



STUDY PROTOCOL

REVISED **Diagnostic accuracy and clinical impact of natriuretic peptide screening for the detection of heart failure in the community: a protocol for systematic review and meta-analysis [version 2; peer review: 1 approved, 1 approved with reservations]**

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Abstract

Introduction: Patients diagnosed with heart failure in primary care have a better prognosis than those diagnosed in hospital. However, most cases are missed in the community. Recent attention has focussed on the potential of early detection through screening. Natriuretic peptides (NPs) are tested by GPs and used to rule out heart failure in patients presenting with symptoms. Evidence is now emerging that they may also have a role in screening but their accuracy in this context and the associated optimal thresholds, have not been established. The impact that NP screening would have on patients and health care systems also remains unclear.

Methods: We aim to undertake a systematic search of the following sources: Ovid Medline, Embase, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials. Screening, data extraction and critical appraisal will be carried out independently and in duplicate by two reviewers. We will include studies based in the community with >100 participants that recruited a screened population. We will not add a study design filter and there will be no language restriction. The primary outcome will be the sensitivity and the specificity of NP screening and optimal thresholds for screening will be explored. Outcomes of interest for the impact analysis will include mortality, hospital admissions and cost effectiveness. This protocol has been developed in accordance with guidelines from the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P).

Open Peer Review

Approval Status ? ✓

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Any reports and responses or comments on the article can be found at the end of the article.

Discussion: This systematic review will identify how accurately NP screen for heart failure in the community and explore where NP screening thresholds should be set. It also aims to summarise the clinical impact of this strategy. Together, these results should inform future interventions that may provide an alternative pathway to facilitate improved detection of heart failure in the community.

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Keywords

Heart Failure, Left ventricular systolic dysfunction, diastolic dysfunction, community screening, detection, natriuretic peptides, diagnostic accuracy

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REVISED Amendments from Version 1

This version includes the addition of co-author Dr Thomas Fanshawe, who contributed to data curation, formal analysis, methodology, software, writing (review and editing), visualisation, validation and supervision.

Any further responses from the reviewers can be found at the end of the article

Introduction

Heart failure (HF) is a common and debilitating syndrome and presents a significant burden both to patients and society. Emerging evidence suggests that patients diagnosed with HF in primary care have a better prognosis than those diagnosed in acute settings¹. However, detecting patients with HF in primary care is challenging². Recent research highlights missed opportunities to diagnose HF in primary care³ and suggests that the diagnosis is most often made in hospitals despite many patients presenting earlier in primary care with suggestive symptoms. Some patients may also delay consulting their GP or community health care professional. For example, patients with breathlessness may modify their behaviour rather than consult a clinician, and older patients may normalise their symptoms, considering them to be secondary to ageing⁴. Patients who do present often describe vague and non-specific symptoms such as fatigue and breathlessness, which can have multiple causes. This can result in inappropriate alternative diagnoses, such as attributing HF to a respiratory condition resulting in ineffective treatment and management.

Given the difficulties in diagnosing HF in the community, recent research has focussed on early detection. Community screening is one potential strategy, especially in those individuals with cardiovascular risk factors^{5–8}. In general, screening for HF meets many of the established criteria required of screening programmes⁹. It is clear that HF is an important health problem. Indeed, it is estimated that 40 million people worldwide are living with HF¹⁰. The estimated incidence rate rises from 1.4/1000 person-years in those aged 55–59 years to 47.4/1000 person-years in those aged 90 years or older¹¹. HF is associated with a high morbidity and mortality. Patients with HF have a lower five-year survival compared to people with most common types of cancer¹². Moreover, HF patients also have a ten-year survival of only 27%, compared to 75% for age-sex matched patients without HF¹³.

The natural history of disease progression in HF is well understood. An early, latent stage is recognised; this preclinical phase is termed left ventricular systolic dysfunction (LVSD) and can be asymptomatic¹⁴. Evidence suggests that identifying patients with LVSD early and commencing treatment with angiotensin-converting enzyme (ACE) inhibitors has been shown to reduce both incidence of HF and reduce rate of hospitalization¹⁵. Moreover, early treatment of high-risk individuals, even prior even to a diagnosis of LVSD, has been associated with reductions in the rate of HF associated

hospitalization¹⁶. It is important to note that the prognosis and treatment of HF due to diastolic dysfunction (DD), more recently referred to as HF with preserved ejection fraction (HFpEF), is complex and currently there is less evidence to support early intervention in this group.

