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RESEARCH ARTICLE

Diagnostic and Prognostic Value of Endocan in Acute Coronary Syndromes: A Meta-Analysis Comparing STEMI, NSTEMI, and Control Groups

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ABSTRACT

Background: The aim of this study is to evaluate the clinical utility of endocan as a biomarker for differentiating among the various forms of acute coronary syndromes (ACS), including STEMI, NSTEMI, and unstable angina.

Methods: We conducted a thorough literature search using the Medline, Scopus, Embase, and Cochrane Library databases, encompassing publications from the databases' inceptions to August 1, 2024.

Results: The meta-analysis includes four studies. The pooled analysis demonstrates endocan levels to be elevated in the STEMI group, with a mean of 1.68 (0.84), compared to 1.20 (0.38) in the control group (*MD* = 0.58; 95% CI [0.10, 1.05]; *p* = 0.02). Endocan levels in the NSTEMI patients and control groups revealed respective levels of 1.16 (0.38) and 1.06 (; *MD* = 0.17; 95% CI [0.01, 0.33]; *p* = 0.03). The pooled analysis indicates no statistically significant difference in endocan levels between the STEMI and UA/NSTEMI groups, with levels at 2.22 (1.22) and 2.64 (1.22), respectively (*MD* = 0.01; 95% CI [-0.20, 0.21]; *p* = 0.95)

Conclusions: The findings indicate endocan levels to be notably higher in patients with STEMI and NSTEMI compared to control groups, suggesting its potential involvement in the pathogenesis of acute myocardial infarction.

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Despite the progress in cardiovascular medicine, acute coronary syndrome (ACS) remains a challenging clinical problem (Costello & Younis, 2020; Vafaie, 2016). Prognosis is closely correlated with the subtype of ACS, with ST-elevated myocardial infarction (STEMI) associated with higher mortality rates than other subtypes of ACS (Martínez et al., 2022). Regardless of the clinical course of ACS, early risk stratification after an ACS event plays a crucial role in improving prognosis, particularly in terms of long-term outcomes. The use of biomarkers has significantly improved ACS diagnosis through the popularization of cardio-selective troponins. A strong effort is now underway to find well-suited biomarkers that facilitate the estimation of a patient's prognosis, thus enabling early risk stratification (Bauer & Toušek, 2021).

As stated by Balta et al., endothelial-specific molecule 1 (endocan) belongs to the novel biomarkers that have yet to be well-characterized. Its mechanism of action is strictly related to endothelial dysfunction and the activation of pro-inflammatory cascades (Balta et al., 2015) (Figure 1). During the COVID-19 pandemic, researchers thoroughly investigated endocan as a potential diagnostic and prognostic biomarker (Görgün et al., 2021; Khalaji et al., 2024). Laloglu and Alay determined a diagnostic cut-off level of 444.2 pg/mL, which differentiates patients with COVID-19 from healthy individuals. At this level, endocan's sensitivity and specificity were 92% and 80%, respectively. Furthermore, what was particularly useful during the COVID-19 pandemic was that endocan could predict the severity of the dis-

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ease's clinical course (Laloglu & Alay, 2022). A preliminary study was also conducted to determine whether endocan levels can distinguish patients with mild, moderate, and severe erectile dysfunction. Karabakan et al. found the average Endocan level to statistically differ between the stages of erectile dysfunction severity (Karabakan et al., 2017). Interest in endocan continues to increase in various fields. It is primarily regarded as an indicator of very early endothelial damage, which can occur in the course of hypertension, even asymptomatic, as well as among patients with metabolic syndrome (Hirooka, 2024; Iwańczyk et al., 2022). Khalaji et al. conducted a meta-analysis suggesting that endocan can also be useful for identifying patients with chronic kidney diseases (Khalaji et al., 2023).

