Reviewer’s report

Title: Deprescribing Preventive Cardiovascular Medication in Patients with Predicted Low Cardiovascular Disease Risk in General Practice - The ECSTATIC Study: A Cluster Randomised Non-inferiority Trial

Version: 0 Date: 07 Nov 2017

Reviewer: Rob Van Marum

Reviewer's report:

This is a well written manuscript on a relevant topic.

This is one of the first large studies in this field and the authors have made considerable effort to make this study a success.

I do have some remarks:

1. It remains unclear why the authors chose to study deprescribing of CVD in a relatively young population with very low CV risk. As I read it now, all participants did not fulfil guideline criteria for primary prevention. Is it justified to conclude that all participants received off-label antihypertensive medication and/or cholesterol lowering therapy? If so, we can expect that stopping medication will not lead to increased morbidity or increased 10-year risk. It's just stopping unjustified medication. This makes the rationale for this study less relevant. Or perhaps the focus should have been: is it possible to deprescribe medication for which no indication exists, but that has wrongfully been prescribed earlier?

2. I would like more explanation on why elderly patients >70 years were excluded. In the introduction, the authors justify their study by referring to polypharmacy as topic in the elderly.

3. The calculated 10 year risk as primary outcome is a little weak (as they also recognize in their discussion) but I can understand why the authors choose this outcome. It would have been interesting to know what the actual effects on CV events would be after 10 years. In a low risk population, you can't expect a lot of CV events within 2 years.

4. The risk of adverse events increases with age, so in this young population, one can't expect that stopping drugs will do much on prevalence of adverse events or QOL. Why the focus on ADR's as rationale for deprescribing in this population?
I don't consider raised blood pressure or increased cholesterol levels adverse events. These are just expected effects of stopping the drugs.

5. Given the fact that these patients shouldn't be treated with CV drugs, the fact that only 27% persisted in quitting is remarkable. Please elaborate more on this. Why did 73% of the patients that were willing to deprescribe restarted? What were barriers to successful deprescribing?

6. Please make clearer why the authors choose to use the PP analysis and not the ITT analysis as primary outcome.

7. Why are body mass index, waist circumference, body weight, smoking behaviour, physical activity, fruit and vegetable intake and alcohol consumption outcomes and not determinants?

8. The authors conclude: "However, an attempt to deprescribe may be considered in low CVD risk patients, e.g., during their routine (yearly) cardiovascular check-up and as the result of a shared decision between a doctor and his/her patient." And: "In conclusion, a structured deprescribing strategy for all patients with low CVD risk in general practice is not recommended because of its low adherence (27% persistent quitters) and low gains in quality of life" Shouldn't the conclusion be that these patients are treated against all guidelines and that continuation of therapy is medically unjustified?

9. You can't say the attempt was safe compared to usual care based on a predicted 10-year outcome alone without knowing 10 year ADR prevalence (454-457). Safety was only monitored for 2 years

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

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I recommend additional statistical review

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