Natriuretic peptides (NPs) are tested by GPs and used to rule out HF in patients presenting with symptoms, so it is possible that NPs may perform well in the screening context. Indeed, a recent randomised control trial demonstrated that NP screening and associated collaborative care reduced the combined rates of systolic dysfunction, DD and HF as well as overall hospital admissions¹⁷. This study did not measure the impact of screening on patient's quality of life and was also underpowered to measure any differences in mortality between control and intervention groups.

Screening with echocardiography alone is too expensive. However a screening strategy combining echocardiography with NP testing to stratify those at highest risk (who could then undergo echocardiography) would be more cost-effective^{18,19}. Indeed, this recommendation has been included in the recent Canadian Cardiovascular Society Guidelines and the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACCF/AHA/HFSA) guidelines although it does not yet feature in European guidelines^{20–22}. Despite this, there have been no recent systematic reviews in this area. Previous reviews on population screening with NP combined patients from community settings with those recruited from secondary care^{23–25}. Other systematic reviews have analysed the performance of NP to detect HF or LVSD in symptomatic, presenting patients^{26,27}, rather than looking at asymptomatic patients or have combined screening with diagnostic studies²⁴. There have been no systematic reviews to consider the overall impact of introducing NP screening for HF and to consider potential negative issues, such as overdiagnosis.

This systematic review will therefore provide an up-to-date summary of all the available evidence, focussing specifically on the diagnostic accuracy and clinical impact of NP screening for the detection of HF, LVSD and DD.

Research aims

The primary aim of this systematic review is to determine the diagnostic accuracy of NP screening for the detection of HF, LVSD and DD in the community. To clarify this question the following PIRT summarises the clinical question:

Population: Patients in community-based NP screening studies

Index test: NP tests (point-of-care or laboratory-based)

Reference standard: Echocardiography or cardiac MRI

Target conditions: HF, LVSD, DD

This systematic review also aims to assess the impact that NP screening may have on both patients and health care systems

and will therefore evaluate the clinical utility of this approach. The following PICO outlines the clinical question:

Population: Patients in community-based NP screening studies

Intervention: NP test (point-of-care or laboratory-based)

Comparison: Usual care (no NP screening)

Outcomes: mortality, overall prognosis, quality of life, NYHA class at diagnosis, hospital admissions and cost effectiveness

Methods

Protocol registration

This systematic review protocol has been registered in the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42018087498). This protocol has been developed according to recommendations from the Cochrane Collaboration²⁸. Checklists from the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement^{29,30} and the Joanna Briggs Institute^{31,32} have also been followed.

Definitions

In the literature, the term HF can have different meanings. For clarity, in this systematic review, the target condition HF refers to the European Society Cardiology (ESC) definition of HF that describes a clinical syndrome combining typical symptoms and signs plus evidence of structural or functional cardiac abnormalities, including elevated levels of NP²².

The term LVSD has also been used to describe different scenarios. It can be used to define an early or precursor stage of HF when there is impairment of the left ventricle, but patients may not yet have developed the clinical syndrome of HF and are therefore asymptomatic. Clinical HF that is due to a reduction in left ventricular ejection fraction (LVEF) may also be called LVSD. Therefore, in more recent guidelines, the term LVSD is also used to describe HF with reduced ejection fraction (HFrEF) when the ejection fraction is below 40%. The ACCF/AHA classify HF in a spectrum from stage A through to D, where A refers to patients at risk of HF and stage D refers to patients with refractory clinical HF. Stage B HF refers to structural heart disease without signs or symptoms of HF and traditionally LVSD would have been included in this category. In order to capture these different scenarios, we are using HF, LVSD and DD as our target conditions, but for the purposes of the review we will use the definitions specified by the included studies and the data will be extracted so that test performance at each ejection fraction can be analysed.

Eligibility criteria

Inclusion criteria

Study design. We will not add a study design filter, and there will be no language restriction. To assess diagnostic accuracy, included diagnostic accuracy studies will follow cross-sectional and case-control designs. For impact analysis, we expect a broader range of study designs to be included, including randomised controlled trials and observational studies (retrospective or prospective) including cohort studies.

Population. We will include studies of adult patients (aged 18 years or older). Some screening studies may only recruit patients who do not have a prior diagnosis of LVSD or HF whereas other studies may adopt a more pragmatic approach to screening (noting that the prior diagnosis is often unreliable). We will include studies with both these recruitment approaches as long as they are based in community settings and recruit a screened population, in contrast to patients that present with HF symptoms. We will only include studies that combine these populations if they provide accuracy data independently for each group.

We will only include studies that included more than 100 participants to avoid introducing bias from studies with small sample sizes. Patients at high risk of HF, will be defined as those who had at least one cardiovascular risk factor such as hypertension or diabetes or conditions known to cause HF such as ischaemic heart disease. Selected non-general populations, such as cohorts of patients who all have chronic obstructive pulmonary disease (COPD), will also be included in the high risk group as the overlap between COPD and HF is known to be high³³.

Intervention. To assess diagnostic accuracy the included studies will compare NP measurement with either echocardiography or cardiac magnetic resonance imaging (MRI) for target conditions of HF and LVSD. For impact analysis, included studies will quantitatively measure the impact of introducing NP screening for HF, LVSD or DD. Studies that also compare NP screening with other strategies such as electrocardiogram (ECG) will be examined. Studies that employed multi-faceted interventions (such as NP screening plus collaborative cardiology care) will be included but will be analysed separately.

Primary and secondary outcomes

To evaluate diagnostic accuracy, the primary outcome will be the sensitivity and the specificity of NP screening. Where possible, the optimal threshold of NP to maximise screening performance will be explored, although this is not an individual patient data analysis so this assessment maybe will be limited by the available data. Outcomes of interest for the impact analysis will include NYHA class at diagnosis, mortality, overall prognosis, quality of life, hospital admissions and cost effectiveness.

Exclusion criteria.

The following studies will be excluded:

- All studies that recruit through secondary care.
- Studies containing duplicate datasets. We will select the papers that most closely align with inclusion criteria or were most recently published if they are otherwise equal.
- Conference abstracts, as these do not provide enough methodological detail to allow adequate analysis of risk of bias.
- Studies evaluating NP screening in restricted patient groups such as patients with rheumatoid arthritis, beta-thalassaemia, Marfan's syndrome and Duchenne's Muscular dystrophy.

- Studies based on participants who consulted their GP or another community healthcare professional with symptoms of HF.

In evaluating diagnostic accuracy, specifically the following additional exclusion criteria will apply:

- Studies that assess NP as a prognostic marker.
- Studies that do not contain sufficient data to construct 2x2 tables, although we will contact all authors first to give the opportunity to provide missing data.

Search strategy

The search strategy was developed by CRG and the librarian/information specialist NR and subsequently refined to ensure that all appropriate papers were captured. The following databases will be searched: Ovid Medline (1946 to 2018), Embase (1974 to 2018), Cochrane Database of Systematic Reviews, Cochrane CENTRAL, DARE, Science Citation Index (1945–present). We will perform citation searches of all full-text papers included in final review. The full search strategy is available in *Extended data*, Appendix A³⁴.

Selection of studies

Each title/abstract will be screened by two reviewers independently and in duplicate. Any disagreements regarding inclusion will be resolved by a third reviewer. The screening process will be managed using [Covidence software](#). Any potentially relevant articles will be selected and the full text obtained. Full-text papers will then be screened using the same process until the final studies are selected.

Data extraction

Data extraction will also be performed independently and in duplicate. A third author will compare extraction results to ensure that these are in agreement and highlight any areas of conflict so these can be resolved through discussion. If any ongoing studies are found, these will be described and the authors will be contacted to see if there are any relevant data that could be incorporated into review. Data extraction will be performed using a template. The minimum planned extraction fields are listed in *Extended data*, Appendix B³⁵. Each row of data will be coded so that data from specific populations (e.g. high risk compared to general), ages, outcomes and thresholds will be categorised and appropriate data combined at the data analysis stage.

Assessment of study quality

Two authors will independently assess risk of bias. The summary extraction fields in appendix B also incorporate a risk of bias template from the QUADAS-2³⁶ criteria, which will be used to assess methodological quality for diagnostic accuracy studies. Studies that assess clinical utility may be randomized trials, in this case the following domains will be assessed as per the Cochrane risk of bias tool: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, similarity of baseline measures, similarity of baseline characteristics, management of incomplete

outcome data, selective outcome reporting, and other risks of bias. As per the recommendations of the GRADE working group, quality assessment will be used to interpret the quality of the evidence and the risk of bias present within the studies.

