Author's response to reviews

Title: Comparison of different vascular risk engines in the identification of type 2 diabetes patients with high cardiovascular risk

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Author's response to reviews:

Prof. Tim Shipley August, 12, 2015
Editor

Manuscript "Comparison of different vascular risk engines in the identification of type 2 diabetes patients with high cardiovascular risk"

Dear Editor,

I enclose the revision of the manuscript (Nº 2010644379145166) entitled "Comparison of different vascular risk engines in the identification of type 2 diabetes patients with high cardiovascular risk". In separate documents included responses point by point to the suggestions and comments of the reviewers and the editor.

I'm very grateful for your interest and I expect your pleasant news.

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Editor's Comment:

* Acknowledgement

By way of a section ?Acknowledgements?, please acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for each author, and for the manuscript preparation. Authors must describe the role of the funding body, if any, in design, in the
collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Please also acknowledge anyone who contributed materials essential for the study. If a language editor has made significant revision of the manuscript, we recommend that you acknowledge the editor by name, where possible.

The role of a scientific (medical) writer must be included in the acknowledgements section, including their source(s) of funding. We suggest wording such as ‘We thank Jane Doe who provided medical writing services on behalf of XYZ Pharmaceuticals Ltd.’

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

* Name of Ethic committee

Please update your ethics statement to include the name of the ethics committee that approved your study.

GEDAPS study was approved by the Consell Assessor de la Diabetes (Advisory Board on Diabetes) of the Health Departament of the Autonomous Government in Catalunya that acted as Institutional Review Board, IDIME study was approved by the Clinical Research Ethics Committee of the IMIM-Hospital del Mar, Barcelona, Spain (Project number 2008/3176/I) and PERCEDIME2 study was approved by Ethical and Clinical Investigation Committee of the Institut d’Assistència Sanitària (IAS), Girona, Spain. All participants provided written informed consent.

Competing interest

The authors declare that there is no duality of interest associated with this manuscript.

Authors’ contributions

ARP contributed to the conception, design, analysis, interpretation of data and wrote the manuscript; GCT and JFN contributed to the conception, design, analysis, interpretation of data and revised manuscript; MSZ contributed to the statistical analysis and interpretation of data; JMT contributed to the conception and revised manuscript; JGM and JBP revised manuscript. All authors contributed to final approval of the version to be published.

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Reviewer: David Preis
Major revisions

1. The quality of written English still needs to be improved in many parts of the paper to improve clarity.

Our manuscript was revised for AJE (American Journal Experts)
We look over the text to improve the quality of the manuscript.

2. Please state somewhere that the participants in the 3 studies gave consent and were ethically approved (apologies if I missed this)

Sorry, you are right. We add this information

FRCV-GEDAPS study was approved by the Consell Assessor de la Diabetes (Advisory Board on Diabetes) of the Health Department of Catalunya; IDIME study was approved by the Clinical Research Ethics Committee of the IMIM-Hospital del Mar, Barcelona, Spain (Project number 2008/3176/I) and PERCEDIME2 study was approved by Ethical and Clinical Investigation Committee of the Institut d’Assistència Sanitària (IAS), Girona, Spain. All participants provided written informed consent.

3. In section 2.1 at the end, definitions are given for ‘high risk’. Please also state here exactly what each equation predicts as this is crucial information.

We add this information

Framingham-REGICOR provided estimates of risk for coronary heart disease and ADVANCE and UKPDS coronary heart disease and stroke.

4. I do not fully understand the use of the ROC curves in this manuscript. I have referred this for a statistical opinion to check that this is needed and that it is a correct approach to take.

We agree with you, thank you. We remove the ROC curves.

Reviewer: Alice Owen

Minor Essential Revisions

1. Page 3, line 3: Correct to ‘Background’
We correct Introduction by

Background

2. Page 3, line 9: What do you mean when you say that “Coronary heart (disease) mortality rates are contradictory..?” This is not clear, please amend.
Thanks. We amend the text “Coronary heart mortality rates are contradictory when comparing a diabetic population to a population with a previous history of coronary heart disease, which may be related to multiple causes, such as those attributable to the different baseline characteristics and different risk profiles of the diabetic patients who participated in the studies” by

Although diabetes is a risk factor for Coronary Heart Disease (CHD), whether diabetes alone is a CHD equivalent in assessing the risk of future CVD events is controversial.

It might be related to multiple causes, such as those attributable to the different baseline characteristics and different risk profiles of the diabetic patients who participated in the studies.

3. Please revise the sentence in lines 23-24 on page 1 of the background, which appears somewhat out of context and may confuse some readers.

We revise this sentence “Currently, several risk functions that calculate CVR are available, among them the following: the Framingham population-based cohort study model, the Girona Heart Registry (REGICOR, for its initials in Catalan) engine of the Framingham model adapted to a Spanish population and the Systematic Coronary Risk Evaluation (SCORE)” by

In Spain, several risk strategies are currently used to estimate cardiovascular risk (CVR). Among these equations, Framingham-REGICOR (Registre Gironí del Cor) and the Systematic Coronary Risk Evaluation SCORE and are the most popular. It has been previously discussed that the former overestimates and the second underestimates CVR.

4. Table formatting for Table 4 needs to be corrected for years since diabetes diagnosis

We correct for years since diabetes diagnosis

5. Page 10, sentence lines 15-20, please provide citation/s.

We provide citation

6. Page 11, lines 7-12, please provide citation/s

We provide citation

Major Compulsory Revisions

7. To support the primary conclusion of the paper; that a model predicting overall CVD risk (not just CHD) is required for type 2 diabetes patients in Southern Europe, it would be useful for the reader to be provided with information about the burden of non-coronary CVD in the diabetes patient population in this region. Generally adding new predictive variables to CVD risk equations provides a somewhat marginal predictive gain, which needs to be justified against the magnitude of the problem and the additional burden for clinical practice to collect these extra variables.
Thank you for your suggestion. We provide this information.