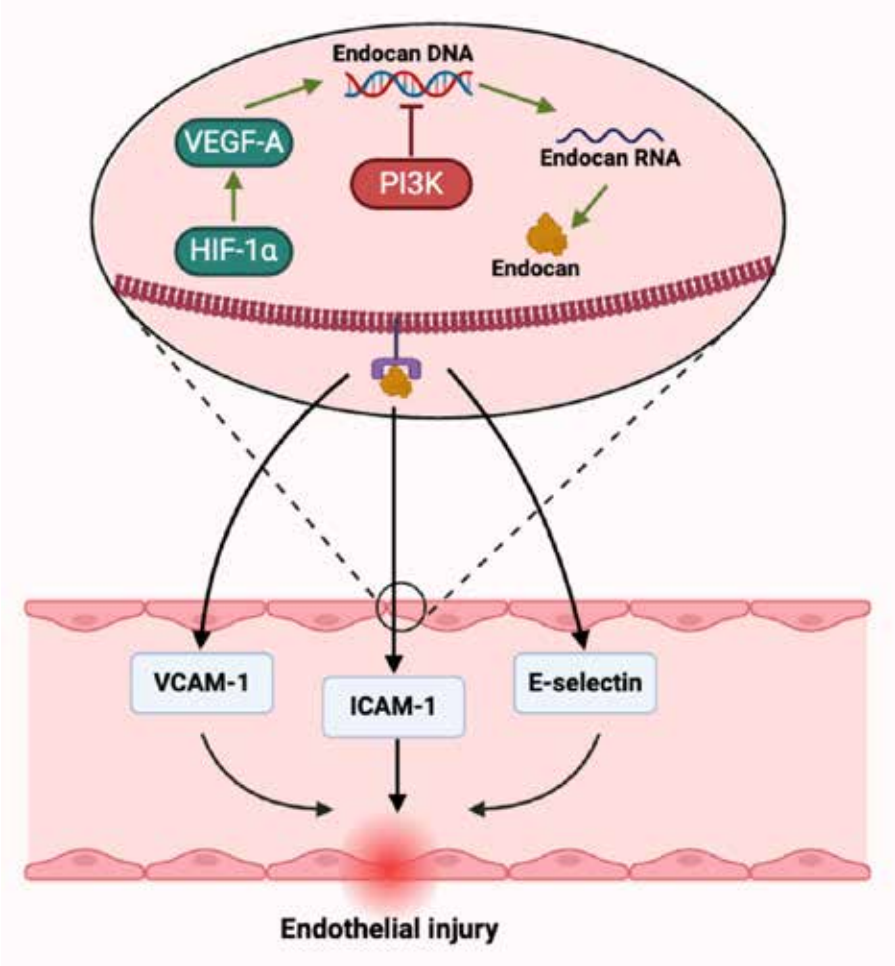

Figure 1. Endocan's mechanism of action.

Katsioupa et al. summarized the use of Endocan in cardiovascular medicine, highlighting its potential for risk stratification following major cardiovascular events (MACEs). Additionally, the difference in endocan levels between ST-elevated myocardial infarction (STEMI) and non-ST-elevated myocardial infarction (NSTEMI) or unstable angina (UA) may have potential diagnostic properties (Katsioupa et al., 2023). A pilot study from 2015 revealed a statistically significant difference in endocan levels among patients with acute myocardial infarction (AMI). However, the results had limited impact due to the small sample size, with only 30 controls and 53 participants with AMI (Kose et al., 2015). Interest in endocan has increased since Qiu et al.'s study, which found endocan serum levels to be significantly higher among patients with AMI compared to controls without AMI. Although the results of this cross-sectional study were ambiguous (no statistically significant difference between endocan and Gensini score), they remain important (Qiu et al., 2017). Based on a small study with a limited number of participants, Cimen et al. revealed endocan levels to significantly decrease after successful coronary artery bypass grafting (CABG). This is not surprising, as successful reperfusion of the ischemic tissues stabilizes endothelial damage, leading to a decrease in biomarkers associated with endothelial dysfunction (Cimen et al., 2019).

As a result, we have conducted this meta-analysis to provide more comprehensive evidence of the predictive value of endocan in patients with ACS.

Methods

This study follows the established recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021). The protocol was registered after the search but in advance of the data extraction using the Prospective Register of Systematic Reviews (CRD42024575085).

Search Strategy

We conducted a thorough literature search in the Medline, Scopus, Embase, and Cochrane Library databases to find original articles that reported on endocan levels among ACS patients. Articles published between the databases' inceptions and August 1, 2024, were selected for review. The keywords applied to the literature retrieval included: "endothelial cell-specific molecular 1" OR "endocan" OR "ESM-1" AND "acute coronary syndrome" OR "ACS" OR "ST Segment Elevation Myocardial Infarction" OR "ST Elevated Myocardial Infarction" OR "ST-elevation MI" OR "STEMI" OR "non-ST elevation myocardial infraction" OR "NSTEMI" OR "myocardial infarction" OR "unstable angina". We also evaluated the reference lists of the included papers to determine if they met the inclusion criteria for this study by taking into account the presence of relevant parameters.

