How to Cite:
Karisnan, K., Maziz, M. N. H., Sasongko, T. H., Karikalan, B., Ibrahim, R., Rafae, I. M., & Mathialagan, A. (2022). Prognostic biomarkers in cardiovascular diseases. *International Journal of Health Sciences*, *6*(S2), 2762–2777. https://doi.org/10.53730/ijhs.v6nS2.5672

Prognostic biomarkers in cardiovascular diseases

Kanakeswary Karisnan
QUEST International University, Faculty of Medicine, Ipoh, Perak
Email: kana.karisnan@qiu.edu.my

Mohammad Nazmul Hasan Maziz
Faculty of Medicine, Bioscience and Nursing, MAHSA University, Selangor, Malaysia

Teguh Haryo Sasongko
Perdana University-Graduate School of Medicine, Perdana University, Kuala Lumpur, Malaysia

Barani Karikalan
Faculty of Medicine, Bioscience and Nursing, MAHSA University, Selangor, Malaysia

Ruziah Ibrahim
Perdana University-Royal College of Surgeons Ireland, Perdana University, Kuala Lumpur, Malaysia

Isriyanti Mohd Rafae
Perdana University-Royal College of Surgeons Ireland, Perdana University, Kuala Lumpur, Malaysia

Amuthaganesh Mathialagan
Perdana University-Royal College of Surgeons Ireland, Perdana University, Kuala Lumpur, Malaysia

***Abstract*---**The use of biomarkers as a reliable and reproducible indicative of the risk, severity, and progression of cardiovascular diseases (CVDs) may greatly enhance the prognostic capability of primary healthcare clinicians. In primary healthcare, the realistic and wise use of reliable biomarkers could minimize the time and costs for effective diagnosis and suitable personalized therapy for CVD patients. Therefore, the aim of the present scoping review is to evaluate the prognostic significance of biomarkers in the progression and monitoring of CVDs. The review was conducted according to the

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
***Corresponding author**: Karisnan, K.; Email: kana.karisnan@qiu.edu.my*
Manuscript submitted: 18 Feb 2022, Manuscript revised: 09 March 2022, Accepted for publication: 01 April 2022

PRISMA-ScR guidelines. Eight databases were searched for articles published as of June 2021 using search terms: cardiovascular diseases AND biomarkers AND prognosis. A total of 21 studies were included in this scoping review. This review identified biomarkers BNP, cTnT yielded better accuracy of disease progression prediction in ACS and HF respectively. The availability of CVDs prognostic biomarkers in primary healthcare clinics could promote improved clinical outcomes of patients.

***Keywords*---**prognostic biomarkers, cardiovascular diseases, primary healthcare, cTnT, BNP.

Introduction

The leading cause of death worldwide is cardiovascular diseases (CVDs), an estimated 17.8 million people died of CVDs in 2017, which accounts for 31 percent of all global deaths. Of these CVDs deaths, 85% are due to heart attack and stroke.[1,2] Importantly, in countries with low and middle incomes, three quarters of the world's deaths are attributed to CVDs. In these nations, people suffering from CVDs have fewer access to reliable and equitable healthcare services. As a result, many people are diagnosed late in the course of the disease and die earlier from CVDs.[3]

CVDs fall under the category of heart or blood vessel disease, that consist of coronary heart disease, cerebrovascular disease, peripheral artery disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism.[4] Coronary heart disease (CHD), strokes, peripheral arterial diseases, and aortic diseases are four of the major forms of CVD.[5] The exact causes remain unclear, but there are many risk factors for CVDs. Hypertension, diabetes, high cholesterol, smoking, overweight or obese, physical inactivity, family history and ethnicity are the major risk factors.[6]

The onset of CVD itself indicates an adverse prognosis with a higher risk of chronic events, morbidity and mortality. It is increasingly evident that while clinical assessment is the keystone of patient care, there are drawbacks to the evaluation. Other approaches have been used by doctors to support clinical evaluation and to improve their ability to recognise vulnerable patients with CVDs that are at risk of poor outcomes. One such tool is the use of biomarkers to better identify individuals with high risk, to diagnose disease conditions promptly and to precisely and efficiently prognosticate and treat patients with CVDs.[7] Biomarkers are classified as prognostics, pharmacodynamics or predictive biomarkers as per precision medicine perspective. The prognostic biomarker would be the one that provides an untreated individual or person treated with conventional treatments with knowledge on the likely course of a disease condition.[8]

Biomarkers have been widely evaluated as guides to CVDs and its progression, for example natriuretic peptides appear to be the gold standard biomarker in the management of heart failure (HF).[9] In the recent years, the proliferation of new

prognostic biomarkers in CVDs has been remarkable, however only few of them showed convincing prognostic value to disease progression.[10]

The developments in CVDs and the advances in biomarker research over the past three decades have led to a more sensitive screening methods, a better importance on its early detection and diagnosis, and enhanced treatments resulting in more positive clinical outcomes for patients. However, whether any biomarker can serve as a reliable guide to CVDs progression or to a favourable therapeutic response remains unclear. Disease progression monitoring and prognostic analysis play a major role in optimizing treatment options. There is not much known on the availability of prognostic biomarkers for improvement of prognostication and treatment optimization in CVDs at primary healthcare clinics. However, utilising prognostic biomarkers have shown to cause a reduction in morbidity and mortality in CVDs. Further, it has shown to reduce cost of healthcare for tertiary hospitals. [11,12,13,14,15,16] Thus, the purpose of this study was to assess the prognostic significance of biosample biomarkers in the progression of CVDs in the primary healthcare settings. This review summarizes studies on prognostic biomarkers for CVDs and evaluate their role in the monitoring of disease progression in the primary healthcare settings.

