PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of provision of cardiovascular disease risk estimates to healthcare professionals and patients: a systematic review
AUTHORS	Usher-Smith, Juliet; Silarova, Barbora; Schuit, Ewoud; Moons, Karel; Griffin, Simon

VERSION 1 - REVIEW

REVIEWER	Fahey, Tom Royal College of Surgeons in Ireland, Department of General Practice
REVIEW RETURNED	20-May-2015

GENERAL COMMENTS	Overall I found this to be a well-structured and well-written systematic review with clear conclusions and reasonable caveats in terms of the shortcomings of the included primary studies. My following comments are minor in nature: 1. The included studies are a mixture of RCTs (n=11) and before/after studies (n=6). Are there differences in effect sizes between the more methodologically robust RCTs in terms of intensification of medicines and/or impact on surrogate outcomes such as BP and cholesterol levels. 2. The authors don't discuss the issues of providing risk information to physicians- usually in the context of using CVS risk as a clinical prediction rule and the subsequent treatment threshold recommendation. So for example if a person's CVS risk was below a recommended treatment threshold, it is entirely reasonable that no addition or intensification of medication takes place. This is often the case in terms of primary prevention and may well account for the authors findings that higher CVS risk levels are associated with greater intensification and subsequent BP or cholesterol lowering. 3. In the same way, providing CVS risk estimates to patients is more a form of shared decision making and it may not necessarily follow that a patient wishes to take advice/recommendations about their level of CVS risk in terms of intensification or not. Patients may be risk averse to the consequences of getting a CVS event and may then take medicines at a lower CVS risk; alternatively the patient may have a "high" CVS risk and exceed the recommended treatment threshold but may be risk-averse to being on lifelong medical (BP and/or statin) treatment. More critical discussion about these issues in the context of the findings from the systematic review would be welcome. 4. Missing RCTs. I have been involved in an RCT that seems to

	meet the inclusion criteria of the systematic review. This RCT provided risk estimates to GPs and had a modest impact on intensification of BP lowering medicines and BP control. See: Montgomery A, Fahey T, Peters T, MacKintosh C, Sharp D. Evaluation of a computer-based clinical decision support for the management of hypertension in primary care: a randomised controlled trial. BMJ 2000; 320: 686-690. PMID: 10710578

REVIEWER	McConnachie, Alex University of Glasgow, Robertson Centre for Biostatistics
REVIEW RETURNED	20-Jul-2015

GENERAL COMMENTS	Usher-Smith et al present a systematic review of studies that assess the impact of providing CVD risk estimates to patients and/or professionals. This review is mainly concerned with the statistical aspects of the paper. Overall, I found the paper to be very readable. I think that the background and methods are well described. The authors have been quite inclusive in their review, and consider a wide range of different study designs and outcomes. The result is that none of the meta analyses includes more than a handful of individual studies, and for the majority of endpoints, they are left to give a descriptive summary of the results. Given this, I think that the authors have done a good job of presenting what could have been quite turgid results in a fairly engaging manner. The only thing I would suggest is to go through the paper carefully and proof-read it. One thing I spotted was in the third line of the blood pressure results section on page 11, which speaks of a "...difference in mean difference in change in SBP or DBP." Is there one too many difference in this sentence? From a statistical perspective, the methods used are appropriate and clearly presented. They have kept things simple, which is fine given that the meta analyses are not the main focus of the review.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name Tom Fahey
Institution and Country HRB Centre for Primary Care Research & Department of General Practice, RCSI
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below Thank you for asking me to review this paper.

Overall I found this to be a well-structured and well-written systematic review with clear conclusions and reasonable caveats in terms of the shortcomings of the included primary studies.

> We are grateful to Professor Fahey for his positive comments about our review and for his helpful suggestions. We have responded to each of them in turn below and feel that these changes have improved the manuscript.

My following comments are minor in nature:

1. The included studies are a mixture of RCTs (n=11) and before/after studies (n=6). Are there differences in effect sizes between the more methodologically robust RCTs in terms of intensification of medicines and/or impact on surrogate outcomes such as BP and cholesterol levels.

> Of the 10 studies that measured changes in intensification of medicines and/or the impact on surrogate outcomes, nine were RCTs with only one (Qureshi) a before-and-after study (nested within an RCT). All were assessed as medium or high quality based on the Critical Appraisal Skills Programme guidelines. The effect sizes between the different studies are, therefore, more likely to reflect differences in the patient populations and delivery of risk information than overall quality of the studies.
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> To make this clearer in the manuscript we have added the following sentences to the second paragraph of the results:
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> > "A summary of the characteristics of those 17 studies is shown in Table 1. They showed considerable heterogeneity in terms of size, setting, risk score used, duration of follow up and outcomes measured. Seven (two randomised controlled trials (RCT) and five before-and-after studies) measured changes in understanding or risk, risk perception, psychological well-being or anxiety with ten (nine RCTs and one before-and-after study) reporting changes in risk factors, prescribing, or calculated risk. Eleven provided risk information to patients alone, 3 to physicians and 3 to both patients and physicians. Study quality assessment is summarised in Table 2. Overall it was variable with only 1 study being judged as high quality. All nine RCTs reporting changes in risk factors, prescribing, or calculated risk were judged as medium or high quality. The effect sizes between the different studies are, therefore, more likely to reflect between study heterogeneity for a number of study characteristics, in particular differences in the patient populations and delivery of risk information, than overall quality of the studies."

