intervention unless contraindicated or clinically inappropriate. These guidelines have replaced the cholesterol lowering and hypertension guidelines.

The cases were constructed in a way that the patients in the cases with high individual risk factors and high absolute risk (set 'B', see also Figure 2) and lower individual risk factors and high absolute risk (set 'C', see also Figure 2) were all eligible for treatment with cholesterol and blood pressure lowering medication according to the Australian guidelines, and none of the patients in the other sets of cases (A & D, see also Figure 2 and Table 1) were eligible for treatment with medication.This is explained in the method section and in the footnote of Table 1 and Figure 2:

T10. *Only the sets of cases B and C were eligible for treatment with cholesterol and blood pressure lowering medication according to the Australian absolute risk guidelines. [11]

C11. As the guidelines referred to were written in 2012 and the experiment took place in 2012 it might be useful to know what the previous guidelines said as GPs might be more influenced by the previous than the more recent guidelines.

R11. Previous Australian guidelines for lipid and hypertension management are consistent with the 2012 guideline recommendations for the commencement of cholesterol lowering and/or blood pressure lowering medication. We have added details of the previous individual risk factor guidelines to the methods section:

T11. Previous Australian guidelines for cholesterol (2005)[29] and hypertension management (2010)[30] are consistent with the 2012 guidelines recommendations for the commencement of cholesterol lowering and/or blood pressure lowering drug treatment in patients with an absolute risk > 15% of a CVD event in the next 5 years, or those with an absolute risk of 10-15% with the presence of additional risk factors but have now been replaced with the 2012 guidelines.

C12. Vignettes invariably are hypothetical decisions but there is also evidence from GPs real decisions in patient records, which can be used to investigate whether real decisions follow the same pattern as those shown in case vignettes. Other studies looking at this could be referred to in the Discussion. Others have looked at the pattern of prescribing statins and antihypertensives to patients in relation to their individual risk factors and their absolute risk in UK primary care.[4] UK general practices that are high prescribers of statins to high risk patients appear also to be high prescribers of statins to low risk patients. [5] This echoes the findings among Australian GPs who reported using absolute risk in the paper based vignettes. Some individual risk factors appear to correlate more strongly with statin prescribing than absolute risk in UK primary care.[6]

[4] Mohammed MA. El Sayed C. Marshall T. Patient and other factors influencing the prescribing of cardiovascular prevention therapy in the general practice setting with and without nurse assessment. Medical Decision Making. 32(3):498-506, 2012 May-Jun.
[5] van Staa TP1, Smeeth L, Ng ES, Goldacre B, Gulliford M. The efficiency of cardiovascular risk assessment: do the right patients get statin treatment? Heart. 2013 Nov;99(21):1597-602. doi: 10.1136/heartjnl-2013-303698. Epub 2013 Jun 4.
[6] Wu J, Yao GL, Zhu S, Mohammed MA. Marshall T. Patient factors influencing the prescribing of lipid lowering drugs for primary prevention of cardiovascular disease in UK general practice: a national retrospective cohort study PLoS One 2013 8(7): e67611. doi:10.1371/journal.pone.0067611

R12. We have added further discussion of findings from studies of prescribing decisions in practice, with reference to the suggested papers:

T12. The results suggest that, inconsistent with the Australian guidelines,[10-11] GPs are likely to prescribe blood pressure and cholesterol lowering medication to lower risk patients (5 year risk of CVD event < 15% ) if these risk factors are elevated even when an absolute risk assessment is specifically provided to GPs. Conversely, GPs did not always prescribe medication to higher risk cases when blood pressure or cholesterol were not elevated. These results are in line with our hypotheses, and previous studies of patient records showing overtreatment of low risk patients and undertreatment of high risk patients, and that individual risk factors influence prescribing.[26-28, 31-33]

REVIEWER 2

This is a very interesting article. I have just several minor comments and suggestions.

We thank the reviewer for acknowledging their interest in the manuscript, and their helpful suggestions for improving the paper. We have addressed specific concerns as follows:

C13. In the "Introduction" the authors, of course, refer to the Australian guidelines. However, I think that they should also at least mention several other most important and recently published guidelines such as: 1) ESC/EAS Guidelines for the management of dyslipidaemias: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011; 32:1769-1818.
2) European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). Europ Heart J 2012:33;1635–1701 and
3) 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults, Circulation, 2013

R13. We have added references to the suggested international guidelines to the introduction, and also added a reference to a review of guideline recommendations (ref#6. Ferket BS, Colkesen EB, Visser JJ, et al. Systematic review of guidelines on cardiovascular risk assessment: which recommendations should clinicians follow for a cardiovascular health check? Archives of internal medicine 2010;170(1):27-40):

T13. International guidelines for cardiovascular disease (CVD) prevention encourage the use of absolute risk to guide treatment with blood pressure and cholesterol lowering medication [1-6].

C14. In "Introduction" in the sentence: "Past research includes studies exploring barriers to GP's use of absolute risk[13-16] and studies quantifying treatment gaps using clinical databases[6,10,11,17..." after "17" one more reference should be added: Reiner Z, Sonicki Z, Tedeschi-Reiner E. Physicians' perception, knowledge and awareness of cardiovascular risk factors and adherence to prevention guidelines: The PERCRO-DOC survey. Atherosclerosis. 2010;213:598:603.

R14. We have added the suggested reference to the introduction:

T14. Past research includes studies exploring barriers to GP's use of absolute risk[19-22] and studies quantifying treatment gaps using clinical databases[12, 16-17, 23-24]

C15. In the "Discussion" I am not sure that "The strengths of this study include its sample size..." since the number of GPs was sufficient but not very big. Therefore I would suggest to omit this part of

the sentence.

R15. We agree with the reviewer and have removed the suggested part of the sentence in the discussion

C16. Also in the "Discussion" after the sentence "proposals such as the use of the "polypill" based solely on an age cut off.[22]" another sentence should follow. It might be something like: However, it has to be mentioned that the "polypill" concept has been heavily criticized exactly because of danger of medicalization a major part of population without physicians' control (ref. Reiner Z. Polypill is not a "Vaccine-like" solution for primary cardiovascular disease prevention in all parts of the world. J Epidemiol Community Health 2013; 67:981-982.)

R16. The reviewer raises an important point, which we cannot sufficiently discuss within the scope of this paper. We have therefore decided not to specifically mention the polypill approach in the discussion. We still refer to the Wald & Law paper and have added the Reiner reference:

T16. Age appeared to be largely ignored as a risk factor, and GPs prescribed less blood pressure lowering medication for 72-year-old cases in comparison with 61 year olds despite similar descriptions in the scenarios (a relatively healthy fit x year old). This finding is worthy of further exploration, given that age is one of the strongest risk factors for CVD, as it runs counter to the concept of absolute CVD risk and proposals based solely on an age cut off.[34-35]