The specific objectives of the current scoping review are:

(1) to identify the availability of biosample biomarkers for monitoring the progression of CVDs at primary healthcare clinics.
(2) to evaluate the prognostic significance of biosample biomarkers in the progression of CVDs at primary healthcare clinics.

Methodology

We used a scoping review approach to examine the CVDs prognostic biomarkers, its specificity and sensitivity and the strength of its prognostic index. The review was conducted according to the iterative stages of the Arskey and O'Malley, and Levac advanced scoping review framework.[17,18] This report supplemented with Preferred Reporting Items for Systematic reviews and Meta-Analyses-extension for Scoping Reviews (PRISMA-ScR) checklist guidelines (Appendix A).[19] The review protocol is published at OSF (DOI 10.17605/OSF.IO/EG57K).Eight databases (Google Scholar, Dynamed, Medline, Access Medicine, PubMed, Science direct, British Medical Journal and Cochrane) were searched for articles published as of May 2019. An updated search was carried out in June 2021. As the objective of our review was to identify articles that measured suitable biomarkers to predict disease progression of cardiovascular diseases, our search terms were: *cardiovascular diseases AND biomarkers AND prognosis*.

Screening

The two authors retrieved and analysed critically valuable publications, and the reference lists of the screened literatures. Previous relevant reviews and meta-analyses have also been checked to find other relevant publications. Two sequential levels of article screening were undertaken (Figure 1). Firstly the review of titles and abstracts and secondly is the review of full-text articles. Two review

team members independently screened all papers at each stage. Inclusion criteria were as follows: (1) articles must be original research; (2) involve human subjects; (3) methods must identify measurement of a prognostic biomarker and (4) articles must include a method or tool for assessing prognosis of cardiovascular diseases. We included studies that used tools that the authors defined as a measure, even if the tool was not explicitly developed for that reason, as the purpose of this review was to be as broad as possible. If articles were written in a language other than English and animal research, they were disqualified.

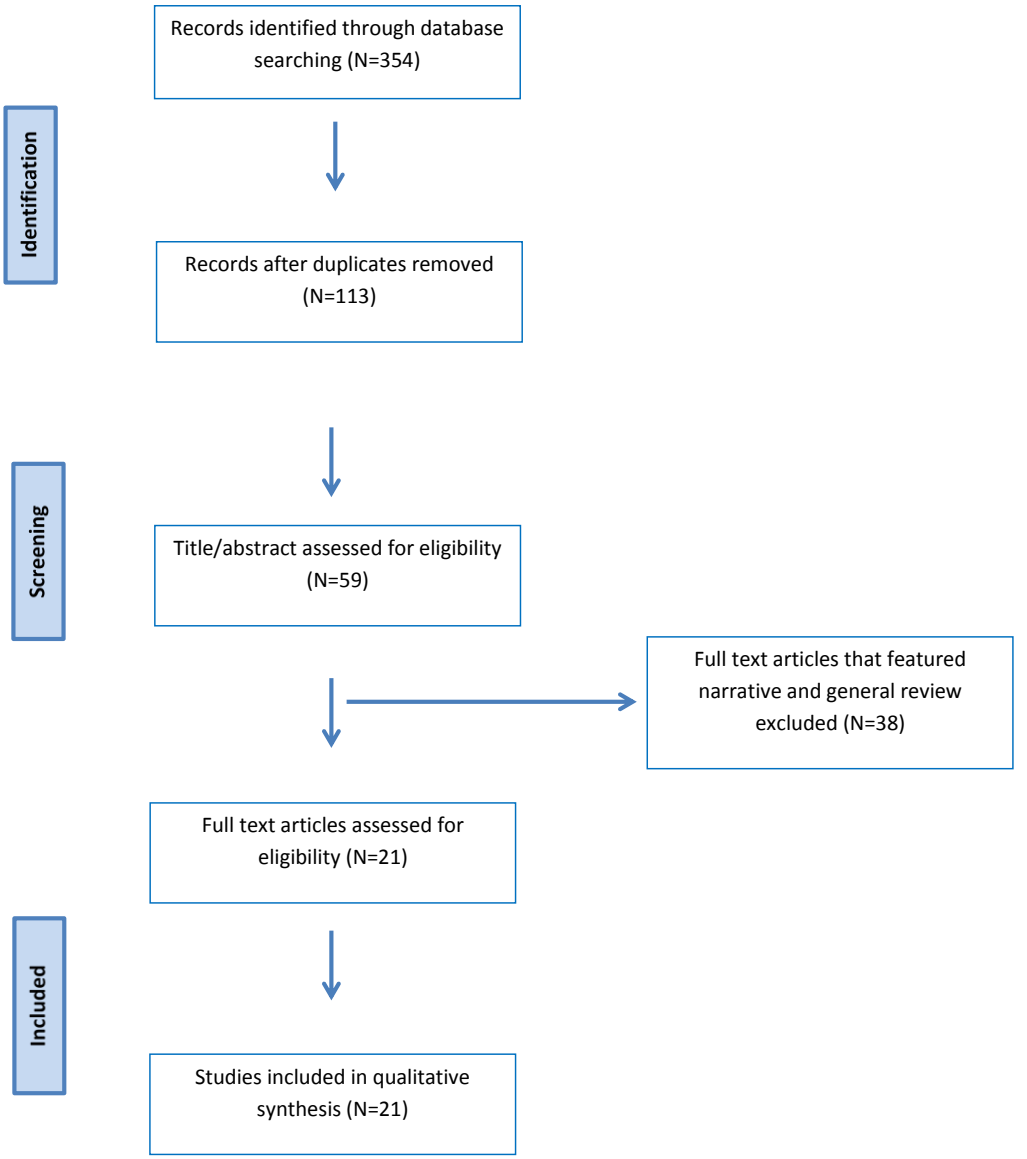

Figure 1: Flowchart showing the selection process for articles reporting studies of prognostic biomarkers in CVDs

Data Charting

Data charting consisted of abstraction of 21 data points, including study design, sample size, average age of participants, gender, biomarkers sensitivity and specificity and prognostic index. Data were extracted by two reviewers independently using a designated form program, with any disagreements resolved by consensus. The Data items are as per the data extraction form in the supplementary files (Appendix B). The quality of studies was assessed according to the Newcastle Ottawa quality assessment scale for case control and cohort studies; Cochrane risk-of-bias tool for RCTs.