Sha AD et al. observed that type 2 diabetes was positively associated with peripheral arterial disease (adjusted HR 2.98 [95% CI 2.76-3.22]), ischaemic stroke (1.72 [1.52-1.95]), stable angina (1.62 [1.49-1.77]), heart failure (1.56 [1.45-1.69]), and non-fatal myocardial infarction (1.54 [1.42-1.67]). In BASCORE Study, Spain, type 2 diabetes was associated with greater complications and mortality [Incidence rates (1,000 person-years)]: coronary heart disease (21.6 [95% CI 17.9-25.9]); Stroke (14.6 [11.7-18.1]) and peripheral arterial disease (12.3 [9.6, 15.5]). And Cañón Barroso L et al. found that incidence of stroke, coronary and global cardiovascular events in diabetic patients were 14.7%, 9.3% and 21.3%, respectively.

8. The background section identifies that some have suggested that secondary CVD prevention strategies should be applied to all diabetes patients. The capacity of lower resource health settings to accommodate this is an important issue (as highlighted by the authors), but also there is the issue of overtreatment of those who might be at low risk.

We add

Moreover overtreatment, in patients at low risk, might be associated with a higher risk of drug interactions; more significant cost, inconvenience, and side effect burdens that might engender higher rates of non-adherence.

Did the authors examine the level of agreement for those classified as low risk by these equations?

Thank you for the comment. True, it is important to avoid an overestimation of the risk that is associated with overtreatment. However, low risk levels for each of the equations is not well defined. For this reason it has not done this analysis.

9. It is well described from previous studies of many CV risk prediction models that the models tend to predict only moderately when applied to different population settings and need to be recalibrated and validated in the population to which they are being applied. It has been shown that both UKPDS (which was developed from a pre-statin era cohort) and ADVANCE tend to overestimate risk in high risk patients, and without outcome data in the current analyses it is not possible to assess to what extent REGICOR might be underpredicting risk and/or ADVANCE or UKPDS overpredicting. However the utility of the REGICOR algorithm against 5-year observed event rate in patients with diabetes has previously been reported (Marrugat et al in the Journal of Epidemiology and Community Health in 2007, Figure 4 of that paper). Could the authors please justify why they did not cite and discuss that work?

It is an interessant issue. We amend the text, cite and discuss Marrugat et al. work and introduce new information.

Marrugat J et al. observed that the REGICOR-adapted function’s estimate did not differ from the observed cumulated incidence. In men and women with diabetes...
(16.4%), the Kaplan-Meier observed overall 5-year CHD event rate was 4.9%. The original Framingham function significantly overestimated the event rate by a factor > 2.6; the prediction of the Framingham-REGICOR adapted function did not differ from the observed rate (Marrugat et al). Cañón Barroso L et al. observed that the comparison between the mean coronary risk estimated by the original Framingham equation (Framingham-Wilson) and the calibrated one for the Spanish population (Framingham-REGICOR) in diabetic patients showed that Framingham-REGICOR underestimated the actual coronary risk (11.3 versus 15.0%) while Framingham-Wilson overestimated the risk (27.4 versus 15.0%) and Jimeno Mollet et al. found that Framingham-REGICOR underestimated the coronary risk at 10 years, 20% and 40% for men and women respectively. European guidelines on diabetes don’t recommend to assess the risk for CVD in patients with DM based on risk scores developed for the general population.

10. Page 9, line 21-22: Please clarify what you mean by ‘patients classified as high risk by REGICOR are excluded from the UKPDS and ADVANCE functions’ Do you mean that there was insufficient data from these patients for the UKPDS and ADVANCE to be used? Or that they were not classified as high risk by these alternate risk algorithms?

We correct the text

In addition most of the patients classified as high risk by REGICOR function doesn’t match those classified as high risk by the UKPDS and ADVANCE functions, as indicated by the low agreement between the three functions. In fact, it is observed (Table 2) that high risk patients according REGICOR are smokers and have a more desfavorable lipid profile compared to patients with high risk according UKPDS and ADVANCE functions. Many of these patients classified as high risk by REGICOR probably not fall into this category according to the UKPDS and ADVANCE functions.

11. The population prevalence of diabetes in the Spanish population is in the order of 10-15% (eg refer Soriguer et al, Diabetelologia 2012), however the major basis for criticism of the REGICOR risk equation by the authors is that the proportion of diabetic patients in validation cohort was “very low” (Discussion, page 10 line 16) at 16.4%. I am not convinced that the “very low” criticism is reasonable. Could the authors please respond?

Framingham-REGICOR risk scores was developed for the general population, not for people with diabetes, and only 16.4% were patients with diabetes, whilst in UKPDS and ADVANCE 100% had diabetes. The risk charts based on the Framingham Study equations tend to underestimate the risk in people with diabetes as these studies involved relatively few people with diabetes. European guidelines on diabetes don’t recommend to assess the risk for CVD in patients with DM based on risk scores developed for the general population.

We amend the text
In the Framingham cohort study calibrated to a Spanish population (REGICOR), the percentage of diabetic participants was very low, with a total of 16.4%, a mean age of 56.3 years, and most likely with few years of evolution of the disease, while in the UKPDS study, the number of diabetic patients who participated in the study did not represent the general population with DM2 by Framingham-REGICOR risk scores was developed for the general population, and only 16.4% were diabetic patients, whilst in UKPDS and ADVANCE all were diabetic patients.