Inclusion and Exclusion Criteria

Two reviewers independently investigated the full texts of eligible studies that met the following inclusion criteria: (1) adult patients (aged ≥18 years); (2) studies reporting sufficient information about endocan levels among ACS and healthy patients (at baseline); (3) outcomes involving functional recovery, cognitive dysfunction, death, hemorrhagic transformation, vascular events, depression, and recurrence; (4) cohort studies or case-control studies; and (5) studies published in English. Exclusion criteria: (1) duplicated publication; (2) studies with no primary data (review articles, editorials, comments); (3) animal studies; (4) studies with a sample size of five or less or ongoing studies with no results; and (5) conference abstracts, case reports, and letters.

Two authors (MP and DS) independently screened the titles and abstracts after removing duplicate studies both automatically (Endnote X8, Clarivate, Philadelphia, PA, USA) and by hand. We consulted a third and fourth author (ER for screening and AK for full-text review) in order to reach a consensus on the inclusion and exclusion of each article. We also searched the references cited in the identified publications to find additional studies.

Data Extraction

We extracted the first author, year of publication, study design, type of ACS, number of patients, age, sex, patient comorbidities, and endocan levels from each eligible study. Additionally, the image digitization software GetData Graph Digitizer 2.26 extracted the corresponding results from studies that provided bar charts or curve graphs but did not provide relevant data. Two authors (M.P. and D.S.) performed these processes independently, with a third author (L.S.) participating in the discussion in case of disagreement.

Risk of Bias Assessment

Two reviewers (D.S. and M.P.) separately rated the quality of the included studies using the Newcastle-Ottawa Quality Scale (NOS) (Stang, 2010). We discussed any concerns about the quality score with the third reviewer (L.S.). The NOS instrument's score consists of three components: selection and representativeness, study group comparability, and subjective perception of the outcome or exposure. A star rating system ranging from 0-9 determines the quality score. A study with a NOS score of 4 was classified as low quality, research with a score of 4-6 was categorized as moderate quality, and a NOS score greater than or equal to seven was classified as high quality.

Statistical Analysis

We performed statistical analyses using Review Manager software version 5.4 (Nordic Cochrane Centre, Cochrane Collaboration, Denmark). The p values are two-sided, with significance at $p < 0.05$. Dichotomous outcomes were expressed as relative risks (RRs) with 95% confidence intervals (CIs), and continuous outcomes were expressed as the mean difference (MD) with 95% CI. When reporting the continuous outcome as a median and interquartile range, we estimated the means and standard deviations using the formula described by Hozo et al. (2005). We visualized the re-

sults using forest plots. We examined the statistical heterogeneity between studies using Cochran's Q test and Higgins I^2 statistics, with $I^2 < 25\%$ indicating low, $25\% < I^2 < 50\%$ moderate, $50\% < I^2 < 75\%$ high, and $I^2 > 75\%$ extreme heterogeneity (Higgins et al., 2011). A random-effects model was used in accordance with significant heterogeneity ($I^2 > 50\%$, $p < 0.05$); otherwise, the fixed-effect model was exerted. Additionally, we assessed publication bias using funnel plots and Egger's test. We created funnel plots from a meta-analysis that included at least 10 studies, with $p < 0.05$ in Egger's test indicating the presence of publication bias (Egger et al., 1997). Lastly, we conducted a leave-one-out meta-analysis during the sensitivity analyses.

Results

Search Results and Study Characteristics

In total, 126 studies were identified based on the search strategy. After screening studies according to the inclusion and exclusion criteria and removing duplicates, four articles were at last included in this meta-analysis (Kundi et al., 2017; Qiu et al., 2017; Wei et al., 2021; Ziaee et al., 2019). The selection process and result are shown in Figure 2, and characteristics of the included studies are summarized in Table 1. All studies had high quality based on NOS (Table 1).