Results

Results of the Search Strategy, Screening and Data Charting

A total of 21 studies of good quality were accepted for inclusion in this scoping review. Supplementary Table 1 includes descriptions of the study design and population for each article reviewed. The studies were published recently, between the years 2005 to 2019 with 90% of the studies published after year 2010. Among these studies, a total of 17 separate cardiovascular biosample biomarkers were analysed. The age group of subjects in the studies are adults with age range of 47-73 except one study with paediatric patients with mean age of 1.41. The gender of the subjects are mainly men at percentages range of 38-80% (average 60%).

Summary of the Available Biomarkers in Assessing Disease Progression for CVDs

According to this review, the most prevalent biomarkers of the CVDs are the cardiac troponin T (cTnT) or high-sensitivity cardiac troponin T (hs-cTnT) and B-type natriuretic peptide (BNP) or N-terminal part of its prohormone (NT-proBNP). Other most evaluated biomarkers are Galectin-3 (GAL-3) and Growth-differentiation factor-15 (GDF-15), however these biomarkers are yet to be approved for the monitoring of CVDs by FDA. The remaining biomarkers (CRP, sAXL, PTX3, MPO, Lact/Chol ratio, tPA, miR-133a, tlncRNAs, cMyBP-C, CA-125, sST2) are potential prognostic tools for monitoring cardiovascular disease progression that are yet to be approved by FDA (Supplementary Table 2).

Cardiac troponin T (cTnT) is a specific biomarker of cardiomyocyte injury and is the gold standard for diagnosing myocardial lesions or infarctions. The measured level of cTnT in acute coronary syndrome may rise above 1 ng/mL. In HF, the concentration of measured cTnT is low, consistently <0.1 ng/mL (17)23. The new, high-sensitivity assay (Hs-cTnT) allows the measurement of very low concentrations of cTnT and able to differentiate between values detected in healthy individuals and in patients with minor cardiac damage as that produced by coronary ischemia. Mingels et al found that cardiac events occurred more than three times in patients with the highest quartile of Hs-cTnT >6.7 ng/mL relative to patients with the lowest three quartiles. In addition, the survival analysis showed that Hs-cTnT contributed significantly to the detection of a patient subgroup with a higher risk of cardiac events, and the study concluded that Hs-

cTnT is a valuable prognostic biomarker in patients with chest pain suspected of having CAD.[20] Another study evaluated the prognostic value of two biomarkers, Hs-cTnT and sAXL to predict severe CV events after heart transplantation and showed that plasma concentration of Hs-cTnT, but not sAXL, is a strong negative predictor of the probability for suffering long term CV events.[21] The cut-off value of Hs-cTnT <21ng/L may offer a better prognosis by useful means to detect heart transplant patients at low risk of CV events. Furthermore, James et al reported that measurement of cTnT and NT-proBNP levels improves risk stratification of patients with non–ST-segment elevation ACS and therefore should be included as early management strategy decisions for patients with ACS.[22]

The BNP and NT-proBNP are among the most powerful biomarkers for the prediction of mortality in patients with HF or other heart problems. Harutyunyan et al suggested that increased serum NT-proBNP was a stronger predictor of MI, cardiovascular death than hs-CRP in patients with stable CAD.[23] Morrow et al reported that the serial determinations of BNP levels during outpatient follow-up after ACS were able to predict the risk of death or new congestive heart failure (CHF). Furthermore, the changes in BNP levels over time are associated with long-term medical consequences and may offer a basis for improved clinical decision making in ACS patients after the onset of the disease.[24] Importantly, an integrated examination of BNP, MPO and hs-CRP cardiac biomarkers offers incremental prognostic benefit for long-term clinical adverse effects in ACS patients.[25]

Gal-3 produced by activated macrophages, is a soluble B-galactosidase binding lectin. Interestingly, the generation of Gal-3 is elevated before and after the onset of HF. In patients with HF, it has been proposed as a possible prognostic biomarker that better represents disease progression than cTnT and BNP. In stable HF patients, an upward change in Gal-3 >25-30 percent is likely to be clinically meaningful and Gal-3 has limited intra-person biological variability.[26] Gurel et al corroborated that plasma Gal-3 levels correlated with diastolic dysfunction and could assist in eliminating the risk factor in diastolic HF.[27] Therefore, elevated Gal-3 levels can be a beneficial indicator of deterioration in myocardial relaxation.

GDF-15 is a protein that is part of the transforming growth factor-β family and it plays an important function in regulating the response to injury in many tissues. In the heart, GDF-15 contributes in the modulation of myocardial strain, remodelling, and apoptosis. Evidences suggest that circulating levels of GDF-15 is associated with prognosis of patients with CVDs. Anand et al reported that GDF-15 levels are associated with several pathological processes that are linked to the HF severity and progression.[28] Another study showed that in CHD, GDF-15 was independently associated with cardiovascular mortality.[29] The concentration of GDF-15 in blood was directly related to the concentrations of other biomarkers that are recognized to predict CV events such as cTnT, BNP and CRP. Thus, the measurement of GDF-15 would be valuable for the assessment of the overall risk of adverse outcomes in CHD patients.

