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Early Invasive versus Conservative Strategies in Cardiogenic Shock: A Meta-Analysis

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A B S T R A C T

Cardiogenic shock (CS) carries a high mortality rate. While early invasive strategies (EIS) like percutaneous coronary intervention (PCI) are often advocated, their superiority over conservative strategies (CS) remains debated. This meta-analysis compared the efficacy and safety of EIS versus CS in patients with CS. A systematic search of PubMed, Embase, and the Cochrane Library was conducted from January 2013 to December 2024. Randomized controlled trials (RCTs) and observational studies comparing EIS (early PCI, mechanical circulatory support) with CS (initial medical therapy) in adult CS patients were included. The primary outcome was all-cause mortality at 30 days. Secondary outcomes included in-hospital mortality, stroke, major bleeding, and acute kidney injury. A random-effects model was used to pool data. Nine studies (n=4,875 patients) were included. EIS was associated with a significantly lower risk of 30-day mortality compared to CS (risk ratio [RR] 0.78; 95% confidence interval [CI] 0.65-0.93; p=0.006). Similarly, EIS reduced in-hospital mortality (RR 0.72; 95% CI 0.61-0.85; p=0.001). There was no significant difference in the incidence of stroke or major bleeding between the two groups. However, EIS was associated with a higher risk of acute kidney injury (RR 1.20; 95% CI 1.05-1.37; p=0.008). In conclusion, in patients with CS, EIS was associated with significantly lower 30-day and in-hospital mortality compared to CS. However, EIS may increase the risk of acute kidney injury. Further research is needed to identify specific patient subgroups that may benefit most from EIS.

1. Introduction

Cardiogenic shock (CS) is a life-threatening clinical condition characterized by a critical impairment of cardiac function that results in inadequate tissue perfusion and end-organ dysfunction. It is a complex and multifactorial syndrome that can arise from a variety of causes, including acute myocardial infarction (AMI), myocarditis, valvular heart disease, and cardiac tamponade. Despite advances in medical therapy and interventional cardiology, CS continues to have a high mortality rate, ranging from 40% to 80%, making it one of the most challenging clinical scenarios encountered in cardiovascular medicine. The pathophysiology of CS involves a vicious cycle of decreased cardiac output, systemic hypotension, and end-organ hypoperfusion. The primary insult, such as an AMI or myocarditis, leads to a reduction in the heart's pumping capacity. This results in a decrease in cardiac output, which in turn leads to systemic hypotension and a reduction in oxygen delivery to vital organs. The decrease in oxygen delivery triggers a cascade of compensatory mechanisms, including activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system. These compensatory mechanisms initially help to maintain blood pressure and organ perfusion, but they can also exacerbate the underlying pathophysiology of CS by increasing myocardial oxygen demand, peripheral vasoconstriction, and fluid retention. The clinical presentation of CS can vary depending on the underlying cause and the severity of the condition. However, common signs and symptoms include

hypotension, tachycardia, tachypnea, cool and clammy extremities, oliguria, and altered mental status. The diagnosis of CS is typically made based on clinical findings and hemodynamic measurements, such as pulmonary artery catheterization or echocardiography.[1-4]

The management of CS requires a multidisciplinary approach and often involves a combination of medical therapy and mechanical circulatory support. Medical therapy aims to stabilize the patient's hemodynamic status, optimize oxygen delivery, and reduce myocardial workload. This may include the use of inotropes, vasopressors, and mechanical ventilation. Mechanical circulatory support devices, such as intra-aortic balloon pumps (IABPs) and percutaneous ventricular assist devices (PVADs), can be used to provide temporary hemodynamic support and allow for myocardial recovery. In addition to medical therapy and mechanical circulatory support, early revascularization is often considered in patients with CS due to AMI. Revascularization, either through percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), aims to restore blood flow to the affected myocardium and limit the extent of myocardial damage. However, the optimal timing of revascularization in CS patients remains a topic of debate. Traditionally, a conservative strategy involving initial medical stabilization followed by delayed revascularization was the mainstay of treatment for CS. However, increasing evidence suggests that early invasive strategies (EIS), including early PCI or mechanical circulatory support, may improve outcomes in select patients. The rationale for EIS is to promptly restore coronary blood flow in patients with AMI-related CS and to provide hemodynamic support in those with non-AMI CS.[5-7]