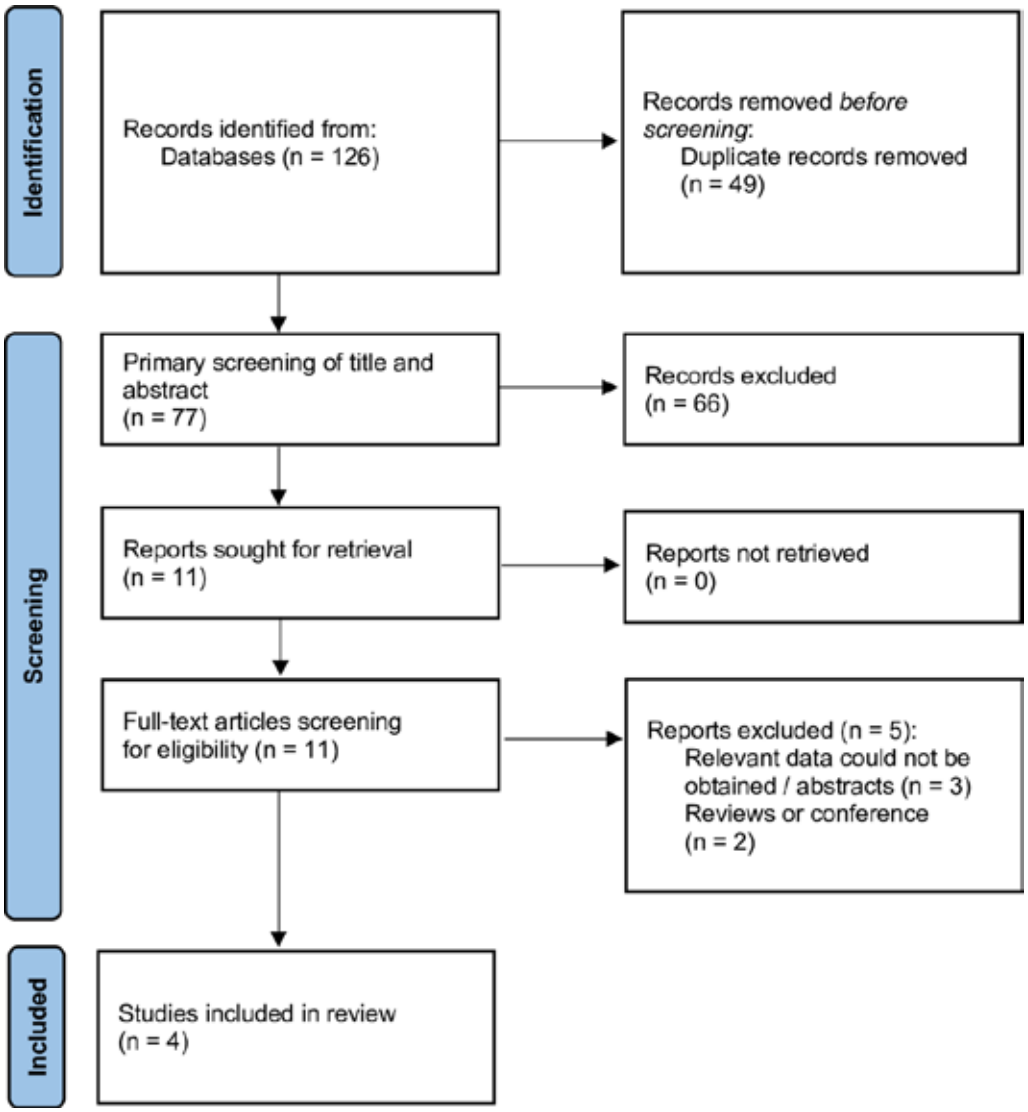

Figure 2. PRISMA flow chart of the included studies.