Consensus qualitative themes

The qualitative themes that emerged from this review is the potential for additive prognostic role that the cardiovascular disease progression biomarkers possess which yield better accuracy of disease progression prediction (Table 1). In the primary healthcare, the measurement of BNP or NT-proBNP or markers of myocardial injury (cTnT) may enhance prognostic information to standard risk factors for predicting new onset HF. A key finding in the review is that biomarkers BNP and cTnT were with established clinical validity to monitor cardiovascular disease progression (Table 2), however these biomarkers are not readily available at most primary healthcare settings.

Discussion

This review was designed to evaluate the predictive biomarkers for the progression of different types of CVDs which may help to improve the monitoring and/or management of CVDs progression. This review summarises that the monitoring of ACS and HF are currently done by monitoring cTnT and BNP respectively, in the hospital settings. However, these biomarkers are not readily available in the primary healthcare clinics. Primary care serves are the cornerstone for building a stronger healthcare system, thus an effective primary care services delivering quality healthcare is essential to improve health outcomes and to reduce disparities. Therefore, future research should focus into the cost-effectiveness of setting up cTnT and BNP within primary healthcare settings in order to reduce tertiary costs in the hospital settings.

To improve outcomes of people living with CVDs, an early identification of the risk of rapid progressive loss of cardiac function is vital. The BNP and NT-proBNP have been proven for clinical use in the diagnosis of HF and/or exacerbation of HF. The BNP concentration is closely associated with the incidence and severity of HF. Indeed, BNP's value increases with increasing severity of the disease as categorized by the New York Heart Association (NYHA) functional classification. In primary healthcare, BNP could be utilized to screen HF in high risk asymptomatic patients such as those with hypertension or diabetes by using a cut-off value of 20-40 pg/ml BNP or 100-150 ng/ml NT-pro BNP.[30] Importantly, the cut off value of BNP in acute settings such as acute exacerbation is higher. Therefore, BNP is very useful in predicting a patient's status and establishing appropriate therapeutic strategies. In addition, cardiac troponin has been used for the diagnosis and risk stratification of patients with ACS. The maximum cTnT value was predictive of death, recurrent ischaemic events, and HF in a prospective longitudinal study of contemporary patients with first MI.[31]Therefore, the current established and most widely used biomarkers cTnT and BNP should be utilised to monitor the progression of CS and HF at primary healthcare set up.

Measurement of the BNP or NT-proBNP is useful for forming prognosis of CHF and CAD.[23] Increased BNP levels are parallel to the severity of the condition, and elevated filling pressures or worse hemodynamics indicating worse clinical outcomes and mortality in CHF patients, according to the NYHA assessment.[32] The levels of cTnT add to that obtained from other clinical markers, an incremental prognostic information. Elevations in cTnT both correlate with poor

prognosis and are associated with impaired hemodynamic, progressive decline in LV systolic function and reduced survival.[33] One-year mortality was 71% for patients with pulmonary embolism whose troponin remained elevated compared with 45% for those with decreased level of troponin.[34] In addition, NPs provide useful clinical information in hypertension and in both stable and unstable CAD. Atrial natriuretic peptide gene (NPPA) abnormalities and genetically induced changes in circulating levels of NPs, have a pathogenic causal link with CV diseases and represent emerging markers of CV risk. Novel NP-based therapeutic strategies are currently under advanced clinical development, as they are expected to contribute to the future management of hypertension and HF.

Creatine kinase (CK and CK-MB), myoglobin, and hsCRP are other cardiac biomarker assessments that can be used to diagnose, assess and monitor people suspected of having ACS. [35,36] Among these markers, sensitivity and specificity for myocardial cell injury differ greatly, and cardiac troponins are the most sensitive and specific markers of choice.[37] Highly sensitive cardiac troponin (hs-cTn) assays that are very accurate have recently become available.[38] Such assays may test troponin (T or I) levels as low as 3 to 6 pg/mL reliably, and assays may detect as low as 1 pg/mL in some study.[44] Thus, cardiac specific biomarkers, cTnT and BNP should essentially be made available in the primary healthcare settings to allow rapid assessment of the progression of CVDs and to potentially be used as therapeutic targets before the emergence of clinical signs and symptoms.

As the leading cause of death globally, CVDs claims more lives than all forms of cancer combined, which is an estimated 17.9 million lives each year. More than three quarters of CVD deaths take place in countries with low and medium incomes. The estimated global economic burden of HF is at $108 billons per year.[39] Therefore, a good prognostic measures such as the appropriate use of the biosample biomarkers for the monitoring of disease progression at primary healthcare settings could substantially reduce the economic burdens of CVDs.

The incremental benefits of adding multiple biomarkers for the prognosis and management of CVDs yet to be explored widely. Evaluation of a combination of the biomarkers that reflect myocardial cell damage (troponin I), left ventricular dysfunction (NT-proBNP), renal failure (cystatin C) and inflammation (CRP), and in addition to an evaluation focused on the identified risk factors for CVD, the risk stratification of an individual has improved.[40,41] The simultaneous evaluation of several biomarkers of cardiovascular abnormalities may substantially improve the risk stratification for death from cardiovascular origins beyond that of the established risk factors model.

