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APPLICATION CARDIAC TROPONIN IN CARDIOVASCULAR DISEASES OTHER THAN ACUTE CORONARY SYNDROME: A SYSTEMATIC REVIEW

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ABSTRACT

Background: *Increased cardiac troponin concentrations in acute coronary syndrome (ACS) identify patients with ongoing cardiomyocyte necrosis who are at increased risk. However, with the use of more precise assays, cardiac troponin increases are commonly noted in other cardiovascular conditions as well.*

The aim: *This study aims to show application cardiac troponin in cardiovascular disease other than acute coronary syndrome.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 211 articles, whereas the results of our search on SagePub brought up 221 articles. The results of the search conducted for the last year of 2013 yielded a total 65 articles for PubMed and 95 articles for SagePub. The result from title screening, a total 19 articles for PubMed and 30 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.*

Conclusion: *Increased cardiac troponin indicates increased risk for adverse outcome in patients with various cardiovascular conditions beyond ACS. Routine measurement of cardiac troponin concentrations can however, not be generally recommended unless there is a suspicion of ACS.*

Keyword: *Cardiac troponin, cardiovascular disease, acute coronary syndrome.*

INTRODUCTION

Troponins are integral regulatory proteins located on the thin actin filament within the myocytes of striated heart muscle, and are released when cardiac myocyte injury occurs. These proteins are responsible for the intricate contraction-relaxation cycle of myocytes. The cTn complex is composed of 3 different subunits: cardiac troponin-C (cTnC, the calcium-binding component), cTnT (the tropomyosin-binding component), and cTnI (the inhibitory-activity regulator of the myosin-binding sites on actin thin filaments). During depolarization of the cardiac myocyte, calcium enters the sarcoplasm, binds to cTnC, and induces structural changes in the cTn complex. The resulting shift of tropomyosin away from the active site of actin allows the myosin heads of the thick filament to interact with the now-exposed myosin-binding site of the actin filaments, thereby producing contraction of the sarcomere and, consequently, the myocardium as a syncytium. The existence of several isoforms of troponin depends upon differential gene expression in particular tissues. For example, expression of cTnC occurs in both cardiac and skeletal muscle, making it a poor indicator of myocardial injury.[1,2]

Cardiovascular diseases are one of the most common causes of mortality and disability of the world's population; therefore, the search and discovery of new diagnostic capabilities is a priority in current research. The contribution of cardiac troponins (CTs) in the modern diagnostics of cardiovascular diseases cannot be overestimated. These laboratory biomarkers are considered the most sensitive and specific indicators of myocardial injury, which allows them to be considered as the "gold standard" for diagnosing acute coronary heart disease (CHD)—myocardial infarction (MI). CTs are protein molecules that, together with another protein called tropomyosin, form the troponin-tropomyosin system, which is an important component of thin (also called actin) filaments. Among the proteins that are part of thin filaments, only cardiac troponin T (CT-T) and cardiac troponin I (CT-I) have a specific structure characteristic of the main cells of the heart muscular membrane—contractile cardiac myocytes (CMCs). All other thin filament proteins, including actin, tropomyosin and troponin C, have the same structure. CTs are significant contributors due to participating in the regulation of the contraction-relaxation of operating CMCs. The name of cardiac troponins is in accordance with their function. Troponin C binds to calcium ions, which enter the cytoplasm mainly from the sarcoplasmic reticulum, in which calcium channels open when a nerve impulse is transmitted.[3,4]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast application cardiac troponin in cardiovascular disease other than acute coronary syndrome. It is possible to accomplish this by researching or investigating application cardiac troponin in cardiovascular disease other than acute coronary syndrome. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about application cardiac troponin in cardiovascular disease other than acute coronary syndrome. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " application cardiac troponin in cardiovascular disease other than acute coronary syndrome." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *((*"Cardiac troponin*"[MeSH Subheading] OR* "Cardiovascular disease*"[All Fields] OR* "Acute coronary syndrome*" [All Fields]) AND (*"Cardiac biomarker*"[All Fields] OR* " Biomarker of cardiovascular disease*"[All Fields]) AND (*"Biomarker of acute coronary syndrome*"[All Fields]) OR (*"Cardiac troponin in cardiovascular disease" *[All Fields]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