Table 1

Baseline Characteristics of Included Trials

Study	Country	Study design	Study group	No. of patients	Age	Male gender	BMI	Comorbidities			NOS score
								HTN	DM	DL	
Kundi et al., 2016	Turkey	PS	STEMI	88	64 ± 12	51 (59.1)	26.5 ± 3.8	34 (38.6)	21 (23.9)	58 (42.9)	8
			Control	45	62 ± 15	27 (60.0)	26.9 ± 3.9	15 (33.3)	10 (22.2)	55 (40.7)	
Qiu et al., 2016	China	CCS	AMI	216	65.3 ± 12.7	137 (63.4)	25.0 ± 4.0	109 (50.5)	46 (21.3)	NS	8
			Control	60	63.8 ± 8.8	32 (53.3)	24.2 ± 3.0	23 (38.3)	10 (16.7)	NS	
Wei et al., 2021	China	PS	STEMI	37	57.4 ± 11.6	23 (62.2)	24.9 ± 2.6	12 (32.4)	NS	NS	8
			Control	24	57.2 ± 10.3	15 (62.5)	24.0 ± 2.1	6 (25.0)	NS	NS	
Ziaee et al., 2018	Iran	PCCS	STEMI	160	58.4 ± 9.8	126 (78.8)	26.8 ± 3.1	66 (41.3)	29 (18.1)	56 (35.0)	8
			NSTEMI	160	56.1 ± 9.5	110 (68.8)	26.8 ± 3.8	80 (50.0)	32 (20.0)	68 (42.5)	

AMI = acute myocardial injury; BMI = body mass index; CCS = cross-sectional study; DM = diabetes mellitus; DL = dyslipidemia; HTN = hypertension; NS = not specified; PCCS = prospective cross-sectional study; PS = prospective study; STEMI = ST-elevation myocardial infarction.

Meta-analysis

Three studies reported endocan levels among STEMI and control groups. Pooled analysis showed endocan levels to vary at 1.68 ± 0.84 for the STEMI group compared to 1.20 ± 0.38 for the control group (*MD* = 0.58; 95% CI [0.10, 1.05]; $p = 0.02$).

Only Qiu et al.'s (2017) study reported endocan levels among NSTEMI and control groups (1.16 ± 0.38 vs. 1.06 ± 0.19, respectively; *MD* = 0.17; 95% CI [0.01, 0.33]; $p = 0.03$). Pooled analysis showed no statistical significance difference between endocan levels for the STEMI vs. UA/NSTEMI groups (2.22 ± 1.22 vs. 2.64 ± 1.22, respectively; *MD* = 0.01; 95% CI [-0.20, 0.21]; $p = 0.95$).

Discussion

The present meta-analysis has aimed to assess the diagnostic and prognostic value of endocan in patients with acute coronary syndromes (ACS) by focusing on comparisons among STEMI, NSTEMI, and control groups. Our results demonstrate endocan levels to be significantly elevated in patients with STEMI and NSTEMI compared to control groups, reinforcing the biomarker's potential role in the pathophysiology of myocardial infarction. Specifically, the pooled analysis showed a notable increase in endocan levels in the STEMI group (*MD* = 0.58, $p = 0.02$) and the NSTEMI group (*MD* = 0.17, $p = 0.03$) compared to controls. However, no significant differences were observed between STEMI and NSTEMI/UA groups, indicating endocan to perhaps be an insufficient marker for differentiating between these subtypes of ACS.

The association between elevated endocan levels and ACS likely reflects the underlying endothelial damage and pro-inflammatory state associated with acute myocardial infarction (AMI). This is particularly relevant in the case of STEMI, where the rupture of atherosclerotic plaque and the subsequent thrombus formation result in complete occlusion of the coronary artery, leading to extensive myocardial ischemia and necrosis. Several studies have supported the prognostic value of endocan in cardiovascular disease. Ziaee et al.'s (2019) study, which included 340 patients with ACS, reported serum endocan levels to be positively correlated with the myocardial infarction thrombolysis risk score and the occurrence of major adverse cardiac events (MACE), such as recurrent MI, heart failure, and cardiovascular death. In their cohort, patients with higher endocan levels had a significantly higher risk of adverse outcomes, suggest-

ing endocan to perhaps serve as a valuable biomarker for risk stratification in ACS. Despite its evident role in reflecting endothelial damage, our analysis found no statistically significant differences between endocan levels in patients with STEMI and those with NSTEMI or UA (*MD* = 0.01; 95% CI [-0.20, 0.21]; $p = 0.95$). This finding suggests that, while endocan levels are elevated in ACS patients, the biomarker may lack the specificity needed to differentiate among the various subtypes of myocardial infarction. This is consistent with the findings of previous studies, such as Cimen et al.'s (2019), which demonstrated endocan levels to decrease following successful coronary artery bypass grafting (CABG) but to not vary significantly between different ACS presentations (Chen et al., 2021; Lin et al., 2024). The inability of endocan to distinguish between STEMI and NSTEMI could be attributed to the shared pathophysiological mechanisms underlying both conditions. While STEMI is characterized by complete coronary artery occlusion, NSTEMI typically results from partial occlusion; however, both conditions involve similar processes of endothelial damage, inflammation, and atherosclerosis (Chen et al., 2021). Thus, as a marker of endothelial dysfunction, endocan may plausibly reflect the presence of these common underlying mechanisms rather than the specific clinical manifestations of ACS. Additionally, the relatively small sample sizes of the included studies may have limited the power of our meta-analysis to detect subtle differences between STEMI and NSTEMI. Larger studies with more comprehensive data on endocan levels in ACS subgroups are needed to fully elucidate the potential of this biomarker in differentiating among the various forms of myocardial infarction.