One of the vital factor that determines the availability of cardiac biomarkers at primary healthcare settings is the cost. However, cost may be less significant for prognostic markers as only people with the disease are being tested. In the current review, the cost of the CVDs biomarkers testing are not available in the included papers. Accessible and cost effective prognostic tool for the assessment of CVDs progression is essential for a primary healthcare. A study in Scotland highlighted that the use of BNP in diagnosing HF in primary care caused a reduction in one third of the cost for the management of HF. This is an advantage

for the primary care clinics, as not only the echocardiography is costly, it is also not easily accessible.[42] In addition, an Australian study showed that the C-statistic increment per unit cost evaluated for a number of novel biomarkers which is commonly used revealed that the BNP showed the best value for money in terms of improving the prediction of cardiovascular risk.[43] CVDs represent a major economic burden on the healthcare systems in terms of the total costs associated with mortality and morbidity. As of 2016, cardiovascular-related medical care in the United States accounts for more than 20% of all the economic costs of disease, which is equivalent to $555 billion dollars.[44] This highlights how great a problem CVD is, remarkably in comparison with any other cause of medical expenditures. Therefore, feasible and cost effective CVDs biomarkers availability at primary healthcare clinics would allow early diagnosis and implementation of treatment measures that may substantially reduce the cost of healthcare and socioeconomic burdens.

As shown in the supplementary table 2, all of prognostic biomarkers which are available have yet to be approved by FDA for the clinical use. Only cardiac troponin-T (cTnT) have been approved by FDA for the detection of cardiac morphologic damage. This could be due to the additional length of time needed to assess prognostic biomarkers. Prognostic biomarkers evaluate the improvement or deterioration of a particular disease as opposed to identifying the diagnosis of the disease itself. This results in both the randomised control trials (RCTs) and cohort studies taking longer time for completion and hence longer time for approval.[45] Additionally, the FDA has stringent requirement for biomarkers which are categorised under ideation and prove of concept and require clear evidence of cohort study or RCT evaluation to determine the benefit and risk assessment conclusively detailing the level of efficacy, specificity and sensitivity in CVD patients.[46] The general expectation of a CVD biomarker is to improve the clinician's ability to treat the patient optimally.

Conclusions

Qualitative themes derived from this review is that a number of biomarkers (BNP, cardiac troponin-T) have yielded better accuracy of disease progression prediction in ACS and HF. However, the majority of these biomarkers are only available in hospital or private settings. Cardiac troponin and BNP have been identified as the most suitable and probably the most cost effective CVD biomarkers to be made available at the primary healthcare clinics for the prognosis of HF and ACS. Thus, the current scoping review highlights the urgent need for further research for identifying if the availability of CVD biomarkers at primary healthcare settings would be cost effective.

This paper provides primary health care professional and stakeholders with an understanding of the role of prognostic biomarkers that help in improving the quality of healthcare delivered to patients with cardiovascular disorders through prognostic monitoring. Biomarkers are not only capable of enhancing cardiovascular disease confirmation but for identifying higher risk patients for more personalized disease management interventions and determining patients at risk for targeted prevention effort. This article provides justification for *in vitro* diagnostics industry to undertake the responsibility of developing more

economical methods of biomarker measurement and to disseminate the potentially valuable technology more extensively.

Ethics approval and consent to participate
None

NoneFunding
None

Acknowledgments
None.

References

1. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR et al. . M doi: 10. 1161/CIR. 0000000000000659. E in: C 2020 J 14;141(2):e33. P 30700139. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation*. 2019;139(10):e56-e528.
2. Deaton C, Froelicher ES, Wu LH, Ho C, Shishani K JT. . The global burden of cardiovascular disease. *Eur J Cardiovasc Nurs*. 2011;10(2):00111–3.
3. Yusuf S, Reddy S, Ôunpuu S AS. . . Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation*. 2001;104(22):2746–53.
4. CDC.
https://www.cdc.gov/globalhealth/healthprotection/ncd/cardiovascular-diseases.
https://www.cdc.gov/globalhealth/healthprotection/ncd/cardiovascular-diseases.
5. Roger VL, Go AS, Lloyd-Jones DM et al. Heart disease and stroke statistics–2012 update: A report from the American Heart Association. *Circulation*. 2012;125:e2–e220.
6. Joseph P, Leong D, McKee M, Anand SS, Schwalm JD, Teo K, Mente A YS. Reducing the Global Burden of Cardiovascular Disease, Part 1: The Epidemiology and Risk Factors. *Circ Res*. 2017;121():.(6):677-694. doi:10.1161/CIRCRESAHA.117.308903.
7. Vasan RS. Biomarkers of Cardiovascular Disease: Molecular Basis and Practical Considerations. *Circulation*. 2006;113:2335–2362.
8. Dhingra R VR. Biomarkers in cardiovascular disease: Statistical assessment and section on key novel heart failure biomarkers. *Trends Cardiovasc Med*. 2017;27(2):123-133. doi:doi:10.1016/j.tcm.2016.07.005
9. Sunil K Nadar and Muhammed Mujtaba Shaikh. Biomarkers in Routine Heart Failure Clinical Care. *Card Fail Rev*. 2019;5(1):50–56.
10. McLean, A. S., Huang, S. J., & Salter M. Bench-to-bedside review: the value of cardiac biomarkers in the intensive care patient. *Crit care*. 2008;12(3):215. doi:10.1186/cc6880
11. Hemingway H, Henriksson M, Chen R, Damant J, Fitzpatrick NK, Abrams K et al. The effectiveness and cost-effectiveness of biomarkers for the

