What Is the Diagnostic Accuracy of Cardiac Biomarkers for the Prediction of Adverse Cardiac Events in Patients Presenting With Acute Syncope?

TAKE-HOME MESSAGE

The sensitivity of brain-type natriuretic peptides and troponin for identifying syncopal patients at risk for major cardiac adverse events is inadequate.

METHODS

DATA SOURCES

The authors searched for published articles and articles in process within MEDLINE, EMBASE, the Cochrane Central Registrar of Controlled Trials, and the Database of Abstracts and Reviews of Effects from database inception to 2014. Studies were excluded if syncope was induced by medication or tilt-table testing.

STUDY SELECTION

Studies were included if they were randomized or quasi-randomized controlled trials, along with prospective and retrospective studies among adult patients with acute syncope, using cardiac biomarkers for risk stratification to predict the outcome of major adverse cardiac events.

DATA EXTRACTION AND SYNTHESIS

Two reviewers independently assessed the articles for eligibility and extracted data on study characteristics, using a standardized form. Disagreement of article inclusion between the independent authors was resolved by consensus through the use of a 2-phase

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Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: **Thiruganasambandamoorthy V, Ramaekers R, Rahman MO, et al. Prognostic value of cardiac biomarkers in the risk stratification of syncope: a systematic review. *Intern Emerg Med.* 2015;10:1003-1014.**

Results

Pooled test characteristics of cardiac biomarkers for major adverse cardiac events.

Cardiac Biomarker	Studies	n	Sensitivity (95% CI), %	Specificity (95% CI), %	LR+	LR–
Contemporary troponin	4	2,693	29 (24–34)	88 (86–89)	2.31 (1.86–2.84)	0.81 (0.75–0.87)
Natriuretic peptide	4	1,353	77 (69–85)	73 (70–76)	2.87 (2.48–3.21)	0.31 (0.21–0.43)
High-sensitivity troponin	3	819	74 (65–83)	65 (62–69)	2.15 (1.81–2.45)	0.39 (0.27–0.55)

LR+, Positive likelihood ratio; *LR–*, negative likelihood ratio.

The initial search identified 1,595 articles, and 104 met the inclusion criteria and underwent a full test review. Eleven studies met the inclusion criteria for analysis and were included in the review. Four of the included studies used contemporary troponins, 4 used brain-type natriuretic peptides, and 3 used high-sensitivity troponins. The majority of included studies (9) enrolled emergency department (ED) patients, but 2 included hospitalized patients who were admitted from the ED. According to the Quality Assessment of Diagnostic Accuracy Studies instrument, the included studies were at

independent literature-appraisal method. The quality of the included studies was determined by the Quality Assessment of Diagnostic Accuracy Studies methodology.[1] The authors determined the incidence of major adverse cardiac events, myocardial infarction, the diagnosis of cardiogenic syncope, and mortality within 30 days. The authors contacted the authors of the included studies to confirm the accuracy of constructed 2×2 contingency tables for each outcome. Two separate authors validated the accuracy of the tables. The authors evaluated statistical heterogeneity with the Cochrane *Q* statistic.

low to moderate risk of bias. Brain-type natriuretic peptides and high-sensitivity troponins had substantially higher sensitivities than contemporary troponins to detect major adverse cardiac events and mortality. The sensitivity of all biomarkers was similar for the detection of myocardial infarction, but contemporary troponins had the highest specificity for myocardial infarction. Contemporary troponin, brain-type natriuretic peptides, and high-sensitivity troponin had specificities of 87% (95% confidence interval [CI] 85% to 88%), 69% (95% CI 67% to 72%), and 62% (95% CI 62% to 62%), respectively, for myocardial infarction. Among the 2 studies including the outcome of cardiogenic syncope, brain-type natriuretic peptides performed better than high-sensitivity troponin. Contemporary troponins had higher specificity, 86% (95% CI 85% to 87%), to predict 30-day mortality than brain-type natriuretic peptide or high-sensitivity troponin, with values of 69% (95% CI 67% to 72%) and 62% (95% CI 58% to 65%), respectively. However, brain-type natriuretic peptides and high-sensitivity troponin had higher sensitivities, 85% (95% CI 62% to 97%) and 80% (95% CI 56% to 94%), respectively, compared with that of contemporary troponin (50%; 95% CI 32% to 68%).

Commentary

Syncope accounts for up to 2% of all ED visits and up to 6% of ED admissions,[2,3] which exceed $2 billion in annual costs.[4] A substantial proportion of syncope patients do not have a cause identified, and they experience a higher lifetime mortality rate than those who are found to have vasovagal syncope.[3] There has been an increase in advanced imaging for ED syncope patients, whereas ED admission rates for syncope have remained unchanged.[5] Meanwhile, there have been robust research efforts to identify and validate clinical decision rules to identify ED patients at high risk of adverse events who present with syncope.[6] The San Francisco Syncope Rule is the most robustly studied decision rule, and it has a pooled sensitivity and specificity of 86% (95% CI 83% to 89%) and 49% (95% CI 48% to 91%), respectively, for adverse events and the inability to reduce admission rates in some ED locations.[6-8]

Ideally, a syncope patient having nonelevated cardiac biomarkers could be discharged with minimal risk of adverse events during the next 30 days. Although this meta-analysis demonstrates that cardiac biomarker elevation used in isolation should not be used to accurately identify ED patients at risk for short-term adverse events, ED providers should place emphasis on the syncope guideline endorsed by the American College of Emergency Physicians, which emphasizes the role of patient history (including the prodromal symptoms before the syncopal event), physical examination, and especially the ECG in the risk stratification of ED patients presenting with syncope.[9] There are existing clinical decision rules that include cardiac biomarker testing.[10,11] Elevated brain-type natriuretic peptide alone in one study detected 41% of serious outcomes or mortality[10]; and elevated troponin alone detected 21% of adverse events and mortality in another study.[11] These clinical decision rules do not provide the specific degree to which cardiac biomarkers add to their incremental use within these proposed clinical decision tools.[10,11]

This systematic review has limitations through the inclusion of prospective and retrospective studies of various enrollment sizes, the combining of different methods of brain-type natriuretic peptide testing (N-terminal-probrain-type natriuretic peptide and traditional brain-type natriuretic peptide), and variations in cutoff values for positive cardiac biomarker results. Furthermore, the composite outcome of major adverse cardiac events reported in the included studies may be unrelated to the cause of syncope; a nonelevated troponin or brain-type natriuretic peptide level cannot obviate the risk of future cardiac ischemia or overt heart failure. These limitations

underscore the importance of history, ECG, and examination of ED patients presenting with syncope as essential components.[9]

Although cardiac biomarker values may provide incremental increases in an emergency clinician's ability to risk stratify syncope patients, brain-type natriuretic peptides appear to be the most promising. The incorporation of brain-type natriuretic peptides or high-sensitivity troponins to future clinical decision rules may help identify patients at low risk of adverse cardiac events.

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