Endocan's role as a biomarker of endothelial dysfunction places it alongside other well-established cardiovascular biomarkers such as high-sensitivity C-reactive protein (hsCRP), troponins, and B-type natriuretic peptide (BNP). While troponins remain the gold standard for diagnosing myocardial infarction due to their high specificity for cardiac injury, endocan offers unique advantages in that it reflects systemic endothelial dysfunction, a key driver of atherosclerosis and vascular disease (Behnoush et al., 2023; Chen et al., 2021). Endocan has also been compared to hsCRP, a widely used marker of inflammation in cardiovascular disease. Unlike hsCRP, which is a general marker of inflammation, endocan is specifically linked to endothelial activation and has been shown to correlate with endothelial cell injury in conditions such as hypertension, metabolic syndrome, and chronic kidney disease (Behnoush et al., 2023; Chen et al., 2021; Lin et al., 2024). This makes endocan a promising candidate for assessing endothelial health in patients with ACS and for potentially improving the identification of those at higher risk of adverse cardiovascular outcomes. However, the use of endocan as a clinical biomarker is notably still in its early stages, and its diagnostic and prognostic value in ACS remains to be fully established. While our study provides evidence of its potential utility in identifying endothelial dysfunction and myocardial injury, further research is needed to determine whether Endocan can complement existing biomarkers such as troponins and BNP for guiding clinical decision-making regarding ACS patients.

While our meta-analysis provides valuable insights into the role of endocan in ACS, acknowledging the limitations of the available data is important. First, the number of studies included in the analysis was relatively small, and the sample sizes of the individual studies were limited. This may have reduced the statistical power of our findings, particularly in the comparison between STEMI and NSTEMI groups. Second, considerable heterogeneity was present among the included studies in terms of study design, patient populations, and methods for measuring endocan levels. This variability may have influenced the results of our pooled analysis and should be taken into account when interpreting the findings. Third, the lack of longitudinal data on endocan levels limits our ability to assess its prognostic value over time. While elevated endocan levels have been associated with adverse cardiovascular outcomes in some studies, further research is needed to determine whether endocan can reliably predict long-term outcomes in ACS patients and whether it has any incremental value beyond traditional risk factors and biomarkers (Chen et al., 2021; Lin et al., 2024).

Future research on endocan should focus on larger, multicenter studies that include diverse populations of ACS patients. These studies should aim to standardize the measurement of endocan levels and explore its potential utility in combination with other biomarkers for risk stratification and prognosis. Additionally, longitudinal studies are needed to evaluate the temporal changes in endocan levels following ACS and their relationship to clinical outcomes. The integration of endocan into existing risk prediction models such as GRACE or TIMI scores should also be investigated to determine whether it can improve the accuracy of these tools for predicting adverse outcomes in ACS patients. Finally, studies examining the impact of therapeutic interventions (e.g., statins or antiplatelet agents) on endocan levels could provide valuable insights into the role of endothelial dysfunction in managing ACS (Behnoush et al., 2023; Chen et al., 2021; Lin et al., 2024).

Conclusion

In summary, our meta-analysis suggests endocan to be a promising biomarker for detecting endothelial dysfunction and myocardial injury in patients with ACS. While elevated endocan levels were observed in both STEMI and NSTEMI patients, the lack of significant differences between these groups indicates endocan to perhaps not be specific enough for distinguishing among the different types of ACS. Nevertheless, endocan's association with adverse cardiovascular outcomes highlights its potential role in risk stratification, and further research is warranted to fully establish its clinical utility.

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Informed Consent Statement

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Data Availability Statement

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Conflicts of Interest

The authors declare no conflict of interest.

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