prioritisation of patients awaiting coronary revascularisation: a systematic review and decision-model. *Heal Technol Assess*. 2010;14.
12. Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F et al. Guidelines on the management of stable angina pectoris: executive summary: the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *Eur Hear J*. 2006;27:1341-1381.
13. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M et al. . Markers of inflammation and cardiovascular disease: application to clinical and public health practice—a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003;107:499-511.
14. Everett BM, Brooks MM, Vlachos HE, Chaitman BR, Frye RL BDB 2D SG. Troponin and cardiac events in stable ischemic heart disease and diabetes. *N Engl J Med*. 2015;373(7):610-620.
15. Bruno G, Landi A, Barutta F et al. N-terminal probrain natriuretic peptide is a stronger predictor of cardiovascular mortality than C-reactive protein and albumin excretion rate in elderly patients with type 2 diabetes: the Casale Monferrato population-based study. *Diabetes Care*. 2013;36(9):2677-2682.
16. Gerstein HC, Paré G, McQueen MJ et al; . Outcome Reduction With Initial Glargine Intervention Trial Investigators. Identifying novel biomarkers for cardiovascular events or death in people with dysglycemia. *Circulation*. 2015;132(24):2297-2304.
17. Arksey, H., & O'Malley L. *Scoping Studies: Towards a Methodological Framework*. Vol 8.; 2005.
18. Levac, D., Colquhoun, H., & O'Brien KK(). Scoping studies: Advancing the methodology. *Implement Sci*. 2010;5:1–9. doi:10.1186/1748-5908-5-69
19. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, Moher D, Peters MDJ, Horsley T, Weeks L et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med*. 2018;169(7):467-473.
20. Mingels AM, Joosen IA, Versteylen MO, Laufer EM, Winkens MH, Wildberger JE, Van Dieijen-Visser MP HL. High-sensitivity cardiac troponin T: risk stratification tool in patients with symptoms of chest discomfort. *PLoS One*. 2012;7(4):e35059. doi:10.1371/journal.pone.0035059
21. Mirabet S, García-Osuna A, Garcia de Frutos P, Ferrero-Gregori A, Brossa V, Lopez L, Leta R, Garcia-Picart J, Padro JM, Sánchez-Quesada JL, Cinca J, Ordonez-Llanos J RE. High-Sensitivity Troponin T and Soluble Form of AXL as Long-Term Prognostic Biomarkers after Heart Transplantation. *Dis Markers*. Published online 2018:6243529. doi:10.1155/2018/6243529
22. James SK, Lindbäck J, Tilly J, Siegbahn A, Venge P, Armstrong P, Califf R, Simoons ML, Wallentin L LB. Troponin-T and N-terminal pro-B-type natriuretic peptide predict mortality benefit from coronary revascularization in acute coronary syndromes: a GUSTO-IV substudy. *J Am Coll Cardiol*. 2006;48(6):1146-1154.
23. Harutyunyan MJ, Mathiasen AB, Winkel P, Gøtze JP, Hansen JF, Hildebrandt P, Jensen GB, Hilden J, Jespersen CM, Kjøller E et al. CLARICOR Trial Group. High-sensitivity C-reactive protein and N-terminal pro-B-type natriuretic peptide in patients with stable coronary artery disease: a prognostic study within the CLARICOR trial. *Scand J Clin Lab*

Invest. 2011;71(1):52-62. doi:10.3109/00365513.2010.538081.
24. Morrow DA, de Lemos JA, Blazing MA, Sabatine MS, Murphy SA, Jarolim P, White HD, Fox KA, Califf RM BE. Prognostic value of serial B-type natriuretic peptide testing during follow-up of patients with unstable coronary artery disease. *JAMA*. 2005;294(22):2866-2871.
25. Tang WH, Iqbal N, Wu Y HS. Usefulness of cardiac biomarker score for risk stratification in stable patients undergoing elective cardiac evaluation across glycemic status. *Am J Cardiol*. 2013;111(4):465-470. doi:10.1016/j.amjcard.2012.10.027
26. Schindler EI, Szymanski JJ, Hock KG, Geltman EM SM. Short- and Long-term Biologic Variability of Galectin-3 and Other Cardiac Biomarkers in Patients with Stable Heart Failure and Healthy Adults. *Clin Chem*. 2016;62(2):360-366. doi:10.1373/clinchem.2015.246553.
27. Gurel OM, Yilmaz H, Celik TH, Cakmak M, Namuslu M, Bilgiç AM, Bavbek N, Akcay A EB. Galectin-3 as a new biomarker of diastolic dysfunction in hemodialysis patients. *Herz*. 2015;40(5):788-794. doi:0.1007/s00059-015-4303-6
28. Anand IS, Kempf T, Rector TS, Tapken H, Allhoff T, Jantzen F, Kuskowski M, Cohn JN, Drexler H WKO 5;. doi: E 2010 S 20. Serial measurement of growth-differentiation factor-15 in heart failure: relation to disease severity and prognosis in the Valsartan Heart Failure Trial. *Circulation*. 2010;122(14):1387-1395. doi:10.1161/CIRCULATIONAHA.109.928846.
29. Hagström E, Held C, Stewart RA, Aylward PE, Budaj A, Cannon CP, Koenig W, Krug-Gourley S, Mohler ER, Steg PG, Tarka E, Östlund O, White HD, Siegbahn A WL. STABILITY Investigators. Growth Differentiation Factor 15 Predicts All-Cause Morbidity and Mortality in Stable Coronary Heart Disease. *Clin Chem*. 2017;63(1):325-333. doi:10.1373/clinchem.2016.260570
30. Rehman SU JJ. Natriuretic Peptide testing in primary care. *Curr Cardiol Rev*. 2008;4(4):300-308. doi:doi:10.2174/157340308786349499
31. Gerber, Y., Jaffe, A. S., Weston, S. A., Jiang, R., & Roger VL. Prognostic value of cardiac troponin T after myocardial infarction: a contemporary community experience. *Mayo Clin Proc*. 2012;87(3):247–254. doi:https://doi.org/10.1016/j.mayocp.2011.11.013
32. Chow, S. L., Maisel, A. S., Anand, I., Bozkurt, B., de Boer, R. A., Felker, G. M., Fonarow, G. C., Greenberg, B., Januzzi, J. L., Jr, Kiernan, M. S., Liu, P. P., Wang, T. J., Yancy, C. W., Zile, M. R., & American Heart Association Clinical Pharmacology Co P and RC on E and PC on FG and TB and C on Q of C and OR. Role of Biomarkers for the Prevention, Assessment, and Management of Heart Failure: A Scientific Statement From the American Heart Association. *Circulation*. 2017;135(2):e1054–e1091. doi:https://doi.org/10.1161/CIR.0000000000000490
33. Horwich TB, Patel J, MacLellan WR FG. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. *Circulation*. 2003;108(7):833-838. doi:10.1161/01.CIR.0000084543.79097.34
34. Janata KM, Leitner JM, Holzer-Richling N, Janata A, Laggner AN JB. Troponin T predicts in-hospital and 1-year mortality in patients with pulmonary embolism. *Eur Respir J*. 2009;34(6):1357-1363. doi:10.1183/09031936.00033109