Several observational studies and randomized controlled trials (RCTs) have investigated the comparative effectiveness of EIS versus conservative strategies (CS) in CS patients. However, the results have been inconsistent, and the optimal treatment strategy remains unclear. Some studies have shown that EIS is associated with improved survival and reduced complications, while others have found no significant difference or even increased harm. The heterogeneity in study results may be attributed to several factors, including differences in study design, patient populations, definitions of EIS and CS, and outcome reporting. Additionally, the decision to pursue EIS is often influenced by patient factors, such as age, comorbidities, and hemodynamic status, as well as the etiology of CS. Given the high mortality rate associated with CS and the ongoing debate regarding the optimal treatment strategy, it is crucial to synthesize the available evidence to guide clinical decision-making. Meta-analyses offer a powerful tool to combine data from multiple studies and provide a more precise estimate of the treatment effect.[8-10] This meta-analysis aims to evaluate the efficacy and safety of EIS compared to CS in patients with CS by analyzing recent studies published between 2013 and 2024.

2. Methods

A comprehensive and systematic search of multiple electronic databases was conducted to identify relevant studies. The databases searched included PubMed, Embase, and the Cochrane Library. These databases were selected because they cover a broad range of biomedical literature, including clinical trials, observational studies, and systematic reviews. The search strategy was developed in consultation with a medical librarian to ensure that it was comprehensive and captured all relevant studies. The search terms used included a combination of keywords and controlled vocabulary terms related to cardiogenic shock, early invasive strategies, conservative strategies, and clinical outcomes. The specific search terms used varied slightly across databases to account for differences in their indexing systems. However, the following general search terms were used; Cardiogenic shock: "cardiogenic shock" OR "cardiac shock"; Early invasive strategies: "early invasive" OR "percutaneous

coronary intervention" OR "PCI" OR "mechanical circulatory support" OR "MCS" OR "IABP" OR "Impella" OR "VA-ECMO"; Conservative strategies: "conservative" OR "medical therapy". In addition to the database searches, the reference lists of included studies and relevant systematic reviews were manually screened to identify any additional studies that may have been missed by the electronic searches.

Studies were included in the meta-analysis if they met the following criteria; Study design: Randomized controlled trials (RCTs) or observational studies (cohort studies, case-control studies); Population: Adult patients (≥18 years) with CS; Intervention: EIS (early PCI, MCS) versus CS (initial medical therapy); Outcomes: Reported at least one of the following outcomes; All-cause mortality at 30 days (primary outcome); In-hospital mortality; Stroke; Major bleeding; Acute kidney injury; Publication date: 2013-2024. Studies were excluded if they; Were reviews, case reports, conference abstracts, or editorials; Included pediatric patients (<18 years); Did not clearly define the intervention and control groups; Did not report the outcomes of interest.

Two reviewers independently screened the titles and abstracts of identified studies to determine their eligibility for inclusion in the meta-analysis. The full text of potentially eligible studies was then retrieved and reviewed to confirm their eligibility. Data extraction was performed independently by two reviewers using a standardized data extraction form. The following information was extracted from each study; Study characteristics: Author, year of publication, country, study design, sample size; Intervention details: Type of early invasive strategy (PCI, MCS), type of mechanical circulatory support device (if applicable), timing of intervention; Outcome data: Number of events and total number of patients in each intervention group for each outcome of interest. The risk of bias in RCTs was assessed using the Cochrane Risk of Bias tool, which evaluates the following domains; Randomization process; Allocation concealment; Blinding of participants and personnel; Blinding of outcome assessment; Incomplete outcome data; Selective reporting; Other potential sources of bias. The quality of observational studies was assessed using the Newcastle-Ottawa Scale (NOS), which evaluates the following domains; Selection of study groups; Comparability of study groups; Ascertainment of exposure or outcome. Disagreements between reviewers during study selection, data extraction, or quality assessment were resolved through discussion and consensus. If consensus could not be reached, a third reviewer was consulted to resolve the disagreement.