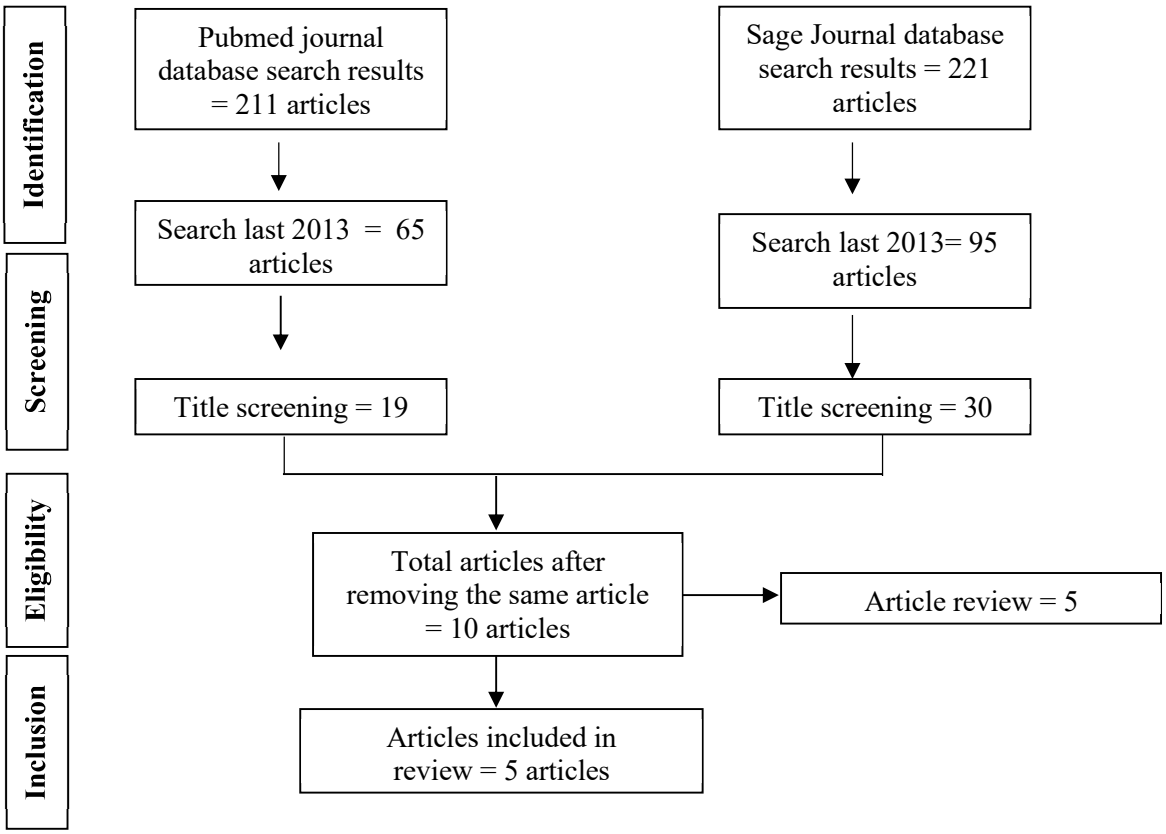

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 211 articles, whereas the results of our search on SagePub brought up 221 articles. The results of the search conducted for the last year of 2013 yielded a total 65 articles for PubMed and 95 articles for SagePub. The result from title screening, a total 19 articles for PubMed and 30 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.

Tveit, SH *et al* (2022)[5] showed Elevated concentrations of hs-cTnI and hs-cTnT are associated with obstructive CAD and higher CAC burden. Our results suggest that hs-cTn have diagnostic value in patients with low baseline CVD risk, while the diagnostic value of hs-cTn measurements in patients with higher risk seems limited. hs-cTnI appears to have superior diagnostic properties to hs-cTnT with regard to CAD, and the added analytical sensitivity of the hs-cTnI assay add discriminatory power in patients with very low hs-cTn concentrations. Future studies randomizing CCS patients to troponin-guided decision-making or standard care, with long term follow-up, is needed.

