Reviewer's report

Title: Scarcity of atrial fibrillation in a traditional African population: a population-based study

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Reviewer: Jared Magnani

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Koopman et al. present an analysis of the prevalence of atrial fibrillation (AF) as identified by electrocardiography screening in a limited-sized (n=924) rural African, middle-aged cohort. Of the 921 individuals screened, only 3 cases of prevalent AF were identified. Electrocardiography data were combined with previous anthropometric measures and clinical assessments in the cohort, as well as with phlebotomy with measurement of biomarkers of inflammatory pathways (IL-6 and CRP) in a selection of the cohort (n=266). The investigators then compare the prevalence of AF risk factors (described by the authors as "traditional" risk factors) between this cohort and NHANES data. The authors attribute the low prevalence of AF to the absence of a Western lifestyle and the absence of chronic inflammation in their cohort. The analysis informs the epidemiology of AF in a non-Western country. It further informs the well-observed racial differences in the prevalence of AF in studies that are cited by the authors. The study is well written and concise. The chief problems identified by this reviewer are several important assumptions being made by the authors: the generalizability of their findings in a limited sized cohort; the relevance of two separate ECGs for AF detection; the relevance of comparing this cohort to NHANES data; the relation of the inflammatory markers to AF; and the attributions of causality with regard to risk factors and inflammation.

Major compulsory revisions are as follows:

1. Population-based. It is not clear how the authors are defining the cohort as being population-based. While there may have been some randomness with regard to the selection of participants, the term suggests that this cohort is representative of the population. No data are provided to support the assertion. There may be none, which does not limit the validity of the study but rather its generalizability. Data on AF prevalence in non-Western countries are informative and provide insight into AF epidemiology. However, Africa is an immense continent, there may be profound geographic differences across Africa, and the assertion of this being a population-based study may not be accurate.

2. NHANES comparison. To this reviewer the exercise of comparing selected risk factors for AF across two very different studies has and limited informative value. The methods between the two studies are very different. Validity (reliability and quality control) are not reported in the present study. NHANES in its current iteration does not report or adjudicate AF; in NHANES III individuals reporting a history of AF were even excluded from the ECG substudy. The effort to this
reviewer only affirms prior research in far larger non-Western cohorts and specifically Africa that selected risk factors for AF have less prevalence than in the NHANES or other US cohorts.

3. Termination and causality. The terminology of "traditional" risk factors lacks specificity and is ambiguous. The authors intend to describe established risk factors that have also been measured within their cohort. There are many established risk factors that are not measured or identified within this cohort, such as history of cardiovascular disease, valvular heart disease, family history of AF, hyperthyroidism, alcohol use. The selection of a limited number of covariates is problematic, because it ignores other potential risk factors that are not included. Residual confounding is a huge problem; maybe all 3 of the AF cases had hyperthyroidism or suffered from mitral stenosis. There is an implicit assumption in describing risk factors as "traditional" that they inform population-attributable risk for AF. More precise, less general terminology describing risk factors is suggested. One overall recommendation for the authors is to concentrate more on describing the present cohort, acknowledge its limitations, and report the findings without making comparisons across cohorts and hemispheres.

4. Generalizability. There are general uses of the term Western or non-Western throughout the description of the cohort and interpretation of the findings. The language and presentation tend to suggest that this cohort is generalizable to anything non-Western, and in turn that AF is defined in Western cohorts by the so-called "traditional" risk factors. The world is very diverse and while Western and non-Western differences exist, the cohort is restricted by number, geography, sampling and inclusion methods, etc. To pretend that 924 people can be compared to a global hemisphere is challenging.

5. Inflammation. Similar to the comment above, there are comments about the interpretation of the inflammatory biomarkers in the limited segment of this cohort that have CRP and IL6 measured. The investigation at present cannot comment on the "chronic inflammation" of the cohort. First, samples were measured at a single time point, and chronicity reflects longitudinal variability, while this study is cross-sectional. Second, the biomarkers were measured prior to the ECGs and identification of AF. Like any cross-sectional study, causality cannot be inferred. Third, the biomarkers are measured in a limited segment of the cohort. How individuals were selected for biomarker measurement, implicit biases, and how similar these individuals are to the remaining ~700 individuals is not described or discussed.

6. AF ascertainment. AF ascertainment is performed by two 10-second electrocardiograms. The authors acknowledge this as a limitation but assert that it is the "best" approach. The authors might qualify very carefully that this is the best approach available to their investigation. Other methods of cardiac rhythm monitoring are conceivable even in isolated, rural, resource-scarce cohorts.

7. Conclusions. The authors assert that the comparison of the epidemiology of AF in this study population with that in a Western population is imperfect but necessary. The validity of cross-cohort and societal comparison is questionable and problematic because it rests on tremendous generalizations that are outside
of the scope of the present investigation. In fact, in this reviewer's estimate, the presentation would be strengthened by simply reporting what was observed, rather than trying to establish differences in very different cohorts with highly contrasting selection and design.

**Level of interest:** An article whose findings are important to those with closely related research interests

**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.