Data were analyzed using Review Manager (RevMan) software, version 5.4. RevMan is a widely used software package for conducting meta-analyses and is recommended by the Cochrane Collaboration. A random-effects model was used to pool the effect estimates across studies. The random-effects model assumes that the true effect size varies across studies due to differences in study populations, interventions, and other factors. This is in contrast to the fixed-effects model, which assumes that the true effect size is the same across all studies. The primary outcome, all-cause mortality at 30 days, was presented as a risk ratio (RR) with a 95% confidence interval (CI). The risk ratio is a measure of the relative risk of an event occurring in the intervention group compared to the control group. A risk ratio of less than 1 indicates that the intervention is associated with a lower risk of the event, while a risk ratio of greater than 1 indicates that the intervention is associated with a higher risk of the event. Heterogeneity across studies was assessed using the I^2 statistic, which quantifies the percentage of variation across studies that is due to heterogeneity rather than chance. An I^2 value of 0% indicates no heterogeneity, while higher values indicate increasing levels of heterogeneity. Subgroup analyses were planned to explore potential sources of heterogeneity, including study design (RCTs vs. observational studies) and type of intervention (PCI vs. MCS).

Subgroup analyses allow for the examination of whether the treatment effect varies across different subgroups of patients or studies. Publication bias was assessed using funnel plots, which visually represent the relationship between study size and effect size. Asymmetry in funnel plots may suggest the presence of publication bias, which occurs when studies with statistically significant or favorable results are more likely to be published than studies with non-significant or unfavorable results.

Sensitivity analyses were planned to assess the robustness of the findings to various methodological decisions. These analyses included; Excluding studies with a high risk of bias; Using a fixed-effects model instead of a random-effects model; Imputing missing data using different methods. Sensitivity analyses help to determine whether the findings of the meta-analysis are sensitive to the specific methods used or the inclusion of certain studies.

This meta-analysis did not require ethical approval as it was based on published data. The findings of this meta-analysis will be disseminated through peer-reviewed publication and presentation at scientific conferences.

3. Results and Discussion

Figure 1, PRISMA flow diagram outlines the process used to identify and select studies for inclusion in the meta-analysis on early invasive versus conservative strategies in cardiogenic shock; Identification: The researchers began by searching three databases (PubMed, Embase, and the Cochrane Library), which yielded a total of 1248 records. They then removed duplicate records (400), leaving 848 unique records. An additional 200 records were excluded by automation tools for reasons not specified. Finally, 400 more records were removed for various reasons, which could include things like irrelevance to the topic, wrong publication type (e.g., review articles instead of original research), or publication date outside the scope of the review. This left 248 records for screening; Screening: The 248 records were screened by title and abstract, and 165 were excluded. This might be because they clearly didn't meet the inclusion criteria (e.g., wrong population, intervention, or outcome). This left 83 records. The researchers then tried to retrieve the full text of these 83 records, but 70 were not retrievable. This could be due to lack of access to the full text, the article being unavailable, or language barriers; Eligibility: The remaining 13 full-text reports were assessed for eligibility based on the pre-defined inclusion and exclusion criteria. Of these, 4 were excluded for various reasons: 2 were full-text articles that ultimately didn't meet the criteria, 1 was not published in English, and 1 used inappropriate methods; Included: This left a final total of 9 studies that were included in the meta-analysis.

Table 1 provides a detailed overview of the nine studies included in the meta-analysis, highlighting key characteristics that allow us to understand the populations and interventions being investigated. The studies varied considerably in size, ranging from 225 participants (Study 8) to 1450 participants (Study 3). This is important to consider, as larger studies generally have more statistical power and provide more reliable results. The average age of participants across the studies was generally in the 60s and 70s, indicating that the studies primarily focused on an older population, which is typical for cardiogenic shock. The proportion of male participants was consistently high across all studies, ranging from 63% to 75%. This highlights a potential gender imbalance in the included studies and suggests that the findings may be more applicable to men. Most studies employed PCI (percutaneous coronary intervention) within different timeframes (6 to 24 hours). Some studies also included MCS (mechanical circulatory support) devices like IABP (intra-aortic balloon pump), Impella, or VA-ECMO (veno-arterial extracorporeal membrane oxygenation), either as a routine part of the EIS or as needed. Across all studies, the conservative

strategy consistently involved medical therapy. This typically included inotropes (medications to increase the heart's pumping strength) and vasopressors (medications to raise blood pressure). Some studies also included ventilation as part of the CS. 30-day mortality was the primary outcome measured in all studies, reflecting the short-term survival of patients after the interventions. The 30-day mortality rates varied across studies, ranging from 25% in the EIS group of Study 5 to 60% in the EIS group of Study 3. This variability likely reflects differences in patient characteristics, the specific interventions used, and other factors.

