Reviewer's report

Title: Brain Natriuretic Peptide Levels are Associated with Peripheral Arterial Disease in Type 2 Diabetic Patients

Version: 1 Date: 27 December 2013

Reviewer: Aldo Clerico

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To the Authors

General Considerations

Authors reported that the aim of this study was “to establish the prevalence of ankle-brachial index abnormalities and to assess the potential relationship between BNP level and peripheral arterial disease among outpatients with Type 2 Diabetes Mellitus”. BNP levels were measured in 507 diabetic patients, 138 of whom had peripheral arterial disease. Adjusted logistic regression models were used to determine the association between BNP levels and the presence of peripheral arterial disease. Moreover, ROC curves were plotted to determine the accuracy of BNP levels in the assessment of the presence of peripheral arterial disease. Authors concluded that the results of this study indicated that higher BNP levels were significantly associated with a higher prevalence of peripheral arterial disease in diabetics, suggesting the potential of BNP as a screening tool for the presence of peripheral arterial disease.

This study reports some interesting and (almost in part) original results. However, I have some specific points, including both concerns and suggestions, to address to the Authors in order to improve the scientific message of this article.

Specific Points

1. The pages are not numbered; therefore, an accurate review of this manuscript is very difficult to do.

2. Abstract. Authors should report a clear and specific aim of the study in the Abstract.

3. Authors should provide an index of the (non-standard) abbreviations used in the manuscript.

4. Background. Authors reported that: “Brain natriuretic peptide (BNP) ... is secreted predominantly from the ventricular myocardium in response to increased ventricular wall stretch [3]”. This reference [3] is very old (i.e., 1993). Authors should update this sentence, according to a more modern vision of the cardiac endocrine function. Some authoritative revisions of the more recent acquisitions on the physiological role and clinical utility of the BNP system has been recently published (for example: Clerico A. et al. Am J Physiol Heart Circ Physiol 2011; 301: H12-20). Furthermore, Authors should revise the Background and Discussion sections of the manuscript according to these more recent
acquisitions concerning the pathophysiological role of the cardiac endocrine system, which better explain the results obtained in this study.

5. Patients, inclusion/exclusion criteria. Authors should better describe how the presence of cardiac systolic and diastolic dysfunction as well as of asymptomatic coronary artery disease was excluded in the patients enrolled in the study. Indeed, Authors reported that patients with cardiac systolic and diastolic dysfunction were excluded by means of echocardiography evaluation; however, Authors reported in Table 1 that mean left ventricular ejection fraction values were 58.4±16.2 and 54.7±14.9 in the two groups of patients, respectively. From these data, I would assume that some patients had less than 40% of left ventricular ejection fraction, and so these patients should have heart failure with reduced ejection fraction according to the more recent international guidelines (Yancy CW et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 62: e147-239). Authors should clearly report whether they have assessed the presence/absence of cardiac diastolic and systolic dysfunction according to the international guidelines.

6. Patients. Authors reported that “subjects using any vasoactive drug” were excluded. The term “vasoactive drug” is not clear (almost for me). Authors should specify this type of drugs. Authors should report whether the diagnosis of arterial hypertension were made according to the more recent international guidelines (Mancia G. et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. Eur Heart J 2013; 34:2159-219).

7. BNP peptide assay. The recommended international units for BNP assay are ng/L, not pg/mL (Apple et al. Clin Chem 2005; 51:486-93). Authors reported that the normal reference range for the ADVIA Centaur method is < 100 pg/mL (i.e., 100 ng/l), but some recent results suggest that the decisional level for this method should be lower (Clerico A. et al. Clin Chim Acta 2012; 414: 112-9).

8. Statistical analysis. Authors reported the significance of statistical tests both with < 0.05 (or p < 0.01) and the exact p value (for example, p=0.021). This may generate confusion in the reader. I suggest that Authors should report only the exact value of p, when this is less than 0.05, while Authors should report that test results are not statistically significant when p > 0.05.

9. Discussion. The data reported in Table 1 suggest that patients with PAD had more frequently higher HbA1c levels, hypertension, hyperlipidemia, and were more frequently aged, smokers and treated with RAAS blockade and calcium channel blockers (even if the statistical analyses reported are not all significant). These data, taking as a whole, indicate that patients with PAD have higher BNP levels because the cardiac endocrine function is more activated in these patients rather than in patients without PAD (see: Clerico A. et al. Am J Physiol Heart Circ Physiol 2011; 301: H12-20). As also reported in the most recent international guidelines, BNP levels are the most powerful predictor of cardiovascular events in general population as well as in patients in all stages of heart failure (from stage A to stage D) (Yancy CW et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology...
Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 62: e147-239). Natriuretic peptides (such as BNP) are hormones with a protective action on endothelial function, but BNP, if used as biomarker of cardiovascular risk, is a powerful index of mortality and adverse cardiovascular events. Accordingly to these considerations, the results of this study indicate that patients with PAD had higher BNP values (than patients without PAD) and so they are at increased risk of major and adverse cardiovascular events even in the short term period.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interest or financial relationship to this paper. I have received no reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript.