Original Article

Is Galectin 3 more Accurate than Brain Natriuretic Peptide in Diagnosing Chronic Heart Failure? A Systematic Review

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ABSTRACT

Introduction: Diagnosis of chronic heart failure is difficult in primary care. The current standard biomarker Brain natriuretic peptide (BNP) has limitations, as it only indicates conditions that cause ventricular overload and does not reveal other important mechanisms in HF. Galectin 3 (Gal-3) is an inflammatory marker and contributes to fibrosis. Gal-3 production is also independent of the loading status. Therefore, this novel biomarker may prove to be useful in CHF diagnosis. **Objective:** The aim of the review was to compare the diagnostic test accuracy of Gal-3 versus BNP for the detection of chronic heart failure. Method: Databases including Embase (1974 to 2019 week 12) and Medline (1946 to March Week 2 2019), Database of Abstracts of Reviews of Effects (DARE; March 2019), the Health Technology Assessment Database (HTA; March 2019) were interrogated. **Results:** Eligible studies evaluated one or more natriuretic peptides and galectin 3 in the diagnosis of chronic heart failure. Two studies (n = 564 participants) met our inclusion criteria. Each study compares gal-3 and BNP. Methodological quality varied considerably among studies, with a substantial amount of biases. The AUC of gal-3 was 0.891 (95% CI 0.808–0.974) and the AUC of BNP was 0.896 (95% CI 0.809 – 0.984) (BNP) whilst the other study reported the AUC of galectin 3 (0.67) and BNP (0.65) without confidence intervals. **Conclusion:** Gal-3 appears to have a good diagnostic biomarker for the detection of CHF although the included studies had methodological shortcomings (selection and performance bias). However, in the future, well-conducted cross-sectional studies regarding the diagnostic accuracy of gal-3 should be undertaken to examine its usefulness in clinical practice.

Key words: Brain natriuretic peptide; galectin – 3; chronic heart failure; heart failure with preserved ejection fraction (HFpEF).

BACKGROUND

Heart failure (HF) is a clinical syndrome in which the pumping action of the heart is impaired. Globally, more than 23 million people are affected by HF[1,2]. Also, about 160,000 people across the United Kingdom and 5.8 million people suffer from HF in the United States of America and contribute to 50,000 deaths annually in the United States of America. The main cause of HF has been attributed to left ventricular failure[3,4]. It has been estimated that about 58% of the population affected by HF following myocardial infarction is often asymptomatic[5]. Therefore, often misdiagnosed or underdiagnosed in primary care[6]. Hence, asymptomatic AMI can lead to symptomatic HF that may masquerade as COPD. This is important as a good biomarker will help identify the problem more accurately before individual suffering from HF deteriorates.

HF as a consequence of an ischemic event is associated with a considerable activation of inflammatory, fibrotic and necrotic mechanisms, unlike dilatory failure which does not activate these mechanisms to the same extent[4,7]. These mechanisms lead to non-contractile cardiac remodelling. According to the European society of heart failure guideline (2012) [8] the diagnosis of chronic HF remains a problem this is because the sensitivity and specificity of BNP are low. Hence it is unable to diagnose chronic HF. Therefore, early and accurate identification of patients with HF is vital to begin appropriate treatment, alleviate symptoms, delay progression of the disorder, and improve prognosis.

Brain natriuretic peptide (BNP) is a hormone or biomarker that has considerable neurohormonal effects influencing blood pressure. It is released when there is excessive stretching of the heart muscle resulting normally from pressure overload. BNP is currently used as a biomarker in diagnosing HF. The ESC (2012)[8] describes levels of BNP above 100 pg/ml as suggestive of acute HF and 35pg/ml in chronic HF. New biomarkers such as gal– 3 have been reported to be useful in diagnosing HF. Gal-3 is a hormone produced by activated cardiac macrophages and involved in the development of cardiac fibrosis, hypertrophy and remodelling in HF[9].

BNP is therefore considered as loading markers whereas Gal-3 is an inflammatory marker and contributes to fibrosis. Gal-3 production could be independent of the loading status[10]. Since BNP only indicates conditions that cause ventricular overload and do not reveal other important mechanisms in HF, new biomarkers, such as Gal-3, could determine structural, inflammatory, fibrosis and remodelling in HF[11] and serve as a possible guide for treatment[12] as well as serve as diagnosis of heart failure with preserved ejection fraction (HFpEF)[13-25]. A preliminary search of the Cochrane library revealed neither an existing review comparing the diagnostics ability of BNP and Gal-3 nor a protocol.

