Assessing the Association Between Cardiovascular Acoustic Biomarkers and Heart Failure: A Systematic Literature Review

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INTRODUCTION

- Heart failure (HF) imposes clinical, economic, and quality of life burdens on patients, caregivers, and healthcare systems
  - All-cause mortality rates and hospital readmission rates are high for patients with HF[1,2]
- Improved diagnosis, monitoring, and prediction tools are needed for better management of patients with HF[2,3]
- Cardiovascular acoustic biomarkers (CABs) are a noninvasive method to assess heart function over time and may predict postdischarge outcomes[4–6]
- CABs can assist in monitoring of electromechanical activation time (EMAT), the presence and strength of the third (S3) and fourth (S4) heart sounds, the duration of left ventricular systolic time (LVST), and systolic dysfunction index (SDI)[4,6] (**Figure 1**)

OBJECTIVE

- To conduct a systematic literature review (SLR) to compile and critically assess evidence supporting the use of CAB measures in patients with HF

METHODS

- Abstract and full-text screenings were conducted on the DistillerSR reviewing platform, and outputs were compiled in Microsoft Excel[7]
- All studies were examined for inclusion by two reviewers blinded to each other's decisions (**Table 1**). Conflicts were resolved through discussion or through mediation by a third reviewer, and 20% of screened studies were subjected to a quality check
- In line with Cochrane guidelines[8], all studies that met inclusion criteria after full-text review were deemed eligible for data extraction
- Data extraction was performed by one reviewer and independently checked for accuracy by a second reviewer followed by an additional 20% accuracy check performed by a senior reviewer. Any uncertainties were also reviewed by a senior reviewer

RESULTS

- A total of 28 publications were included in the SLR (**Figure 2**)
  - Of these, 25 were peer-reviewed journal articles and 3 were conference abstracts; 27 were clinical studies, including 3 randomized controlled trials, 1 case series, and 23 observational cohort, case-control, or cross-sectional studies. One publication was an SLR and meta-analysis
  - S3 and EMAT were the CABs used most often in the included studies (**Figure 3**)

S3-related publications

- S3 is a soft, low-frequency sound occurring during early diastole at the end of the rapid diastolic filling period of the right or left ventricle. Presence of S3 typically indicates volume overload by rapid left ventricular distension along with decreased atrioventricular flow[9]
- The SLR found a total of 16 publications that discussed changes in S3 characteristics and its role in HF detection or outcomes (**Figure 4**)

S3 detection and monitoring of HF

- Six publications[10–15] highlighted S3 assessment among various groups of patients with HF (**Supplemental Table S1**)
- Overall, S3 was reported as a robust CAB measure in HF and may serve as a valuable diagnostic CAB for HF
  - Both S3 amplitude and score were statistically significantly increased in patients with HF and may correlate with a more severe HF

S3 and HF outcomes

- A total of 10 studies reported on the relationship between S3 strength, amplitude, or presence, and clinical outcomes in patients with HF. One study reported on both the amplitude and presence of S3

S3 amplitude

- Five studies[16–20] evaluated the strength or amplitude of S3 (**Supplemental Table S2**)
  - In general, S3 amplitude was statistically significantly increased in patients with HF

S3 presence

- The relationship between the presence of S3 and cardiac-related clinical outcomes was reported across 6 studies[19,21–25] (**Supplemental Table S3**)
  - Presence of S3 could be a useful predictor of mortality among patients with HF, as frequent S3 detection was associated with increased hospitalizations and mortality

EMAT-related publications

- EMAT refers to the time from the beginning of left ventricular electrical activity (as denoted by the beginning of the QRS wave in an ECG) to the mitral component of S1. Prolonged EMAT reflects abnormalities in systolic function[26]
- A total of 11 publications reported on EMAT or its derivatives (**Figure 5**)

EMAT and HF

- In total, 5 publications[10,11,27–29] reported on EMAT and its derivatives, including EMAT/RR, EMAT%, and EMATc, and their relationship with HF, and different presentations of HF (**Supplemental Table S4**)
- EMAT findings across studies were consistent and was found to be statistically significantly prolonged in patients with HF, supporting EMAT as a potential indicator of HF clinical severity

EMAT and HF outcomes

- A total of 6 studies reported on the association of EMAT with clinical outcomes. Two studies focused on patients with acute HF[19,30], 2 on chronic HF[31,32], and 2 on acute myocardial infarction[27] and HF in general[25] (**Supplemental Table S5**)
- A general trend of prolonged EMAT in patients with HF and cardiac-related events was identified compared to those without HF, suggesting EMAT could be a robust CAB in the prediction of major cardiac adverse events
- Only 1 study by Sung et al. (2020) reported on the potential impact of CAB-guided management in HF compared with the current method of symptom-guided management[6]
  - This study used a combination of %EMAT and S3 strength values in the management of patients with HF and observed a statistically significantly reduced all-cause mortality and hospitalization due to HF within 1 year in the EMAT-guided group compared to the symptom-guided group. However, overall survival between the 2 groups was not different[6]