Bularga, A *et al* (2019)[6] showed the use of a risk stratification threshold for high-sensitivity cardiac troponin I in the evaluation of patients with suspected acute coronary syndrome presenting at least 2 hours from symptom onset identifies the majority of patients at low risk of immediate and future cardiovascular events. The use of an optimized risk stratification threshold of 5 ng/L compared with 2 ng/L, classifies twice as many patients as low risk. Although the proportion identified as low risk is reduced in older patients, the safety of this approach is maintained across patients irrespective of age or sex. The adoption of risk stratification thresholds in clinical practice has potential to improve both the effectiveness and safety of the evaluation of patients with suspected acute coronary syndrome with major benefits for patients and healthcare providers.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Tveit, SH *et al*., 2022[5]	Norway	A prospective cohort study	706 patients	A total of 706 patients with suspected CCS, referred for Coronary Computed Tomography Angiography, were included. cTn concentrations were measured using the Singulex hs-cTnI (limit of detection [LoD] 0.08 ng/L) and Roche hs-cTnT (LoD 3 ng/L) assays. Obstructive coronary artery disease (CAD_{50}) was defined as ≥ 50% coronary stenosis. Cardiovascular risk was determined by the NORRISK2-score. Median age of the patients was 65 (range 28–87) years, 35% were women. All patients had hs-cTnI concentrations above the LoD (median 1.9 [Q1-3 1.2–3.6] ng/L), 72% had hs-cTnT above the LoD (median 5 [Q1-3 2–11] ng/L). There was a graded relationship between hs-cTn concentrations and coronary artery calcium. Only hs-cTnI remained associated with CAD_{50} in adjusted analyses (OR 1.20 95% Confidence Interval [1.05–1.38]), $p = 0.009$). The C-statistics for hs-cTnI and hs-cTnT were 0.65 (95% CI [0.60–0.69]) and 0.60 (0.56–0.64). The highest specificity and negative predictive values for CAD_{50} were in the lowest NORRISK2-tertile. hs-cTn concentrations provide diagnostic information in patients with suspected CCS, with superior performance of hs-cTnI compared to hs-cTnT in regard to CAD_{50}. The diagnostic performance appeared best in those with low cardiovascular risk.
Bularga, A *et al*., 2019[6]	UK	Consecutive patients with suspected acute coronary syndrome	32837 patients	In total, 32 837 consecutive patients (61±17 years, 47% female) were included, of whom 23 260 (71%) and 12,716 (39%) had hs-cTnI

		(n=48 282) were enrolled in a multicenter trial across 10 hospitals in Scotland. In a prespecified secondary and observational analysis		concentrations of <5 ng/L and <2 ng/L at presentation. The negative predictive value for the primary outcome was 99.8% (95% CI, 99.7%–99.8%) and 99.9% (95% CI, 99.8%–99.9%) in those with hs-cTnl concentrations of <5 ng/L and <2 ng/L, respectively. At both thresholds, the negative predictive value was consistent in men and women and across all age groups, although the proportion of patients identified as low risk fell with increasing age. Compared with patients with hs-cTnl concentrations of ≥5 ng/L but <99th centile, the risk of myocardial infarction or cardiac death at 12 months was 77% lower in those <5 ng/L (5.3% vs 0.7%; adjusted odds ratio, 0.23 [95% CI, 0.19–0.28]) and 80% lower in those <2 ng/L (5.3% vs 0.3%; adjusted odds ratio, 0.20 [95% CI, 0.14–0.29]).
Kanani, F *et al*., 2023[7]	Pakistan	A retrospective study	5982 patients	There were a total of 5,982 patients (3,031 males, 2,951 females), out of which 878 patients were admitted under the cardiology specialty. In patients who were admitted to the ward, mortality was higher in females (8.2%) with less than a 10-fold rise in Hs-Troponin I while similar in both genders (7.6%) in patients with Hs-troponin I greater than 10-fold of sex-specific 99th percentile URL. Raised low-density lipoprotein-cholesterol was a significant factor associated with 2.4 times higher odds of ACS.
Chapman, AR *et al*., 2019[8]	UK	A stepped-wedge cluster randomized, controlled trial	48282 patients	Implementation increased the diagnosis of type 1 myocardial infarction by 11% (510/4471), type 2 myocardial infarction by 22% (205/916), and acute and chronic myocardial injury by 36% (443/1233) and 43% (389/898), respectively. Compared with those without myocardial injury, the rate of the primary outcome was highest in those with type 1 myocardial infarction (cause-specific hazard ratio [HR] 5.64 [95% CI, 5.12–6.22]), but was similar across diagnostic categories, whereas noncardiovascular deaths were