METHODS

The Cochrane methods the highest quality of evidence identified[13]. A literature search was commenced using Embase (1974 to 2019 week 12) and Medline (1946 to March Week 2 2019). The Database of Abstracts of Reviews of Effects (DARE; March 2019) and the Health Technology Assessment Database (HTA; March 2019). Table 1 shows a summary of the facet analysis utilized Index terms such as 'Heart Failure' 'Galectin 3' and 'brain natriuretic peptide' were exploded to include all sub-headings. Also, free text searching using synonyms and truncation (eg. heart failu*) were done to ensure all possible word endings were included. The results within each facet were combined using the Boolean operator 'OR' and the results between the three other facets were combined by applying Boolean operator 'AND'. Specificity of the results was achieved by limiting the search to humans and English Language.

Findings of the search

The search yielded 384 papers which included abstract only from conference presentations, discussions of gal - 3 as a novel maker and its role in diagnosis and prognosis of heart failure. The search results (Figure 1) from databases (n = 384) papers were returned. Adjustment for duplicates left (n = 297) papers remaining. Following a review of titles and abstracts, 297 papers were removed as irrelevant to the question since those studies focused on prognostic and risk stratification rather than diagnosis. Scrutiny of the abstracts presented six (n=6), in which four (n= 4) were not available in full text therefore two (n = 2) were selected for review. The authors were followed up to supply full text of the abstracts but were unavailable.
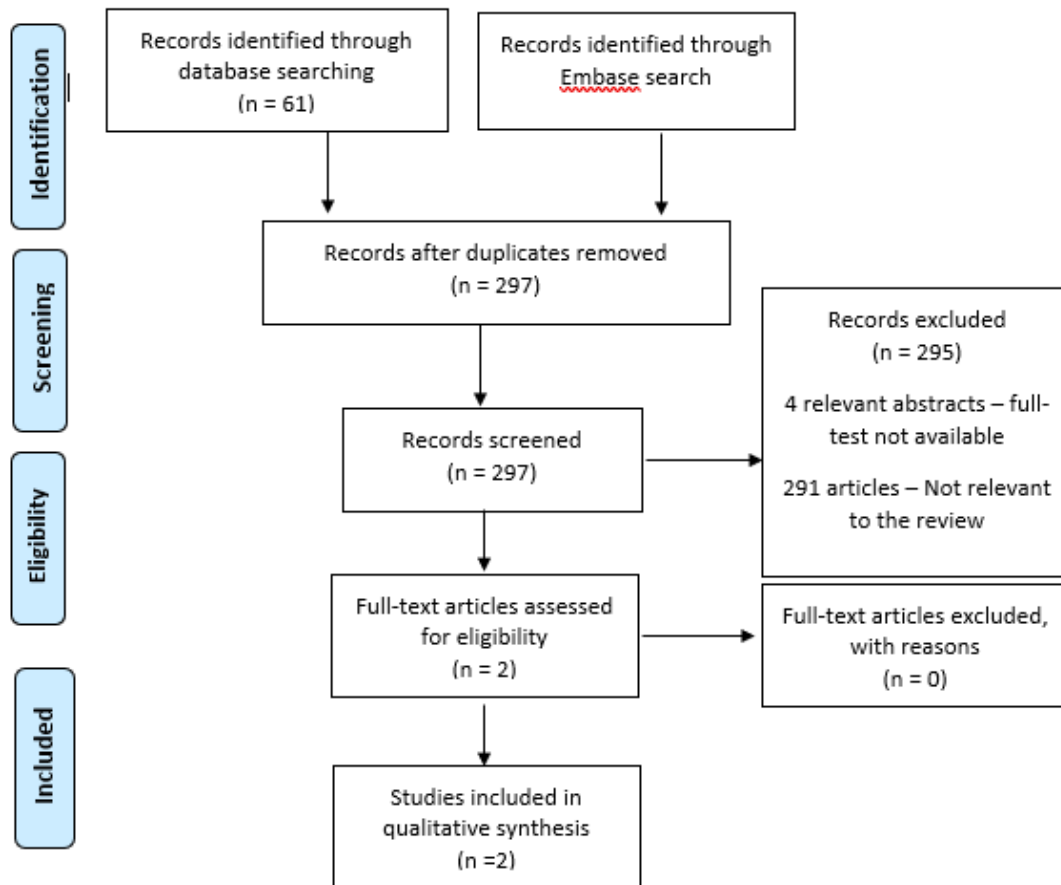
Figure 1: PRISMA 2009 Flow Diagram.