LIMITATIONS

- Few published studies on CABs exist
- The literature search excluded publications predating 2013, which may have impacted the comprehensiveness of the search
- Many included studies lacked directly comparable data, with variations in patient populations and outcome measures

CONCLUSIONS

- Our findings underscore the potential utility of CAB measures, particularly S3 and EMAT, in improving the monitoring of patients with HF
  - Detection of CABs may help identify patients who are at risk of deteriorating heart health and who may require intervention to minimize the potential for adverse clinical outcomes
- CABs may predict the occurrence of a HF event, providing physicians with opportunities for timely intervention, when used in combination with other physical findings and laboratory markers
- While further studies are required to corroborate the validity of CAB measurements, the current literature demonstrates the potential utility of CABs in the prediction and warning of cardiovascular events, which could have far-reaching clinical, economic, and societal impacts

Figure 1. Wiggers diagram showing various CABs

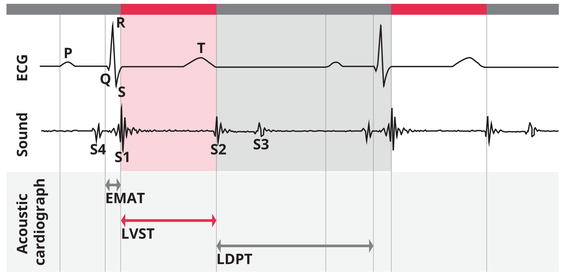
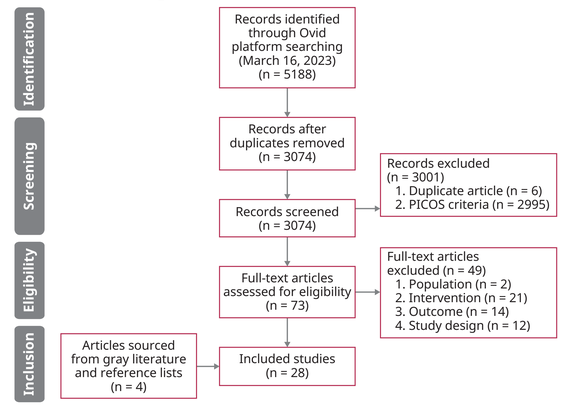


Figure adapted from Wang S et al. *Int J Cardiol.* 2013;168(3):1881–1886, and Sattar Y, Chhabra L. Electrocardiogram. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.

Red shaded area indicates systolic and grey shaded area indicates diatolic phase of cardiac cycle. The P wave indicates atrial depolarization. The QRS complex consists of a Q wave, R wave and S wave and represents ventricular depolarization. The T wave follows the QRS complex and indicates ventricular repolarization. EMAT is the time from the Q wave onset to the mitral component of S1. LVST is the time from S1 to S2. LDPT is the time from S2 to the next Q wave onset. SDI is derived from a nonlinear transformation of [(S3 score ÷ 10) × QRS duration × QR interval × EMAT%] and mapped into a scale of 0–10.

CAB, cardiovascular acoustic biomarker; ECG, electrocardiogram; EMAT, electromechanical activation time; EMAT%, normalized electromechanical activation time; LDPT, left ventricular diastolic perfusion time; LVST, left ventricular systolic time; Qo, onset of Q wave; SDI, systolic dysfunction index; S1, first heart sound; S2, second heart sound; S3, third heart sound; S4, fourth heart sound.

Figure 2. PRISMA diagram



Additional gray literature searches were used to supplement the findings from the initial search. This included publications from conferences, congresses, and pre-prints, limited to a period over two years, from January 1, 2021 to May 22, 2023.

PICOS, Population, Intervention, Comparison, Outcomes and Study; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

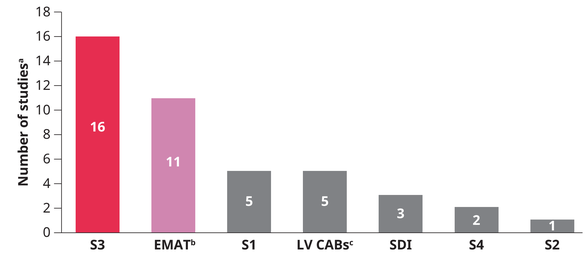
Table 1. PICOS table for screening inclusion and exclusion criteria