				highest in those with acute myocardial injury (cause specific HR 2.65 [95% CI, 2.33–3.01]). Despite modest increases in antiplatelet therapy and coronary revascularization after implementation in patients with type 1 myocardial infarction, the primary outcome was unchanged (cause specific HR 1.00 [95% CI, 0.82–1.21]). Increased recognition of type 2 myocardial infarction and myocardial injury did not lead to changes in investigation, treatment or outcomes.
Oh, AR *et al*., 2023[9]	Korea	Retrospective study	50119 patients	A population of 50,119 patients was divided into two groups, with 43,974 (87.8%) patients included in the no cTnI group and 6,145 (12.2%) patients included in the cTnI group. The multivariable analysis showed a reduction of mortality at one year in the cTnI group [5.9% *vs*. 3.8%, hazard ratio (HR) =0.78; 95% confidence interval (CI): 0.68–0.89; P<0.001]. Among 5,882 propensity score-matched pairs, this trend persisted, and the mortality rate was significantly lower in the cTnI group (5.3% *vs*. 3.9%, HR =0.77; 95% CI: 0.65–0.91; P=0.002). Patients with cTnI measurements taken at admission underwent cardiac evaluation and therapy more frequently.

Kanani F *et al* (2023)[7] showed 5,982 patients seen in the ED with raised Hs-Troponin I, 727 were admitted with an ultimate diagnosis of ACS. Out of these, 237 (32.5%) patients had Hs-Troponin I values less than 10 times sex-specific cutoffs on index ED visits. It is thus crucial to have a high index of suspicion and subject patients with suggestive symptoms to serial troponin testing. However, limitations of space and personnel are some of the practical factors involved in on-the-ground management strategies. Fast rule-in/rule-out protocols for ACS have been evaluated for quick diagnosis. Our center is a free-of-cost, high-quality, tertiary care setup located near a rural populace. The majority of our patients, therefore, come from the underprivileged sector of society and the ED is a busy place with a per-day flux of 700 to 1000 patients.

Chapman, AR *et al* (2019)[8] showed implementation of high-sensitivity cardiac troponin assays and the recommendations of the Universal Definition of Myocardial Infarction identified patients at high-risk of cardiovascular and noncardiovascular events but was not associated with consistent increases in treatment or improved outcomes. Trials of secondary prevention are urgently required to determine whether this risk is modifiable in patients without type 1 myocardial infarction.

Oh, AR *et al* (2023)[9] showed the measurement of cTnI in relatively stable patients at scheduled admission to medical departments was associated with reduced mortality during one year of follow-up. This could be related to more active evaluation and treatment. Further studies are needed to validate our results.

DISCUSSION

The measurement of Cardiac troponin concentration in systemic venous blood has become a core component of the assessment of patients with acute—and chronic—cardiovascular disease. This is enshrined in the Universal Definition of

Myocardial Infarction (UDMI), now in its fourth iteration—with the aim to (i) guide the clinician through the numerous differential diagnoses that result in cardiac troponin elevation, and (ii) provide classification and naming conventions to assist a structured approach. However, the 4th UDMI has stimulated considerable debate. Our previous review covered the basic biology of cardiac troponin, the physiology underlying its release from the heart, the analytic science enabling its detection in the blood, and its use in the diagnosis of myocardial infarction according to the 3rd UDMI. The purpose of this current review is to discuss the pathophysiology that underpins the 4th UDMI and how it is translated into clinical guidelines and practice—with a specific focus on the challenges encountered 'at the coalface' of acute cardiovascular care.[10,11]

Cardiovascular disease (CVD) is the leading global cause of death, resulting in an estimated 18.6 million deaths in 2019. Its most common form, ischemic heart disease, is a prevalent and deadly condition that can lead to acute myocardial infarction (AMI). Only 10.6% of patients survive an out-of-hospital cardiac arrest. After an AMI, patients require screening, preventive care, and coordinated follow-up appointments because of their increased risk of developing heart failure (HF). This comprehensive management may improve patient adherence to treatment guidelines, decrease rehospitalizations, and reduce the chance of developing HF.[12]

Biomarkers are critical tools for probing, assessing, and managing cardiovascular risk. In 2001, the National Institute of Health Consortium defined a biomarker as a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." Given the deadly consequences of undiagnosed CVD—including heart attack and sudden cardiac arrest—the American Heart Association in 2009 unprecedentedly established criteria for assessing the usefulness and accuracy of cardiovascular biomarkers.[12,13]

CONCLUSION

Increased cardiac troponin indicates increased risk for adverse outcome in patients with various cardiovascular conditions beyond ACS. Routine measurement of cardiac troponin concentrations can however, not be generally recommended unless there is a suspicion of ACS.

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