35. Rottbauer W, Greten T, Müller-Bardorff M et al.;. doi:10. 1093/eurheartj/17. suppl_f. . Troponin T: a diagnostic marker for myocardial infarction and minor cardiac cell damage. *Eur Hear J*. 1996;17(Suppl F):3-8.
36. Aydin S, Ugur K, Aydin S, Sahin İ YM. Biomarkers in acute myocardial infarction: current perspectives. *Vasc Heal Risk Manag*. 2019;15:1-10. doi:10.2147/VHRM.S166157
37. Twerenbold R, Boeddinghaus J, Nestelberger T et al. Clinical Use of High-Sensitivity Cardiac Troponin in Patients With Suspected Myocardial Infarction. *Am Coll Cardiol J*. 2017;70(8):996-1012. doi:10.1016/j.jacc.2017.07.718
38. J M. High-sensitivity cardiac troponins in everyday clinical practice. *World J Cardiol*. 2014;6(4):175–182. doi:https://doi.org/10.4330/wjc.v6.i4.175
39. Cook, C., Cole, G., Asaria, P., Jabbour, R., & Francis DP. The annual global economic burden of heart failure. *Int J Cardiol*. 2014;171(3):368–376. doi:https://doi.org/10.1016/j.ijcard.2013.12.028
40. de Lemos JA L-JD. Multiple biomarker panels for cardiovascular risk assessment. *N Engl J Med*. 2008;358(20):2172-2174. doi:doi:10.1056/NEJMe0801721
41. Ruwanpathirana T, Owen A RC. Review on cardiovascular risk prediction. *Cardiovasc Ther*. 2015;33(2):62-70. doi:10.1111/1755-5922.1211
42. Chapman AR, Leslie SJ, Walker SW, Bickler C DM. Potential costs of B-type natriuretic peptide for the identification of people with heart failure in primary care in Scotland - a pilot study. *J R Coll Physicians Edinb*. 2015;45(1):27-32. doi:doi:10.4997/JRCPE.2015.107
43. Tarride JE, Lim M, DesMeules M et al. A review of the cost of cardiovascular disease. *Can J Cardiol*. 2009;25(6):e195-e202. doi:doi:10.1016/s0828-282x(09)70098-4
44. Schade DS, Obenshain SS, Ramo B ER. A Feasible, Simple, Cost-Saving Program to End Cardiovascular Disease in the United States. *Am J Med*. 2019;132(12):1365-1367. doi:10.1016/j.amjmed.2019.03.043
45. R S. Clinical trial designs for evaluating the medical utility of prognostic and predictive biomarkers in oncology. *Per Med*. 2010;7(1):33–47. doi:https://doi.org/10.2217/pme.09.49
46. Amu S, LaVange L, ZinehI B-GS and W. Biomarker Qualification: Toward a Multiple Stakeholder Framework for Biomarker Development, Regulatory Acceptance, and Utilization. *Clin Pharmacol Ther J*. 2015;98:1.
47. Batlle M, Campos B, Farrero M, Cardona M, González B, Castel MA, Ortiz J, Roig E, Pulgarín MJ, Ramírez J et al. Use of serum levels of high sensitivity troponin T, galectin-3 and C-terminal propeptide of type I procollagen at long term follow-up in heart failure patients with reduced ejection fraction: Comparison with soluble AXL and BNP. *Int J Cardiol*. 2016;225:113-119. doi:10.1016/j.ijcard.2016.09.079
48. Sato Y, Yamamoto E, Sawa T, Toda K, Hara T, Iwasaki T, Fujiwara H TY. High-sensitivity cardiac troponin T in essential hypertension. *J Cardiol*. 2011;58(3):226-231. doi:10.1016/j.jjcc.2011.07.009.
49. Mjelva ØR, Pönitz V, Brügger-Andersen T, Grundt H, Staines H ND. Long-term prognostic utility of pentraxin 3 and D-dimer as compared to high-sensitivity C-reactive protein and B-type natriuretic peptide in suspected acute coronary syndrome. *Eur J Prev Cardiol*. 2016;23():(11):1130-1140.