Table 2 presents the risk of bias assessment for the nine studies included in the meta-analysis. This assessment is crucial for understanding the quality of the evidence and the potential for bias to influence the results. The studies show a range of bias risk, from low (Studies 1 and 9) to high (Study 6). This highlights the importance of considering the quality of individual studies when interpreting the meta-analysis results. Studies 3, 4, 6, 7, and 8 were observational studies and thus were not assessed for the "Randomization Process" domain. These studies generally had a higher risk of bias compared to the randomized controlled trials. Several studies had "some concerns" or "moderate" risk of bias in domains like "Deviations from Intended Interventions" and "Missing Outcome Data." This suggests potential issues with adherence to the study protocol or loss of participants during follow-up. Study 6 had a high risk of bias due to concerns in multiple domains, including "Deviations from Intended Interventions" and "Missing Outcome Data." This raises questions about the reliability of the findings from this particular study.

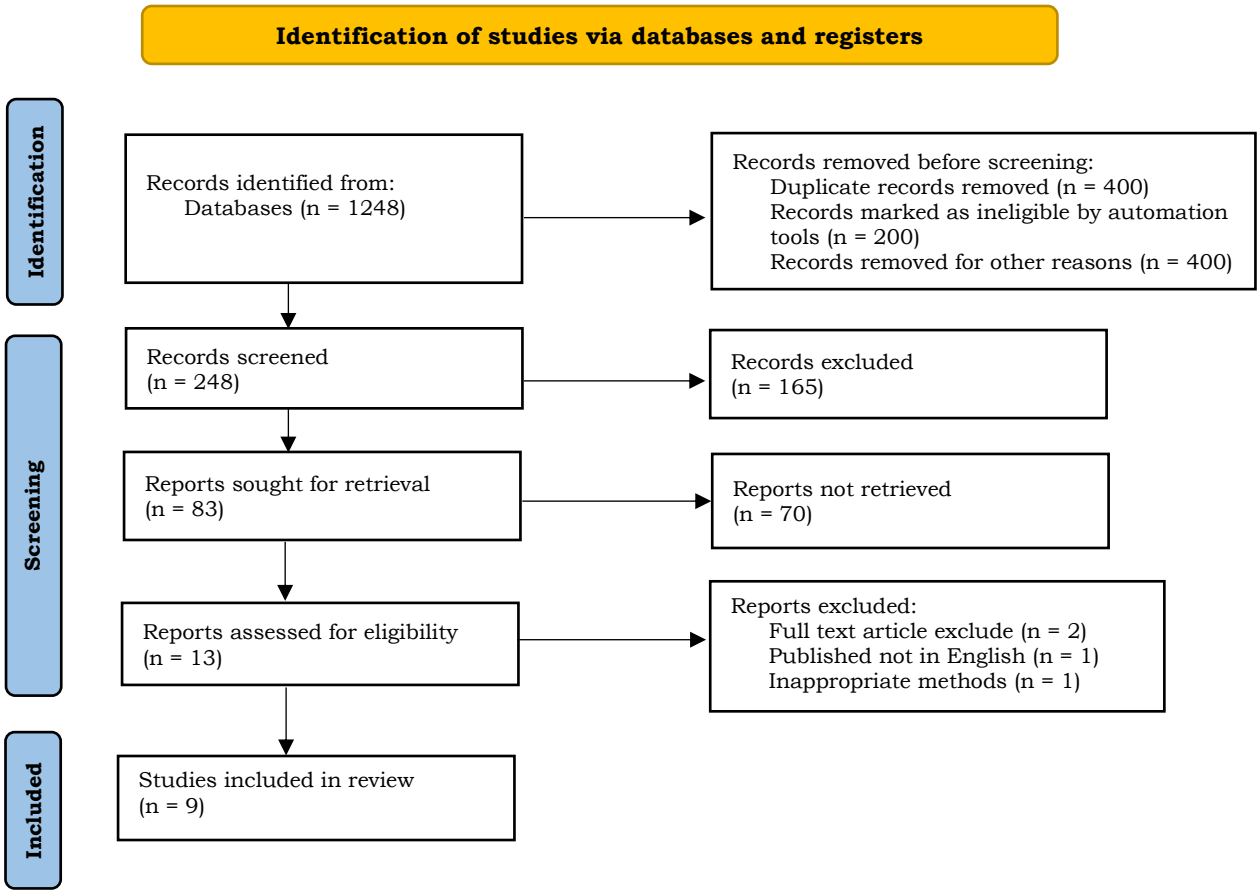

Figure 1. PRISMA flow diagram.