Table 1: Facet analysis of the question.

	Population		Intervention (Index test)		Comparison (standard or reference test)	
INDEX TERMS	Left ventricular dysfunction		Galectin 3		Brain natriuretic peptide	
FREE TEXT	Left ventricular dysfunct$ Or Left ventricular fail$ Or Ventricular dysfunct$ Or Congestive heart fail$ Or Left heart dysfunct$ Or Heart fail$ Or Left heart fail$	A N D	Galect$ Or Gal-3	A N D	Brain Natriuretic Peptid$ Or B- Natriuretic peptid$ Or B type natriuretic peptid$ Or BNP$	

$- truncation

Selected studies

Randomised controlled trials (RCTs) are often ranked as the best method of evidence in primary research. However, RCTs are best used in intervention studies and not appropriate in diagnostic studies[13,14]. This is because individuals selected may not be experiencing the signs and symptoms or not harboring the target condition[13]. Therefore, cross-sectional studies often called 'cohort type accuracy studies were considered which include participants with the target condition at the time of inclusion [13, 14]. In addition, the Cochrane collaboration includes 'case-controlled type accuracy' whereby patients experiencing a particular disease are identified and matched with controls (patients without the disease).

Therefore, cross-sectional/prospective diagnostic studies and case-controlled type accuracy studies that compared galectin-3 alone or with other biomarkers in which BNP served as the reference standard were eligible for inclusion. The main features of the studies (Table 2). The first study Yin et al.[15] is a case-controlled study which assessed the diagnostic accuracy of gal - 3 with BNP in heart failure patients using 78 samples to conclude that galectin 3 was as accurate as BNP in diagnosis heart failure. The second study deBoer et al.[16] is randomised prospective study which assessed the predictive value of galectin 3 and other biomarkers in heart failure patients using 529 samples to conclude the similarity in diagnostic accuracy between galectin and BNP.

Table 2: Description of selected studies.

Reference	Yin et al. 2014	deBoer et al. 2011
Title	Comparative study of gal-3 and B-type natriuretic peptide as biomarkers for the diagnosis of heart failure	Predictive value of plasma gal-3 levels in heart failure with a reduced and preserved ejection fraction
Study type	case-control diagnostic study	Prospective study
Number of participants	35 HF Males = 30 Females = 5 43 control Males = 39 Females = 4	529 Males = 344 Females = 185
Participant characteristics	Mean age 82.31 ± 6.72 29 hypertensions, 25 coronary heart disease, 10 infarctions, 17 diabetes mellitus. Control group Mean age - 63.36 ± 11.14 35 hypertensions, 9 coronary heart disease, 16 diabetes mellitus.	Mean age 72 +/- 12 years Hypertension = 174 Myocardial infarction = 162 Diabetes = 120 Atrial fibrillation = 182 COPD = 112 CVA = 41
Exclusion	New York Heart Association (NYHA) Classes II-IV. Valvular heart disease, cardiomyopathy, cardiac hypertrophy	New York Heart Association (NYHA) Classes II-IV. None stated
Intervention	Galectin 3	Galectin 3
comparison	BNP	BNP
ASSAY for galectin	The galectin-3 assay is using an enzyme-linked immunosorbent assay (ELISA) from BG Medicine (Waltham, MA, USA)	The galectin-3 assay is an enzyme-linked immuno-sorbent assay (ELISA) developed by BG Medicine (BG Medicine, Inc., Waltham, USA).
ASSAY for BNP	BNP ELISA	Not stated
Length of study	January 2013 to May 2013.	6 months
Outcome measure	shows a high degree of diagnostic accuracy and clinical relevance for the diagnosis of heart failure	Shows statistical significance in diagnostic accuracy

Critical appraisal

The critical appraisal of the two papers was carried out using the risk of bias tool developed by Cochrane collaboration to assess biases in studies and QUADAS - 2 tools for assessing the quality of diagnostic test studies[17] were used as shown in Table 3. These two tools were merged to identify any biases.

Selection bias

There was insufficient information regarding the sampling technique by Yin et al [15] therefore unclear bias. On the other hand, deBoer et al. (2011)[16] randomly selected the samples but insufficient information regarding the process was reported.

Performance bias

Both studies used the same index test (Gal-3) and enzyme-linked immunosorbent assay from BG Medicine (Waltham, MA, USA). However, they did not report in detail the reference standard (BNP) hence difficult to assess whether it followed standard practice and can be reproducible. Thus, high risk of performance bias.