2. The authors don't discuss the issues of providing risk information to physicians- usually in the context of using CVS risk as a clinical prediction rule and the subsequent treatment threshold recommendation. So for example if a person's CVS risk was below a recommended treatment threshold, it is entirely reasonable that no addition or intensification of medication takes place. This is often the case in terms of primary prevention and may well account for the authors findings that higher CVS risk levels are associated with greater intensification and subsequent BP or cholesterol lowering.

> Thank you for raising this very important issue. We agree that the baseline level of risk is an important factor affecting treatment decisions, as well as lifestyle changes as in the point below. We had hoped to adjust the effect sizes in each study for baseline risk but that was not possible from the data available. We had already mentioned this in the discussion but in this revised version we have added further analysis where possible to take account of the baseline risk levels and made a number of changes to make this issue more explicit and to add to the interpretation of the results. These include:
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> 1. Adding the following two sentences to the description of table 3 in the third paragraph of the results:
>
> > "Table 3 shows additional details about the participants in each of the studies, including the inclusion criteria, methods of recruitment and randomisation and the baseline CVD risk of participants. Of the nine RCTs reporting changes in risk factors, prescribing or calculated risk, five included only high risk patients (CVD risk estimate ≥ 20%) or those with uncontrolled hypertension or untreated hyperlipidaemia[28,29,33–35]. The other four[25,31,32,36] included both high and low risk participants, with the proportion of each well balanced between the intervention and control groups."
>
> 2. Adding descriptions throughout the results relating to the risk profile of the participants in each study, for example:

"Only one study used an objective measure of changes in diet (plasma vitamin C) and also showed no significant effect of risk information amongst those with CVD risk >20% (standardised difference in means -0.079 (-0.37 to 0.21), p = 0.589) at 1 month[29]."

"Two studies reported on intention to increase physical activity. Both showed no effect with one before-and-after study including 11.4% of participants with CVD risk >20% showing no change in the number of participants…"

"No significant differences were found with HDL-C or total cholesterol to HDL ratio after adjusting for baseline risk[36], or with triglycerides[29] or the number of patients who had had their LDL-C repeated and in whom it was 30 mg/dl or more lower than baseline at 9 months (OR 0.99 (0.56 to 1.74))[28] amongst those with CVD risk >20% or with raised LDL. One RCT of participants with untreated hyperlipidaemia did, however, find that…"

3. Adding further details of the one report of the interaction between the level of risk (age gap) and effect of the intervention in the results:

"One RCT of participants with untreated hyperlipidaemia did, however, find that patients were more likely to reach lipid targets if they received risk information (OR 1.26 (1.04 to 1.53), n = 1163 (intervention) and 1193 (control)) and there was a significant interaction (p = 0.04) between being given a risk profile and the age gap (estimated cardiovascular risk age minus actual age) with the OR for reaching lipid targets in individuals who were reassured that they were at low risk 0.92 (0.64 to 1.31) compared to 1.69 (1.21 to 2.36) for those in the highest age gap quintile[34]."

4. Adding further analysis to the section on Lipid lower medication prescribing in the results:

Four RCTs reported changes in lipid lowering medication. One in which risk scores were provided to physicians blinded to the trial showed at 42% increase in the probability of having a change in lipid lowering medication amongst all patients but this was not statistically significant (p=0.29). In the same study patients with a CVD risk >20% were twice as likely to have their medication changed when physicians were presented with the risk score (RR 2.32 (1.01 to 5.29), p=0.03)[32]. The other three trials reported the difference in the number of new prescriptions for lipid lowering medication. Two gave risk information to physicians treating patients with HIV[31], or patients with CVD risk >20% or raised LDL[28] and one to patients with a CVD risk >20%[29]. When pooled there was RR of 1.35 not achieving statistical significance (p=0.08, I^2=0%) (Figure 5) but when only those studies including participants with CVD risk > 20% or raised LDL are pooled there is a significant increase in initiation of lipid medication (RR 1.83 (1.13 to 2.98)) which increases to 2.11 (1.27 to 3.49) when only the two studies providing risk information to physicians are included.