We will summarize the results of the risk of bias assessment across studies in a table.

Data synthesis

For the diagnostic accuracy analysis, bivariate meta-analysis will be used to calculate pooled performance estimates. Forest plots will be used to visually explore paired sensitivity and specificity of included studies and these will be generated in [RevMan](#). Where studies measured sensitivity and specificity at multiple thresholds, the lowest threshold will be selected for inclusion in the forest plots. The most important role of community screening is to detect patients with the target condition and therefore to capture the highest sensitivity recorded by each study, it is for this reason that the lowest threshold was selected. If there are at least four studies with available data, then further analysis to create summary receiver operating characteristic (SROC) curves from pooled sensitivity and specificity at every specific threshold will be followed. This approach, outlined by Steinhäuser *et al.*³⁷, also enables the optimal threshold across studies to be determined. If there is insufficient data to generate SROCs with multiple thresholds, then hierarchical summary ROC curves will be drawn from the accuracy data provided on the lowest threshold per study data.

For the impact analysis, meta-analyses will be conducted separately for randomised controlled trials and cohort studies if the same outcome is reported from trials with similar contexts. RevMan software will be used to calculate and plot pooled effects. The differences between screening-related outcomes will be measured through comparison of relative risks (RRs) and mean differences (MDs). Random effects models will be used unless statistical and clinical heterogeneity are sufficiently low to warrant a fixed effects model. For those outcomes for which meta-analysis is not possible, we will construct evidence tables to report results descriptively. Statistical heterogeneity will be analysed using the I² statistic.

Data will also be reported on the search statistics including the number of references in the original search, and those included at full text stage and in the final review. The number of excluded papers will be recorded with the reasons for exclusion being noted. Included study characteristics will be summarised in Table 1 of the full systematic review.

Subgroup analysis

Where possible, subgroup analyses will be performed. These will include looking at different types of NP, including plasma brain natriuretic peptide (BNP) and N-terminal prohormone (NT-proBNP) as well as considering point-of-care (POCT) and laboratory tests. We will also consider factors which are may affect NP measurement including participant:

- Demographics (age, sex)

- Body mass index (BMI)
- Renal function

Different populations of interest will also be included to compare screening in high risk populations (as defined above) and in general populations. Where possible, we also aim to investigate whether there is any difference in NP performance in asymptomatic participants compared to those in whom symptoms were described. We could also aim to explore whether the performance of NP changes with severity of LVSD/DD.

Sensitivity analysis

If studies with high or unclear risks of bias are found, we will use sensitivity analyses to explore the effect of excluding these studies from the data analysis.

For the analysis of diagnostic accuracy, sensitivity analysis will evaluate NP screening performance in studies that exclusively recruited participants who did not have a prior diagnosis of HF, LVSD or DD in comparison with those studies that pragmatically recruited a screened population.

Discussion

Identifying patients with HF in the community is crucial. Treatment improves patient survival and quality of life, and early diagnosis can prevent disease progression. A potential strategy to screen patients for HF by measuring NP presents an alternative diagnostic pathway, although evidence underpinning this is lacking. This systematic review aims to change this

by providing an up to date summary of the literature on both the diagnostic accuracy and the impact of NP screening. Dissemination of results will be through publication in peer-reviewed journals and the presentation of this work at relevant conferences. We also plan to share our results with the public through organisations such as the British Heart Foundation.

Data availability

Underlying data

No underlying data are associated with this article.

Extended data

Figshare: Appendix A.docx. <https://doi.org/10.6084/m9.figshare.10062191.v1>³⁴.

This file contains the search strategy for the systematic review.

Figshare: Appendix B.docx. <https://doi.org/10.6084/m9.figshare.10062215.v1>³⁵.

This file contains an outline of the data extraction plan.

Reporting guidelines

Figshare: PRISMA-P checklist for 'Diagnostic accuracy and clinical impact of natriuretic peptide screening for the detection of heart failure in the community: a protocol for systematic review and meta-analysis'. <https://doi.org/10.6084/m9.figshare.10068140.v1>³⁰.

