Reviewer’s report

Title: Novel Association Patterns of Cardiac Remodeling Markers in Patients with Essential Hypertension and Atrial Fibrillation

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Reviewer: Iosif Kelesidis

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Atrial fibrillation is one of the most common arrhythmias. As the authors comment various factors, including atrial remodeling and inflammation, have been implicated in the pathogenesis and perpetuation of AF; nevertheless the exact mechanism still remains uncertain. The main findings drawn from their study were that increased MMP-2 is associated with paroxysmal whereas increased MMP-9 with permanent AF. Additionally, lower levels of TIMP-1 had a strong association with AF incidence.

The paper is well written and the results are potentially useful when considering potential biomarkers for atrial fibrillation. The paper could potentially be improved by providing more details in some parts as follows.

My comments by order of the section of the manuscript are below

Materials and Methods
1. Page 4 1st paragraph line 7:
All patients were under anti-hypertensive treatment with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) for at least a year from the moment of arterial hypertension diagnosis.

It has been shown that ACEI and ARBs are drugs that hinder inflammation. Given that the authors studied inflammatory biomarkers in patients with and without atrial fibrillation and hypertension it would be interesting to see if there was any difference in the dose of ACEI/ARB between patients with and without atrial fibrillation. Do the authors have any data on doses of ACEI? If yes it would be an interesting addition for tables 1 and 2.

2. Statistical analysis Page 6
In the authors’ definitions: “The first group consisted of subjects with symptomatic, paroxysmal AF of recent onset defined as spontaneously or pharmacologically terminated AF within a maximal period of less than 72 hours from arrhythmia onset. The latter was estimated based on patient recall of the onset of symptoms suggestive of AF, such as palpitations, shortness of breath and/or chest discomfort. The second group consisted of patients with permanent AF defined as sustained AF of more than six months in duration, without any intervening periods of SR that resisted to all attempts of SR restoration including pharmaceutical or direct current cardioversion".
The authors state that in patients with permanent AF there were no intervening periods of SR. How was this determined? Are there any Holter or loop recorder data for these patients or these patients were defined by follow up ECGs in the clinic?

Results and Discussion

3. The authors conclude that “Serum paroxysmal AF was associated with higher MMP-2 levels compared to either SR or permanent AF (p<0.001 for both comparisons) whilst paroxysmal and permanent AF patients had higher MMP-3 than SR (p<0.001 for both comparisons). Matrix metalloproteinase-9 but not MMP-3 was higher in permanent compared to paroxysmal AF group (p<0.001)”.

In the discussion (page 13, paragraph 2) the authors explain clearly in a well written paragraph why they believe paroxysmal AF was associated with higher MMP-2 levels and they state that “It could be considered, therefore, that MMP-2 can emerge as a molecule that can act on a far quicker time-scale in response to subtle cellular changes like those during initial stages of AF and contribute to early atrial stunning and contractile remodeling”. However, it is not clear from the discussion what could be a potential explanation for the higher levels of MMP-9 in patients with permanent AF. It would be a useful addition to the discussion session if the authors could elaborate more on this.

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'