Detection bias

The measurement of the reference and index was done in different centres therefore each test results were interpreted independently of each other. Thus, diagnostic reviewers were unbiased regarding the outcome of the results.

Attrition bias

Attrition bias was low due to the fact that all participants were reported to receive both test and analysed in both studies. Also, no missing data was recorded in both studies as well as all samples taken were measured and interpreted.

Reporting bias

The outcomes of interest in the review (sensitivity, specificity of the biomarkers for both studies as well as confidence interval for area under the curve in deboer et al.[16] were not reported so authors are unable conduct a meta-analysis and give clinical interpretation of the results. There is high risk of reporting bias.

Verification bias

Verification bias occurs when samples with negative results of the test under investigation do not receive the standard test. Thus, they are assumed not to have the disease[18]. This could bring about false negatives and influence the sensitivity of the test results. However, all samples were verified by the reference test (BNP) in both studies and had a low risk of bias.

Spectrum bias

The spectrum of participant was limited in both studies since the mean age was 64 – 88.7. In addition, Yin, et al's[15] were gender bias with 85% men participants whilst deboer, et al[16] had an even distribution among

Table 3: Assessment of bias.

Type of bias	Sources of bias	Judgment
Selection	No Randomisation	High risk of bias in Yin et al. 2014
	Sequence generation	Unclear risk of bias in deBoer et al. 2011
Performance	Insufficient information on the procedure for BNP measurement in both studies	Unclear risk
Attrition	All participants	Low risk
Detection	Different centers analysed the results in both studies	Low risk
Reporting	Missing information on the outcomes of interest	High risk
Spectrum bias	the mean age for both studies was 64 – 88.7	High risk
Verification bias	All samples were verified by the reference test (BNP) in both studies	Low risk

Source - (Higgin & Green 2012)

gender (50 % each). In light of this, therefore both studies are likely to be spectrum bias since the biomarkers may conceivably be sensitive to particular gender or age groups. For instance, BNP has been shown to increase significantly with age and higher in women than men[19].

In summary, the validity of the study results is moderate in view of the biases detected.

Synthesis of results

The area under the curve (AUC) of Receiver operating characteristic (ROC) curves is an outcome measure used to assess the accuracy of a diagnostic test. AUC for the diagnostic test ranges from 0.5 (indicative of a test useless in diagnosis) to 1.0 (indicative of a test that is perfect in diagnosis)[20]. Although the primary outcome of the two studies was the diagnostic accuracy of gal-3 and BNP, and AUC was the outcome measure, it was inappropriate to combine the statistics from these studies using a meta-analysis due to incomplete statistical parameters, such as sensitivity/specificity at cut off values as well confidence intervals of the AUC for both test in Deboer, et al.[16].

An attempt was made to calculate and convert the values to determine the confidence intervals however the skewness of the population made it impossible to make these estimations. For instance the standard deviations can be calculated using the interquartile range provided the population is normally distributed by approximating the width of the interquartile range to be 1.35 standard deviations, therefore, the interquartile range is divided by 1.35 to estimate the standard deviation [15].

Therefore, the findings (Table 4) are synthesized below in a narrative format. The two studies showed statistical significance in which the p-value of AUC for both gal-3 and BNP (p= 0.000) in Yin et al's (2014) and p-value of AUC for galectin 3 (P < 0.004), BNP (P < 0.001) in deBoer et al (2011). In the light of the absence of confidence intervals in deBoer et al's, only Yin et al's 2014 could be analysed which showed narrow confidence intervals for galectin 3 and BNP as (95%CI 0.808–0.974) and (95%CI 0.809 – 0.984) respectively therefore clinically significant. The AUC of Yin et al's had higher effect size of 0.891 (galectin 3) and 0.896 (BNP) than the AUC of deBoer et al's 0.67 (galectin 3) and 0.65 (BNP). The quality of available evidence has been explained in table 5. Since an AUC cut off point in a diagnostic between 0.5-1 indicative of a test useful in diagnosis, the AUC of galectin 3 and BNP are clinically significant and can be used in the diagnosis of HF.

