PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The potential role of NT-proBNP in screening for and predicting prognosis in heart failure: a survival analysis.
AUTHORS	Taylor, Clare; Roalfe, Andrea; Iles, Rachel; Hobbs, Richard

VERSION 1 - REVIEW

REVIEWER	Jay N. Cohn University of Minnesota Minneapolis, MN
REVIEW RETURNED	16-Feb-2014

GENERAL COMMENTS	Authors have echo data on all patienhts. Paper would be strengthened by analysis of usefulness of NP-ProBNP data vs. or in addition to echo data. Additional analysis of echo data would strengthen paper and should be encouraged

REVIEWER	Borut Jug University Medical Center, Ljubljana Slovenia
REVIEW RETURNED	24-Feb-2014

GENERAL COMMENTS	**Overall appraisal** This is an interesting paper exploring the potential of NT-proBNP as a diagnostic and prognostic marker in diverse cohorts, including i) a general adult population from 16 general practices (original ECHOES cohort), ii) patients with previous diagnosis of heart failure by GP, iii) patients on diuretic therapy and iv) patients at high cardiovascular risk. The paper adds important information to physicians managing heart failure patients (or individuals with suspected heart failure) in the primary care setting; it follows the STROBE statement and is overall well-written. **Major comment** The long-term follow-up (10 years) represents a major strength, but also a major limitation of the study. The long-term follow up provides enough endpoints to make sound prognostic assumptions despite

the relatively small sample (sub study included <10% of the ECHOES cohort); however, both heart failure diagnosis and management have changed significantly over the past decade and this should be emphasised when discussing the results.

1. In terms of heart failure diagnosis, it was based on the ESC 1995 guidelines and thus focused on reduced ejection fraction (HF-REF), and atrial fibrillation and valve disease. Although some patients with preserved ejection fraction might have been included in the later two categories, HF-PEF was not a widely recognised diagnosis at the time. Reinforcing the notion that the study focused on HF-REF, most of the patients in the heart failure-labelled group had ischemic heart disease (table 1: 69% of patients had either angina or MI) which is usually associated with HF-REF. This probably also explains a somewhat unusual finding that hypertension emerged as a »protective« factor against heart failure (table 3, OR for hypertension to predict heart failure 0,39). I believe these findings along with the issue of evolving diagnostic criteria for heart failure deserve a paragraph in the discussions section.
2. In terms of heart failure prognosis, heart failure patients seemed to fare better than in previously reported community-based cohort studies (e.g. Framingham or Rotterdam cohorts). Should this be attributed to a low overall risk in the studied population, to the introduction of life-prolonging therapies (at baseline in 1999, only 50% of patients were on an ACE inhibitor or an ARB) or to referral bias (i.e. patients diagnosed with heart failure in the study were referred for appropriate management)?

Additional comments

1. In terms of the studied cohort, the pooling of four categories seems reasonable (i.e. reflecting fast and rational real-life clinical categorisation of individuals), but I would ask the authors to better define how categories were selected. In the original paper by Davies et al (Lancet 2001) only the general cohort was described in detail (i.e. selection of practices, screening, and number of responders). Were the categories constructed afterwards or added as part of a study extension? How was the diuretic group defined (85% of patients in this group were taking diuretics, though I would expect 100%)?
2. Cardiovascular death was defined by the Office of National Statistics. Though a reasonable means for providing such information, it can be highly biased. Along with possible report bias of cause of death, lack of interim and non-fatal endpoints (hospitalizations being a major concern in heart failure patients) should be discussed/pointed out.
3. Along with AUC; sensitivity and specificity data, positive and negative predictive values (as prevalence of heart failure varies significantly in the four cohorts) and accuracy (possibly in a table) would be welcome.

Minor comments:

1. Table 1: according to table, 17 patients in the heart failure

	group with NT-proBNP ≥150 mg/ml (n=82) were taking diuretics; this does not add up to 85%!
	2. Table 2: is there a need for mean and SDs – NT-proBNP has a skewed distribution (shown by SDs larger than the mean) and is usually reported in median and IQRs?
	3. Table 4: Sex should be specified (I assume it is male sex that is associated with worse prognosis) and table title should emphasize that it is the overall study cohort (not the general population). Also, quote table 4 in manuscript text.
	4. Abstract: line 15 NT-ProBNP should be spelled NT-proBNP, line 18 instead of (adjusted odds ratio=17.7 (95% CI 4.9-63.5) should be (adjusted odds ratio=17.7, 95% CI 4.9-63.5)

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 – Thank you for your suggestion. We are in the process of reporting echo and natriuretic peptide data from the ECHOES extension study and will submit this as a separate paper. This work was specifically examining the role of NT-proBNP in prognosis.

Reviewer 2 – Thank you for your summary comments.
Major comment:
1. We have added a paragraph to reflect change in HF definition and management in to the discussion, referencing the changing definitions and pointing out the HFREF/HFPEF issue.
2. We have added a paragraph on HF prognosis, highlighting the differences in survival, to the discussion.
Additional comments:
1. We have explained this more clearly in the methods.
2. We have added a paragraph in the discussion to address the limitations of cause of death reporting and absence of non-fatal outcomes.
3. We have added a table which summarises performance statistics (table 3).
Minor comments:
1. Thank you for noticing this. Our statistician has checked this and we have now corrected this error.
2. We agree and have removed mean and SDs.
3. Table amended as advised.
4. Changes to abstract made as suggested.