Author's response to reviews

Title: Why do Hypertensive Patients of African Ancestry Respond Better to Calcium Blockers and Diuretics than to ACE Inhibitors and beta-Adrenergic Blockers? A Systematic Review

Authors:

LIZZY M BREWSTER (L.M.BREWSTER@AMC.UVA.NL)
YACKOOB K SEEDAT (seedaty1@gmail.com)

Version: 3 Date: 28 January 2013

Author's response to reviews: see over
Amsterdam, 25 January 2013

Dear Madam,

Thank you for considering our work for publication in your esteemed journal. We are also grateful to the reviewers, for the time spend reading the manuscript and their useful comments.
As requested, a point by point reply to the reviewers is attached, as well as a manuscript with the changes ‘tracked’, and a ‘clean’ version.
Hopefully, the paper is now eligible for publication,

Yours faithfully,

On behalf of Prof. Y.K. Seedat,

Lizzy Brewster, MD, PhD
Hypertension Group
Depts. of Internal and Vascular Medicine, F4-222
Academic Medical Center, University of Amsterdam
Meibergdreef 9, 1105 AZ Amsterdam
The Netherlands
Tel: *31-20-566 3039; Fax: *31-84-872 3752
E-mail: l.m.brewster@amc.uva.nl
Web: www.amc.nl/hypertension
Reviewer's report

Title: Why do Black People Respond Better to Calcium Blockers and Diuretics than to ACE Inhibitors and beta-Adrenergic Blockers? A Systematic Review

Version: 1 Date: 5 December 2012
Reviewer: Keith C Ferdinand

Reviewer's report:

Major compulsory revisions:

1. Clearly define operational definitions or terms. The title should reflect these definitions. For instance, there are no "black people", consider black patients, or sub-Saharan blacks or persons of African descent, and for major papers clarify in U.S. or African Americans or South, or Africans. Lumping all studies as blacks is problematic.

2. Clarify that race is usually used for blacks (FDA) although Johnson paper Circulation 2008 uses ethnicity—each cited paper may use different terms?

3. The significant limitation of these demographic terms should be highlighted.

4. Black "people" should be avoided as a term.

Reply

We thank Prof. Ferdinand for this his willingness to review our manuscript and his important comment. We realize this is a very important topic, with different countries having different nomenclature for the ill-defined social construct of ethnicity or race.

As the reviewer rightly suggested, we changed the term ‘black people’ throughout the manuscript were possible into ‘persons of African ancestry’ and added text on the significant limitations of these terms (Please view the manuscript with tracked changes).

5. Clarify grams sodium in "salt" discussion vs. low salt, high salt, etc.

Reply

We added grams of sodium, throughout the manuscript where applicable, according to the suggestion of the reviewer.

6. Simplify discussion of genetics that have no significant finding of significance to focus and streamline the text.

Reply

We considerably shortened the text throughout the manuscript, where genetic studies yielded no significant findings.

Quality of written English: Needs some language corrections before being published

Reply

The manuscript was critically re-evaluated by a native English speaker.

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

Declaration of competing interests:

I have no competing interests.
Reviewer's report
Title: Why do Black People Respond Better to Calcium Blockers and Diuretics than to ACE Inhibitors and beta-Adrenergic Blockers? A Systematic Review
Version: 1 Date: 27 December 2012
Reviewer: Ferrán Catalá López

Reviewer's report:
Thank you for the opportunity to review this report entitled “Why do Black People Respond Better to Calcium Blockers and Diuretics than to ACE Inhibitors and beta-Adrenergic Blockers? A Systematic Review”.

This is a timely and well written review and the topic is of clinical importance in its field. The authors conclude, however, that “available data are inconclusive regarding why black patients display the typical response to antihypertensive drugs. In lieu of biochemical or pharmacogenomic parameters, self-defined black ethnicity seems the best available predictor of individual responses to antihypertensive drugs”.

When reading the title and the introduction I had the feeling the authors were seeking to answer the question above on clinical grounds, but from the description of the results I understood that their aim was much more exploratory and non-clinical in nature (PK/PD variations, pharmacogenetics), though, that keeps confusing me. Could you please revise?

Reply
We thank the reviewer for her kind words, and this important comment. Indeed we sought to answer a clinical question, why patients of African ancestry have a different, often decreased response to drugs, in the face of greater mortality from hypertension. To understand this, we felt the clinician needs information on the environmental, pharmacokinetic, pharmacodynamics, and other potential factors potentially affecting this response. Therefore, to us as authors, it was essential discuss also for example the question whether a decreased effect of beta-adrenergic blockade could be because of lower bioavailability. We understand the reviewer’s viewpoint of this being non-clinical, but we regard these data to be an integral of the potential explanation of the clinical differences. To make this more clear, we edited the text, and highlighted more the clinical implications, throughout the manuscript. (Please view the manuscript with tracked changes)

For example, at Page 6:
Was:
Pharmacokinetic variations considered included polymorphisms in cytochrome P450 family of enzymes
Became:
To answer the clinical question, why there was a difference in response between patients of African vs European ancestry, we considered pharmacokinetic variations including polymorphisms in cytochrome P450 family of enzymes

Methods: - Basically give more details of the search strategy, selection/inclusion criteria, databases servers, description of 71 reports (quality was assessed?) etc in the main text and/or incorporating a webappendix (please check PRISMA items). I would also suggest to give reason why complementary databases were not covered for unpublished reports/information (e.g. US FDA, European Medicines Agency)

Reply
We fully support the use of guidelines for a systematic review, and have used the PRISMA/QUORUM guideline in our previous systematic review meta-analysis on trials in hypertension, including scoring all papers on quality (Brewster, Ann Int Med). Unfortunately, the PRISMA guideline is not designed for narrative systematic reviews. To produce a rigorously conducted narrative systematic review, we used the “narrative synthesis approach”. This is a completely new format, and the recently developed methodology is applied when one expects considerable heterogeneity among the studies of interest.

Distinctively, a narrative systematic review includes a systematic search strategy (we now include the strategy in the text of the paper, including the databases, and including FDA and EMA searches, according to the suggestion of the reviewer).

The selection and inclusion criteria were depicted in detail in Figure 1 in the submitted version (Flow Diagram), accounting for every single of the +3500 citations with reason of in or exclusion. However, according to the suggestion of the reviewer, we now include more details in the text on the in-and exclusion.

The description of the 71 included papers as requested, is in the narrative data synthesis approach the main body of text, rather than a statistical summary of the findings of studies and statistical meta-analysis. In the narrative synthesis approach, this is done to preserve information and to yield a more detailed analysis of heterogeneous data with less loss of information (please see reference 13, Method section, submitted paper). Thus, we create the narrative summary that characterizes this new type of systematic review.

We followed the valuable suggestion of the reviewer, and added to the search the US FDA (n=2) and EMEA (n=229; censored at June 2012, to match the search in the other databases). We found only 1 eligible report in these databases. The review was edited throughout, to align with the addition of this newly included paper (text, figure 1, references). However, the conclusions of our paper did not change.

The apparent discrepancy in search yield of FDA and EMEA database led us to study whether we could have a better yield in FDA. However it appeared that FDA just returns more specific results than EMEA, with potential differences in the software of the web-based Search Engines. However, the yield in useful papers, none in FDA and 1 in EMEA was similar.

**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 have no competing interests.