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

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Abdallah Al-Mohammad 

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The group of Goyder *et al.* are from a nationally and internationally renowned department in Oxford with an excellent track record of designing and executing trials, and performing meta-analyses in the field of heart failure diagnosis.^{1,2,3}

The authors are proposing to meta-analyse data from studies that included more than 100 patients and in which natriuretic peptides were used as screening test in a population rather than using it in patients with symptoms suggestive of heart failure (HF).

I would summarise the aims of their work as the use of natriuretic peptide to screen the population for HF, asymptomatic left ventricular systolic dysfunction (LVSD) or asymptomatic left ventricular diastolic dysfunction (LVDD).¹

While I would support their aims, I have a number of concerns about the report and the plans as they stand.

The reader of the introduction spends most of the time learning about a bland entity called HF and gets the impression of this being mainly preceded by an asymptomatic phase of LVSD [*The natural history of disease progression in HF is well understood. An early, latent stage is recognised; this preclinical phase is termed left ventricular systolic dysfunction (LVSD) and can be asymptomatic.*], for which there is benefit from intervention with angiotensin converting enzyme inhibitors (ACEi).^{4,5} While the progression from asymptomatic LVSD into one of the forms of HF is correct, the initial impression is inaccurate and potentially misleading.

Only towards the end of the introduction, does the reader get confronted by the concept of DD (meaning diastolic dysfunction of the left ventricle), as though this was an after-thought or something that is so uncommon that is not worthy of the prominence given to the LVSD as the main predecessor to HF.¹

In fact, LVSD is an important predecessor to one of the types of HF, namely heart failure with reduced left ventricular ejection fraction (HFrEF), the difference between the two is the presence of symptoms in the latter. HF and HFrEF should not be used interchangeably, as less than 50% of the patients diagnosed with HF have HFrEF.⁶ The authors mention that HFrEF used to be called LVSD, which is not accurate, it used to be called HF due to LVSD.

The largest group of symptomatic patients with raised natriuretic peptides are patients with HF other than HFrEF. Indeed, the most commonly encountered phenotype of HF in the community is heart failure with preserved ejection fraction (HFpEF).⁶ Less common HF phenotypes are those caused by pulmonary hypertension (PH), right ventricular systolic dysfunction (RVSD) or valvular heart disease (VHD). Of course, one expects there to be a much larger number of people with asymptomatic cardiac dysfunction (Stage B-AHA) than those with symptomatic cardiac dysfunction and thus HF (Stage C-AHA).⁷

The asymptomatic patients who will be picked up through the screening process may either have reduced left ventricular ejection fraction (LVEF), thus they would have asymptomatic LVSD; or they may have preserved LVEF with evidence of diastolic dysfunction, hence they have asymptomatic LVDD. The latter two are the predecessors of both HFrEF and HFpEF, respectively. I would expect the authors to amend their introduction and methodology to demonstrate clarity of understanding of the problem being screened for, with proportional attention being paid to all aspects of this problem. Of course, one would not wish to dilute the exercise into small subgroups of patients with PH, RVSD or VHD. Thus, limiting the process to those with overt (symptomatic) HF and those with asymptomatic LVSD or LVDD as seen in their aims is evidently appropriate.

Unlike the treatment implication of detecting asymptomatic LVSD, we may not be able to alter the management considerably if we were to detect asymptomatic LVDD, unless one considers the potential attention being made to tighter control of hypertension and other co-morbidities on the basis of discovering target organ damage (LVDD).

While there is no guideline mandated therapeutic interventions for patients with HFpEF and similarly in those with asymptomatic LVDD;⁸ we need to be cognisant of the post-hoc analysis of the cohort of patients with HFpEF recruited into the TOPCAT study in the Americas which showed reduction of HF hospitalisation,⁹ in addition to the findings from sub-group analyses of the PARAGON-HF trial that led to the recent licensing by the FDA of Sacubitril-Valsartan for patients with HFpEF if the LVEF was between 45% and 57%.¹⁰

The authors in their (research aims) section appear to give a clearer remit to their work which is the detection through screening with NP of HF, asymptomatic LVSD and asymptomatic LVDD. However, it would be best if they were to specifically say LVDD instead of DD.¹

The diagnosis of HFpEF is based on demonstration of structural and functional changes in the left atrium and the left ventricle, while the LVEF is >50%. Similarly, patients with asymptomatic LVDD will have a LVEF>50%, but with a number of abnormal structural and functional parameters not unlike those used in the diagnosis of HFpEF.¹¹