doi:10.1177/2047487315619733
50. Desmoulin F, Galinier M, Trouillet C, Berry M, Delmas C, Turkieh A, Massabuau P, Taegtmeyer H, Smih F RP. Metabonomics analysis of plasma reveals the lactate to cholesterol ratio as an independent prognostic factor of short-term mortality in acute heart failure. *PLoS One*. 2013;8(4):e60737. doi:10.1371/journal.pone.0060737
51. Lee CW, Ahn JM, Park DW, Kim YH, Hong MK, Song JK, Kim JJ, Park SW, Chi HS PS. Tissue plasminogen activator on admission is an important predictor of 30-day mortality in patients with acute myocardial infarction undergoing primary angioplasty. *Atherosclerosis*. 2008;196(1):327-332.
52. De Rosa R, De Rosa S, Leistner D, Boeckel JN, Keller T, Fichtlscherer S, Dimmeler S ZA. Transcoronary Concentration Gradient of microRNA-133a and Outcome in Patients With Coronary Artery Disease. *Am J Cardiol*. 2017;120(1):15-24. doi:10.1016/j.amjcard.2017.03.264
53. Zhang X, Nie X, Yuan S, Li H, Fan J, Li C, Sun Y, Zhao Y, Hou H, Wang DW CC. Circulating Long Non-coding RNA ENST00000507296 Is a Prognostic Indicator in Patients with Dilated Cardiomyopathy. *Mol Ther Nucleic Acids*. 2019;7(16):82-90. doi:10.1016/j.omtn.2019.02.004
54. El Amrousy D, Hodeib H, Suliman G, Hablas N, Salama ER EA. Diagnostic and Prognostic Value of Plasma Levels of Cardiac Myosin Binding Protein-C as a Novel Biomarker in Heart Failure. *Pediatr Cardiol*. 2017;38(2):418-424. doi:10.1007/s00246-016-1532-2
55. Ordu S, Ozhan H, Alemdar R, Aydin M, Caglar O, Yuksel H KH. Carbohydrate antigen-125 and N-terminal pro-brain natriuretic peptide levels: compared in heart-failure prognostication. *Tex Hear Inst J*. 2012;39(1):30-35.
56. Kontny F, Andersen T, Ueland T, Åkerblom A, Lakic TG, Michelsen AE, Aukrust P, Bertilsson M, Becker RC, Himmelmann A, James SK, Siegbahn A,, Storey RF WL. PLATO Investigators. Pentraxin-3 vs C-reactive protein and other prognostic biomarkers in acute coronary syndrome: A substudy of the Platelet Inhibition and Patients Outcomes (PLATO) trial. *Eur Hear J Acute Cardiovasc Care*. Published online 2019:2048872619846334. doi:10.1177/2048872619846334
57. Dieplinger B, Egger M, Haltmayer M, Kleber ME, Scharnagl H, Silbernagel G, de Boer RA, Maerz W MT. Increased soluble ST2 predicts long-term mortality in patients with stable coronary artery disease: results from the Ludwigshafen risk and cardiovascular health study. *Clin Chem*. 2014;60(3):530-540. doi:10.1373/clinchem.2013.209858
58. Wallace, T. W., Abdullah, S. M., Drazner, M. H., Das, S. R., Khera, A., McGuire, D. K., Wians, F., Sabatine, M. S., Morrow, D. A., & de Lemos JA. Prevalence and determinants of troponin T elevation in the general population. *Circulation*. 2006;113(16):1958–1965. doi:https://doi.org/10.1161/CIRCULATIONAHA.105.609974
59. Lopez-Calle, E., Espindola, P., Spinke, J., Lutz, S., Nichtl, A., Tgetgel, A., Herbert, N., Marcinowski, M., Klepp, J., Fischer, T., Brueckner, T., Boehm, C., & Keller T. A new immunochemistry platform for a guideline-compliant cardiac troponin T assay at the point of care: proof of principle. *Clin Chem Lab Med*. 2017;55(11):1798–1804. doi:https://doi.org/10.1515/cclm-2016-1078

Table 1: Consensus qualitative themes

No	Theme	References
1.	A number of combination biomarkers (BNP, cardiac TnT, CRP, sAXL) have yielded better accuracy of disease progression prediction in ACS and HF.	Harutyunyan et al 2011, Batlle et al 2014, Tang et al 2013, James et al 2006
2.	The approved biomarkers are only available in hospital setting except for cTnT and BNP with availability at limited primary healthcare centers. Most other markers are potential prognostic biomarkers that yet to receive approval for clinical and/or diagnostic use.	All references included

Table 2: Analytical and clinical validity for selected prognostic biomarkers

Biomarkers	Sensitivity	Specificity	PPV	NPV
cTnT & Hs-cTnT	cTnT lowest detectable concentration above the 99th percentile that has <10% coefficient of variation (CV) is 0.03 g/L, whereas the lower detection limit is <0.01 g/L[58] Hs-cTnT, lower detection limit 3.0 ng/L. At a concentration of 14 ng/L, the 99th percentile value from the hs-cTnT assay in the Elecsys® system, the imprecision (CV) was 3.8%. The functional sensitivity for a CV <10% was 6.8 ng/L.[59]	Specific to myocardial tissue	Low 1-year mortality in patients without troponin-T or NT-proBNP elevation. Troponin-T and NT-proBNP markers not only help to stratify the risk of non-ST segment elevation ACS patients, but also tend to classify patients with decreased mortality associated with early coronary revascularization.[22]	Hs-cTnT has negative predictive value of 99.4% (95% CI, 96.6%–100.0%) for ruling out AMI
BNP & NT-proBNP (& CRP)	BNP levels greater than 80 pg/mL have a sensitivity greater than 98% in the diagnosis of heart failure.	BNP is released from the myocardium in response to myocardial stretch,	Serum NT-proBNP correlated significantly with MI (hazard ratio (HR), 1. 65 (refers to a serum level increase of 2.72 fold, p 0.0005), CVD	BNP cutoff of 80 pg/mL yielded 95% accuracy, with negative predictive value of 98%.

		specific CVD biomarker.	(HR, 2.42, p 0.0005) and non-CVD (HR, 1.79,p 0.0005). Increased serum NT-proBNP in patients with healthy CAD has been a better indicator of MI, cardiovascular death and non-cardiovascular death than hs-CRP.[23]	