Reviewer's report

Title: Correlation of Renin Angiotensin and Aldosterone System Activity with Subcutaneous and Visceral Adiposity: the Framingham Heart Study

Version: 2 Date: 24 October 2011

Reviewer: Gian Paolo GP Rossi

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In a large, community-based sample from the Third Generation Framingham Heart Study O'Seaghdha et al sought for correlations between indexes of the renin-angiotensin-aldosterone system (RAAS) and indexes of regional adiposity. At variance with previous studies that described a correlation between BMI and plasma aldosterone in salt-loaded normotensive individuals and in overweight and obese essential hypertensive subjects they found no correlation in either crude or covariate-adjusted analyses.

The manuscript is nicely organized and written, but unfortunately, albeit probably adequately powered, it is a negative study.

Strengths of this study entail the accurate CT-based method for assessing regional adiposity indexes and the large sample size. Unfortunately the latter is not a valid surrogate for the poor patients preparation at the time of RAAS measurement and for paying no attention to major determinants or renin and aldosterone.

Major Compulsory Revisions

In my view a likely potential bias entails the facts that the indexes of the RAAS were not measured under the proper conditions as they should have. Moreover, no attention to ongoing pharmacological treatment and sodium intake, which are major determinant of renin and aldosterone, was given.

Hence, it is uncertain if the findings are real or just deriving from a poor study design.

In my opinion the Authors should report data on sodium intake and/or urinary sodium excretion and should confine their analysis to the patients without pharmacologic treatment. With this large sample size even after exclusion of the subjects not fulfilling tighter inclusion criteria they should be able to provide valuable data.

A further point regards the possibility, which was largely neglected in Introduction and Discussion, that factors other the component of the RAS can account for a secretagogues effect on aldosterone. For example, Adiponectin receptors were described in the human adrenocortical zona glomerulosa and some CTRPs were suggested to stimulate aldosterone in vitro (Wang et al Faseb J).
Minor Essential Revisions

Despite quoting an excessive number of references some more relevant references documenting a relationship between BMI and aldosterone are overlooked.

Some sentences are odd and need to be changed. For example, the sentence “Internal validity is supported by prior reports using these data, including associations with sodium excretion and pulse pressure,28 as well as the observation that increased aldosterone levels within the physiologic range increase the risk of incident hypertension in normotensive individuals” is unacceptable from the standpoint of validation of any assay.

Discretionary Revisions

Page 12.

The statement on page 12 “Larger studies in obese individuals with hypertension have generally failed to replicate this association between obesity and circulating RAAS components.” is not correct. I can recall at least two papers published in JCEM in 2008 that depicted a correlation between aldosterone and BW or BMI. The Authors should use their judgement to better select the relevant papers to be quoted.

**Level of interest:** An article of limited interest

**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'