I welcome the authors' plan, under subgroup analysis, to explore whether the performance of NP changes with severity of LVSD/LVDD. This is both important and an excellent opportunity for us to

understand if there is a difference between asymptomatic patients with LVSD and asymptomatic patients with LVDD, along with whether there is a graded impact on the NP level by different degrees of LVSD or LVDD.¹

The authors correctly decided to include trials that looked at the incidence of either HFrEF, HFpEF, asymptomatic LVSD or asymptomatic LVDD; as the aim is to assess the role and utility of using natriuretic peptides as screening test.¹ Beyond wanting the clarity of definitions as cited above, I would like the authors' plan to handle the different emphasis between trials: what if one trial looked at the role of natriuretic peptides in detecting only one type of the several abnormalities they are looking for while another is looking at more than one? How are they going to manage this heterogeneity?

Another problem likely to face the authors is the variable criteria used over time for the diagnosis of both asymptomatic LVDD and HFpEF. It is attractive to suggest concentrating on the most recently agreed criteria; but one would expect the literature to be reflecting the historical development of these criteria. This is not a criticism of the planned work by the group, but is an inevitable limitation that ought to be managed in a manner that maximises the value of the meta-analysis they are undertaking. As a clinician I would like to not only know the summary of what the studies have suggested would the rise in natriuretic peptides be predicting in terms of the myriad of diastolic markers over the past 15 years, but in particular the specific markers of diastolic impairment that are most reliable. The most reliable marker of diastolic dysfunction are left atrial dilatation, raised E:e' ratio, raised TR velocity, low e' wave, low s' wave, low GLS and the presence of LVH. Whether that is achievable remains to be seen.¹¹

In conclusion, Gayder *et al.* are embarking on an excellent project that I believe would teach us a lot and may contribute in the future to possible changes in the guidelines and the practice. They are advised to improve certain aspects of the report for the sake of clarity. I am certain they will consider the limitations cited above as a constructive criticism aiming to assist them in delivering another excellent product their unit has become famous for producing.

Typing errors:

1. Under primary and secondary outcomes, line 3 the authors stated (so this assessment maybe will be limited by the available data). They should state either may be or will be.
2. Under subgroup analysis, line 3, the authors stated (We will also consider factors which are may affect NP measurement), the authors are advised to remove (are) from that sentence.

Professor Abdallah Al-Mohammad

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Is the rationale for, and objectives of, the study clearly described?

Partly

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Heart Failure diagnosis and management

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 27 May 2020

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Kenneth McDonald

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This is an important question that is being addressed. I agree with the authors that it warrants a thorough review of the literature to help guide next steps for use of natriuretic peptide in screening and helping in the diagnosis of heart failure.

I have one central concern with the way the manuscript is presented at present and it is substantively a matter of improved clarity around the issue of the population under study, and how comparison will be made across the studies.

It is important that a clear distinction is made between Stage B and symptomatic heart failure (Stage C), presently differentiated solely by symptoms. Is the primary purpose to look only at Stage C as the text drifts occasionally into discussion on Stage B (section on Subgroup Analysis)?

The authors state that they will use of definitions for LVSD and LVDD that the respective study authors have used. For LVSD that will pose relatively few problems but the definition of LVDD is more complex, varied and has changed significantly over the recent past. How do the authors plan to compare across studies where definitions of the metric under study are significantly different? There is a comment in the section on Definitions that “test performance at each ejection fraction can be analysed” which by omitting comment on metric of LVDD indirectly refers to this challenge.

In considering variables that will impact on NP levels the authors mention age, BMI and renal function –the authors should mention AF in this section as well as it is a well-established modifier of NP levels.

In the Introduction third paragraph the authors talk about the preclinical phase of HF, but comment in the second line that this phase is characterized by a reduction in LVEF—it is only at the end of that paragraph that comment is made that asymptomatic LVDD is also a preclinical phase –clarity would be improved if this were mentioned at the same time as comment made on asymptomatic LVSD.

The comment in the fourth paragraph on use of echocardiography and NP as screening tools would be more clearly stated as NP being used a gateway test to decide on who needs echocardiography.

Is the rationale for, and objectives of, the study clearly described?

Partly

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Partly

Are the datasets clearly presented in a useable and accessible format?

Partly

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.