Reviewer’s report

Title: The effect of hormone replacement therapy on all cause and cardiovascular mortality in women with chronic kidney disease: protocol for a systematic review and meta-analysis

Version: 1
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Reviewer: Caroline Main

Reviewer’s report:

General comments
1. In the general medical literature the term “hormone replacement therapy” (HRT) has been replaced by “hormone therapy” (HT) as the older term infers that hormone therapy is replacing the function of a defective organ. Hormone therapy (HT) is now the preferred term for this intervention. (Discretionary Revision)

Background
2. Page 4: ESKD (End-Stage Kidney Disease) needs to be written in full time first time. (Minor Essential Revision)
3. Page 4; Para 3; line 4: “In contrast to healthy women[27], women with ESKD have similar mortality rates compared to men[28-30]”. Does this refer to CV or overall mortality, and are these age matched controls? Could the authors please clarify? (Minor Essential Revision)
4. Page 4; Para 3; line 6: “compared older women”. Addition of with needed. (Minor Essential Revision)
5. Page 5; Para 1; line 9: “In amenorrheic women with CKD, estrogen therapy has favorable effects on atherosclerosis risk parameters”.

It would be useful for clarity to state which parameters. (Minor Essential Revision)
6. Page 5; Para 2; line 1: “Although a recent meta-analysis of postmenopausal hormone therapy in healthy postmenopausal women found no evidence of cardioprotection”.

It should be noted that 8 out of 13 of the trials included in this review were in secondary prevention, and therefore participants had established CV disease having undergone a previous CV event (revascularization procedure, MI or TIA, angina or thrombo-embolic event, PE or DVT) and were therefore high risk CV populations. (Minor Essential Revision)

7. Page 5; Para 2; line 10: “and to determine whether age at
administration of hormone treatment modifies outcomes”.

Surely it is the underlying level of atherosclerosis potentially mediated by severity or length of CKD that is that likely to impact upon CV mortality/morbidity, rather than age? I assume the authors are using age as a proxy for underlying atherosclerosis, but am unclear as to how they envisage this relationship to be having stated in the background that “women with ESKD <45 years of age have a higher risk of cardiovascular mortality compared older women with ESKD”.

However, it is well established that older women with later onset ESKD will also have a higher base line risk of CV events, due to age related atherosclerotic processes, and therefore using age as a proxy for baseline CV risk appears to be overly simplistic. Could the authors please clarify the supposed relationship between age and outcome, and how this is mediated. (Minor Essential Revision)

Methods

8. PECOD Questions used for the review:-

Population: Women with Chronic Kidney Disease (as defined by eGFR or presence of kidney damage)

Could the authors clarify whether studies of participants with other co-morbidities will be eligible for inclusion? If so, do they intend to conduct sub-group analysis with participants stratified according to baseline level of CKD or presence/absence of other co-morbidities?

Exposure: Hormone Replacement Therapy (HRT) (all types of HRT including estradiol alone or estradiol and progesterone)

The route of administration needs clarification. Does this include only oral HT or HT delivered via patches, tablets, creams, troches, intrauterines device (IUD), vaginal rings, gels or injections as well? There are significant differences between oral and transdermal estrogens in terms of hormonal bioavailability and metabolism, with implications for clinical efficacy, potential side effects, and risk profile. If the authors intend to include all routes of administration of HT in the review, how do they intend to quantify the differences between administration routes in their analysis? Could this please be clarified?

Comparator: Placebo or No HRT: No comments

Outcome: All cause and cardiovascular mortality.

The stated outcomes of interest are inconsistent within the protocol. In some places it is stated that all cause and cardiovascular mortality will be assessed, and is some cardiovascular morbidity is stated in addition. If CV morbidity of interest, it needs to be stated how this is defined.

Design: RCTs and cohort studies. This is not consistent both between different parts of the protocol and the methods used to construct the electronic search. The abstract and the PECOS bullet points in the text state RCTs, cohort studies
and case-control studies will be eligible for inclusion. Table 1 indicates that only RCTs and cohort studies will be included. Case control studies are not of a suitable design to address the review question and therefore should be removed from the inclusion criteria. (All above Major Compulsory Revisions)

9. Electronic search

The search strategy in Table 2 is comprehensive and appears complete. Line 60 however is redundant given the patient population. (Minor Essential Revision)

10. The Medline search is from 1950 to 2014; have the authors considered the impact of changes in diagnosis and definition of CKD within this time period. Much of the older literature may be redundant in relation to the present patient populations. It may therefore be more economical to consider searching from only 1980 onwards to be consistent with the EMBASE search. (Discretionary Revision)

11. It is unclear why two separate searches need to be conducted.

The first search will yield studies of women with CKD who are treated with or without HT.

The second will yield studies of HT (in any patient population) which report CV outcomes. These have then been limited to RCTs.

Given the stated inclusion criteria, search 2 appears to be redundant. For efficiency search 1 should be combined with the outcomes stated in search 2 (without limits to RCTs) in order identify the relevant literature. (Minor Essential Revision)

12. How will the authors handle the management of the electronic searches and in what software? This needs to be explicitly stated. (Minor Essential Revision)

13. Identification of Articles for Eligibility

Initial screening

Could the authors clarify the meaning of a ‘calibration’ exercise, as it is unclear what this means within this context. (Discretionary Revision)

14. Identification of Articles for Eligibility

Initial screening

The authors need to refer to the initial PECOD criteria for both the initial electronic title and abstract screening and full-text screening. The inclusion criteria for both stages need to be consistent in order for the review to be reproducible. (Minor Essential Revision)

15. Data synthesis and analysis

More details needs to be provided in the section. Is the HR or RR for all cause mortality, CV mortality and morbidity of primary interest, and if both are reported
what methods do authors intend to use to combine both HR’s and RR’s?

How will the level of magnitude of heterogeneity between trials be assessed?

Are the authors intending to undertake sub-group analyses to assess the impact of clinical heterogeneity? If so these need to be stated a priori.

References for publication bias need to be added. (Discretionary Revisions)

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests