Reviewer's report

Title: Diagnostic accuracy of plasma NT-proBNP levels for excluding cardiac abnormalities in the very elderly

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Reviewer: Thomas Mueller

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Summary:
This is a study on the diagnostic accuracy of NT-proBNP plasma concentrations for the detection of structural and functional cardiac abnormalities in very elderly patients. The authors used a convenient sample of 80 patients with the age of 90 years who were derived from the Leiden 85-plus study. The authors found associations of NT-proBNP plasma concentrations with various structural and functional cardiac abnormalities. In addition, they found increasing NT-proBNP plasma concentrations with a greater number of echocardiographic abnormalities. Applying ROC curve analyses, the areas under curve of NT-proBNP were between 0.68 and 0.85 for various echocardiographic abnormalities with high sensitivities but rather low specificities for the chosen cut off value (i.e., the upper limit of the lowest NT-proBNP tertile which was 270 pg/mL). Therefore, the authors concluded that NT-proBNP is a marker for ruling out echocardiographic abnormalities in very elderly patients. They further argue that increased NT-proBNP plasma concentrations thus indentify patients who need to be referred for further cardiovascular examination.

Comments:
1. It is not clear of whether the present work is a prospectively conducted sub-study of the Leiden 85-plus study or a retrospective analysis of the previously described cohort? In other words, did the authors intend to study the diagnostic accuracy of NT-proBNP for echocardiographic abnormalities in individuals with the age of 90 years before starting enrolment of patients into the Leiden 85-plus study in 1997, or was this a post hoc decision?

2. When did the authors perform echocardiographies and NT-proBNP measurements in their patients?

3. The aim of this study is not appropriately defined. I do not know of whether the authors studied symptomatic or asymptomatic patients with respect to cardiac disease. I suppose the authors are aware of the recent ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult.

One possibility is that the authors aimed at detecting patients progressing from stage A to stage B of the heart failure pathway. Thus, the rationale of this study would have been to evaluate NT-proBNP as a screening test to be performed before echocardiography. As a consequence, the authors should have enrolled...
only patients who were asymptomatic and in whom no evidence of structural/functional heart disease was evident from the patient history. Is this true for this study? The relevant information on these issues is missing in the present manuscript. For example, the authors described a significant proportion of patients with well known cardiac diseases. Those same patients should have had an extensive cardiac evaluation (including echocardiography) before inclusion into this study.

Another possibility is that the authors studied patients symptomatic for heart failure (e.g., patients with acute dyspnea). Thus, the rationale of this study would have been to evaluate NT-proBNP as a tool to differentiate between cardiac and non-cardiac causes for the patients’ symptoms. If this is true, asymptomatic patients must not be included in such a study.

The approach of the authors to include both symptomatic and asymptomatic patients as well as individuals with and without well known cardiac diseases is not convincing for me. Thus, the authors are advised to clarify the exact study hypothesis (null hypothesis H0 vs. alternative hypothesis H1). According to this study hypothesis the whole results section should be rearranged. The authors should stick to their proposed message (i.e., study hypothesis). Therefore, unnecessary results such as extensive description of data not being related directly to this issue should be deleted in a revised version.

4. It is clear that the index test of this diagnostic study is NT-proBNP. However, the reference standard(s) of this study is(are) not clear as well. The authors state that they aimed to exclude structural and functional cardiac abnormalities by NT-proBNP measurements. In the results section, last paragraph they describe that they calculated the test performance of NT-proBNP to exclude 3 or more echocardiographic abnormalities. Does this make sense from the clinical point of view? Usually, at least in younger patients, an index test such as NT-proBNP should be used to exclude any structural or functional cardiac abnormalities (i.e. choosing a cut off value with a high negative predictive value). This is important, because even conditions with only one structural or functional cardiac abnormality should be detected by an extensive cardiac evaluation (including echocardiography) in order to initiate the adequate treatment. Therefore, I cannot understand the authors are satisfied to find 3 or more cardiac abnormalities by their approach. What is the therapeutic consequence of such a strategy?

5. In asymptomatic patients, a variety of structural/functional cardiac diseases can be detected by echocardiography such as systolic or diastolic dysfunction, left ventricular hypertrophy, wall motion abnormalities, pulmonary hypertension, valvular abnormalities, left atrial dilatation and left ventricular dilatation, etc. Each of these conditions may be an indicator of increased intracardiac pressure and might thereby increase NT-proBNP plasma concentrations. Consequently, NT-proBNP plasma concentrations depend on the severity of each condition and also on the number of eventually coexisting conditions. Thus, it is not appropriate to perform correlation analyses or ROC curve analyses of NT-proBNP with each condition in patients with more than one structural/functional cardiac
abnormalities (Table 3 and 4) and it is also not appropriate to describe a relationship between NT-proBNP and number of structural/functional cardiac abnormalities without adjusting for the severity of each condition (Figure 1) (e.g., severe aortic stenosis alone definitely rises NT-proBNP to a greater extend than coexisting mild left ventricular hypertrophy and wall motion abnormality). Instead, the authors should stick to multivariable analyses (i.e., logistic regression analyses with NT-proBNP as the dependent variable and echocardiographic findings as independent variables) in order to account for the complexity of the situation.

6. No information is given on, e.g., arterial hypertension or diabetes mellitus. These conditions are also known to be associated with increased NT-proBNP plasma concentrations. So, how did the authors correct their results for these conditions?

7. The description of the patients’ medications is missing in the manuscript (especially as they are mentioned as confounding variables).

8. In the description of the index test (i.e., NT-proBNP) information on how long the plasma samples were stored before analysis is missing. What about analyte stability in this context? What was the specimen type (EDTA plasma, heparin plasma)? Usually NT-proBNP is measured in serum (according to the package insert)!

9. In the methods, the authors describe that 82 patients with 90 years of age were invited for echocardiography. All but one underwent echocardiography, this makes 81 patients. In the results the authors state that they had 80 patients for analysis. What about one missing patient?

10. It is unclear why the authors sometimes used gender-specific cut off values (Table 3) and sometimes not (Table 4).

11. In the discussion, third paragraph, the authors describe: “The present study confirms that low plasma NT-proBNP levels are most efficient in excluding echocardiographic abnormalities. Moreover our study shows NT-proBNP is related to the severity of cardiac disease and might be used to indicate who needs to be referred for further cardiovascular examination including echocardiography”. According to my previous comments, this statement is definitely overenthusiastic!

**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