DISCUSSION

Gal-3 appears equivalent to BNP in the diagnosis of chronic heart failure. An interpretation of the quality of evidence (Table 5) explored here is impacted upon by the aforementioned biases, inconsistencies, samples sizes and the differences in research designs. There was serious imprecision since confidence intervals of the AUC were not reported. Therefore, the clinical significance of AUC in both studies could not be determined. Also, there was substantial heterogeneity due to widely

differing estimates of effect in the AUC values of galectin and BNP (Table 5) whereby Yin et al's was higher than deBoer et al's. A possible explanation to these differences could be as a result of sampling error in Yin et al's due to the fact that their sample size was seven times smaller than deBoer et al's. Also, cut off points for both biomarkers were absent in deBoer et al's which could have led to inconsistencies in interpretation of the results. In addition, the process of BNP measurement was not stipulated in both studies, therefore, differences in assays may have accounted for the differences in outcomes. Also, the limited age and gender spectrum could have influenced the results.

The evidence is directly related to the participants for both studies since they were not restricted to a particular underlying cause of left ventricular dysfunction. Thus there was no serious indirectness. The lack of rigorous research process and paucity of evidence influences the overall quality of the review. Ultimately, the body of evidence supports the diagnostic accuracy of gal-3 in diagnosing heart failure which can cater to the inadequacies of BNP (standard biomarker) in clinical practice. In future, well-conducted cross-sectional studies regarding the diagnostic accuracy of gal-3 should be undertaken to examine its usefulness in clinical practice.

Applicability of findings to the review question

Gal-3 appears comparable to BNP for the detection of HF, however, routine use of BNP will need to take into account practicality. Although BNP is widely used in clinical practice throughout the world, there are limitations that affect the interpretation of results. In the absence of heart failure, there are differences between individuals regarding their age, gender and body mass index[21] which may decrease the specificity of the results[22]. Patients with renal failure have increased BNP concentrations relative to those with normal renal function[23]. For non-acute patients, the optimum exclusion cut-off point pf BNP should be 35 pg/mL whilst acute HF is 100pg/ml. On the other hand, Gal-3 appears to have stable cut off points to predict HF. BNP immunoassay may be more accessible due to its increased use making it a more practical option for diagnosis patients however it's sensitivity and specificity to non-acute HF are low[8]. Although Gal-3 is less available than BNP, interpretation of its findings has not been shown to be influenced by age, gender and disease conditions. Although there appeared to be a substantial heterogeneity between the two studies it is possible that the accuracy of Gal-3 compared with BNP may further improve with advancing technology. The expectation, therefore, will be that the summary estimate of the diagnostic accuracy of gal-3 will continue to compare favourably with BNP in detecting chronic heart failure as more evidence accrues.

CONCLUSION

With the available very low-grade evidence (Table 5), a weak recommendation can be made for the use of gal-3 in diagnosing left ventricular dysfunction in clinical practice. This shows that gal-3 can be considered as an alternative in the diagnosing of heart failure.

Table 4: Outcome measure.

		Effect size (AUC)	95% Confidence intervals	P value	Interpretation (statistical and clinical significance)
Yin et al. 2014[15]	Gal-3	0.891	0.808–0.974	p = 0.000	Statistically significant. Clinically significant.
	BNP	0.896	0.809 – 0.984	p = 0.000	Statistically significant. clinically significant
deBoer et al. 2011[16]	Gal-3	0.67	Not stated	P < 0.004	Statistically significant.
	BNP	0.65		P < 0.001)	Clinical significance undetermined.

Table 5: Grade profile

Quality assessment							№ of patients		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gal-3	BNP	AUC (95% CI)	
2 1	observational studies 2	serious 3	serious 4	not serious	serious 5	none	572/572 (100%)	572/572 (100%)	Not estimated	⊕◯◯◯ VERY LOW	IMPORTANT

Source (23) Guyatt 2008)
CI: Confidence interval
Yin et al. 2014, deBoer et al. (2011)[1,2]
case-control, prospective studies[2]
Both studies have spectrum bias and missing data[3]
substantial differences estimate of AUC Gal-3 (0.809) in Yin et al. 2014 Gal-3 (0.67) in deboer et al. 2011, lack of statistical outcome in deboer et al 2011 to make clinical conclusions[4]
deBoer et al. 2014 did not report confidence intervals[5]

However, it is impossible to confirm its use in practice based on the weak body of evidence.

There were limitations with regards to the less rigorous review process done by one reviewer. Also only two databases were searched other methods of searching, such as 'grey' literature and hand searches were not done due to time constraints. Also, the inadequate amount of data on the chosen topic is a limitation to this paper. This has been recognized to limit the scope and findings of this review.

CONFLICTS OF INTEREST

None declared

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