5. Adding the following interpretation of these findings and reference to the fact that, as you say, it is entirely reasonable that people below the threshold for treatment would not have their treatment intensified in the discussion:

"The effect of the provision of risk information on intermediate measures of CVD and modelled CVD risk was more consistent with studies consistently showing reductions in cholesterol, systolic and diastolic blood pressure, and modelled CVD risk. Whilst the effect sizes are small, they may be of clinical significance at the population level and those studies including only high risk participants showed significant reductions in cholesterol and systolic blood pressure. It is possible these effects are mediated through changes in prescribing: although only on the border of statistical significance, patients were 1.4 to 1.5 times more likely to have a change of lipid lowering or blood pressure medication when risk information was provided to their physicians and this increased to over twice as likely when only those with a CVD risk >20% were included. This difference in prescribing is not unexpected. Guidelines for prescribing lipid lowering and blood pressure medication are based on assessment of CVD risk

and so the increased prescribing for those at high risk likely reflects a greater number of physicians following existing guidance and the smaller effect in those studies including low risk participants the effect of including participants in whom no change in treatment would be expected."

3. In the same way, providing CVS risk estimates to patients is more a form of shared decision making and it may not necessarily follow that a patient wishes to take advice/recommendations about their level of CVS risk in terms of intensification or not. Patients may be risk averse to the consequences of getting a CVS event and may then take medicines at a lower CVS risk; alternatively the patient may have a "high" CVS risk and exceed the recommended treatment threshold but may be risk-averse to being on lifelong medical (BP and/or statin) treatment. More critical discussion about these issues in the context of the findings from the systematic review would be welcome.

We also agree that patient choice is an important consideration and that, as you describe, the decision to start treatment or make lifestyle changes is a complex process with the level of risk that patients consider 'high' differing between individuals. To address this we have added the following text to the discussion:

"Trends towards small reductions in cholesterol and blood pressure were also seen in studies in which risk information was only provided to patients. This highlights the central role patients have in making decisions about their treatment and the impact their risk perception and views about preventive medicine have on the outcome. Whilst some may be risk averse and start medication at low risk levels, we know from existing literature that many patients are reluctant to start medication with 5% of people on the streets of London stating that they would not take a statin even if it gave them another five years of life[47] and people responding to a US based internet survey prepared to pay an average of $1445 (£948; €1265) to avoid taking one pill a day for cardiovascular disease prevention[48]. The impact of provision of risk information is, therefore, complex and is likely to reflect a combination of factors from initial risk perception, peer comparison, beliefs about the disease, and to-date unmeasured effects such as medication adherence."

4. Missing RCTs. I have been involved in an RCT that seems to meet the inclusion criteria of the systematic review. This RCT provided risk estimates to GPs and had a modest impact on intensification of BP lowering medicines and BP control. See:
Montgomery A, Fahey T, Peters T, MacKintosh C, Sharp D. Evaluation of a computer-based clinical decision support for the management of hypertension in primary care: a randomised controlled trial. BMJ 2000; 320: 686-690. PMID: 10710578

We did review the RCT you mention when screening papers for inclusion. The reason we did not include it was that it was not possible to separate the data from the patients without existing cardiovascular disease from those with existing disease and one of our inclusion criteria was the inclusion only of participants with no history of cardiovascular disease. To make this clearer we have amended the exclusion criteria to now read:

"We included studies that met the following criteria: (1) primary (randomised and non-randomised) studies published in a peer reviewed journal; (2) inclusion of participants with no history of CVD; (3) intervention strategy consisted of provision of a CVD risk model estimate to either physicians or patients (i.e. not just providing a means by which physicians or patients could calculate CVD risk score); and (4) the only difference between the intervention group and control group (or the only intervention in the case of before-after studies) was the provision of a CVD risk model estimate. Observational and qualitative studies, studies calculating CVD scores for the secondary prevention of CVD or including both primary and secondary prevention where it was not possible to separate out the primary prevention group, and conference abstracts, editorials, commentaries, letters and reviews were excluded."

Reviewer: 2

Reviewer Name Alex McConnachie

Institution and Country Robertson Centre for Biostatistics, University of Glasgow, Scotland
Please state any competing interests or state 'None declared': Non declared

Please leave your comments for the authors below Usher-Smith et al present a systematic review of studies that assess the impact of providing CVD risk estimates to patients and/or professionals. This review is mainly concerned with the statistical aspects of the paper.

Overall, I found the paper to be very readable. I think that the background and methods are well described. The authors have been quite inclusive in their review, and consider a wide range of different study designs and outcomes. The result is that none of the meta analyses includes more than a handful of individual studies, and for the majority of endpoints, they are left to give a descriptive summary of the results. Given this, I think that the authors have done a good job of presenting what could have been quite turgid results in a fairly engaging manner.

The only thing I would suggest is to go through the paper carefully and proof-read it. One thing I spotted was in the third line of the blood pressure results section on page 11, which speaks of a "...difference in mean difference in change in SBP or DBP." Is there one too many difference in this sentence?

> Thank you for your support of our work and for highlighting this typographical error. As you suggest, it should read "..difference in mean change in SBP or DBP." and we have corrected this in the resubmitted version. We have also carefully proof-read the article again.

From a statistical perspective, the methods used are appropriate and clearly presented. They have kept things simple, which is fine given that the meta analyses are not the main focus of the review.