Category	Inclusion criteria	Exclusion criteria
Population(s)	Patients with HF	Studies reporting on populations not of interest
Interventions/comparators	No limitations[a]	Other non-CAB interventions
Outcomes	• Association between CAB measures and HF outcomes • Impact of CAB-guided management of HF on clinical, humanistic, and economic outcomes • Clinical outcomes – Major adverse cardiac events – Mortality – Hospitalization/re-hospitalization – Emergency room or outpatient care visits • Humanistic outcomes – QoL – HRQoL – Impact on functioning/daily life – HF-related QoL • Economic outcomes – Direct costs – Indirect costs – Healthcare resource utilization	Studies reporting on outcomes not of interest
Study design	• Retrospective and prospective observational studies • Epidemiological studies • Clinical trials • Randomized control trials • SLRs[b] • meta-analyses and cost-effectiveness models[b]	• Abstract-only publications[c] • Letter • Editorial • Commentary • Expert commentary • Non–peer-reviewed publications[c]
Time	Publications from 2013–March 16, 2023[d]	Publications prior to 2013
Other	English language No geographical limits were applied	Non-English language

[a]Any CAB-guided intervention related to HF management including diagnosis, prediction, monitoring, and treatment; [b]For bibliography checks only; [c]Non–peer-reviewed publications published before 2021 were excluded; [d]Gray literature sources were limited to those published between January 1, 2021 and May 22, 2023.

CAB, cardiovascular acoustic biomarker; HF, heart failure; HRQoL, health-related QoL; PICOS, Population, Intervention, Comparison, Outcomes and Study; QoL, quality of life; SLR, systematic literature review.

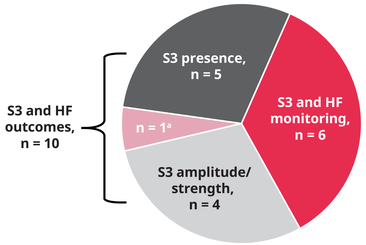
Figure 3. Frequency of reported CAB types



[a]Some publications reported data for multiple CABs; [b]Included EMAT and derivatives EMAT/RR, EMAT%, EMATc, and EMAT/LVET; [c]Included LDPT, LDPT/RR, LVET%, LVST, LVST/RR, LVST%, and PEP/RR.

CAB, cardiovascular acoustic biomarker; EMAT, electromechanical activation time; EMAT%, normalized electromechanical activation time; EMATc, corrected electromechanical activation time; EMAR/RR, EMAT normalized to heart rate; LDPT, left ventricular diastolic perfusion time; LV, left ventricle; LVET, left ventricular ejection time; LVST, left ventricular systolic time; LVST%, difference in LVST; LVST/RR, LVST normalized by heart rate; PEP, pre-ejection period; PEP/RR, PEP normalized by heart rate; S1, first heart sound; S2, second heart sound; S3, third heart sound; S4, fourth heart sound; SDI, systolic dysfunction index.

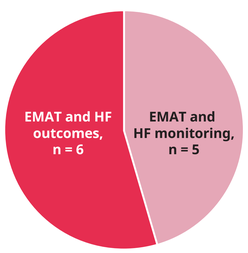
Figure 4. Publications that discussed S3 characteristics and HF



[a]n = 1 publication reported both S3 presence and S3 amplitude.

HF, heart failure; S3, third heart sound.

Figure 5. Publications that discussed EMAT and HF



EMAT, electromechanical activation time; HF, heart failure.

Acknowledgments

This work was supported by Astellas Pharma Inc. Medical writing support, provided by Priyanka D. Pinky, PhD, of Oxford PharmaGenesis, Inc., Newtown, PA, USA and in accordance with International Committee of Medical Journal Editors and Good Publication Practice 2022 guidelines, was funded by Astellas Pharma Inc.

Disclosures

JB is a consultant for Abbott, American Regent, Amgen, Applied Therapeutic, AskBio, AstraZeneca, Astellas, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardiac Dimension, Cardiocell, Cardior, CSL Bearing, CVRx, Cytokinetics, Daxor, Edwards, Element Science, Faraday, Foundry, G3P, Innolife, Impulse Dynamics, Imbria, Inventiva, Ionis, Lexicon, Lilly, LivaNova, Janssen, Medtronics, Merck, Occlutech, Owkin, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Prolaio, Regeneron, Renibus, Roche, Salamandra, Sanofi, SC Pharma, Secretome, Sequana, SQ Innovation, Tenex, Tricog, Ultromics, Vifor and Zoll. **MB** is an employee of Astellas Pharma, Addlestone, England, UK. **PP** and **JS** are employees of Astellas Pharma Global Development Inc., Northbrook, IL, USA. **ACH**, **SP**, **OW** are employees of Adelphi Values PROVE, Bollington, England, UK and received study funding/support from Astellas. **OE** is a former employee of Astellas Pharma DMCC, Dubai, UAE. **BM** is an employee of Astellas Pharma Europe BV, Leiden, Netherlands.

Supplementary Materials

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Presented at The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual Meeting, May 5–8, 2024, Atlanta, GA, USA