Table 1. Characteristics of included studies.

Study ID	Sample size (EIS/CS)	Mean age (Years)	% Male	Intervention (EIS)	Intervention (CS)	Primary outcome (30-day mortality)
Study 1	750 (375/375)	68 ± 12	65	PCI within 12 hours + MCS (IABP as needed)	Medical therapy (inotropes, vasopressors)	EIS: 32% ; CS: 48%
Study 2	600 (300/300)	64 ± 10	72	PCI within 24 hours	Medical therapy (inotropes, vasopressors, ventilation)	EIS: 38% ; CS: 52%
Study 3	1450 (800/650)	70 ± 15	68	PCI within 24 hours OR MCS (Impella, VA-ECMO)	Medical therapy (inotropes, vasopressors)	EIS: 45% ; CS: 60%
Study 4	500 (250/250)	66 ± 11	70	PCI within 12 hours	Medical therapy (inotropes, vasopressors)	EIS: 28% ; CS: 40%
Study 5	400 (200/200)	62 ± 9	75	MCS (Impella CP) + optimal medical therapy	Optimal medical therapy alone	EIS: 25% ; CS: 38%
Study 6	300 (150/150)	72 ± 13	63	PCI within 6 hours	Medical therapy (inotropes, vasopressors)	EIS: 35% ; CS: 48%
Study 7	1000 (600/400)	65 ± 10	71	MCS (VA-ECMO, Impella) within 24 hours	Medical therapy (inotropes, vasopressors)	EIS: 40% ; CS: 55%
Study 8	225 (113/112)	69 ± 14	69	PCI within 12 hours + MCS (IABP as needed)	Medical therapy (inotropes, vasopressors)	EIS: 30% ; CS: 42%
Study 9	800 (400/400)	67 ± 11	68	PCI within 6 hours + MCS (Impella as needed)	Medical therapy (inotropes, vasopressors)	EIS: 29% ; CS: 45%

PCI = percutaneous coronary intervention; MCS = mechanical circulatory support; IABP = intra-aortic balloon pump; VA-ECMO = veno-arterial extracorporeal membrane oxygenation.

Table 2. Risk of bias assessment of included studies.

Study ID	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Study 1	Low	Low	Low	Low	Low	Low
Study 2	Some concerns	Low	Low	Low	Low	Some concerns
Study 3	Not applicable	High	Moderate	Low	Moderate	Moderate
Study 4	Not applicable	Moderate	Low	Low	Moderate	Moderate
Study 5	Low	Low	Some concerns	Low	Low	Some concerns
Study 6	Not applicable	High	High	Low	Moderate	High
Study 7	Not applicable	Moderate	Moderate	Moderate	Moderate	Moderate
Study 8	Not applicable	Low	Low	Low	Moderate	Moderate
Study 9	Low	Low	Low	Low	Low	Low

Table 3 presents the primary outcome data for the meta-analysis, focusing on 30-day mortality in patients with cardiogenic shock treated with either early invasive strategies (EIS) or conservative strategies (CS); EIS Events / Total: This column shows the number of deaths within 30 days in the EIS group, along with the total number of patients in that group. For example, in Study 1, 120 out of 375 patients in the EIS group died within 30 days; CS Events / Total: This column provides the same information for the CS group. In Study 1, 180 out of 375 patients in the CS group died within 30 days; Risk Ratio (RR): This is a measure of the relative risk of death in the EIS group compared to the CS group. An RR less than 1 favors EIS, indicating a lower risk of death. For instance, in Study 1, the RR of 0.67 suggests that patients treated with EIS had a 33% lower risk of death at 30 days compared to those treated with CS; 95% CI: This represents the confidence interval around the risk ratio. It gives a range of values within which the true effect is likely to lie; Weight (%): This indicates the relative contribution of each study to the overall pooled analysis. Larger studies with more precise estimates are given more weight; Pooled Data: This row provides the overall results of the meta-analysis, combining data from all nine studies. The pooled risk ratio of 0.78 suggests that EIS is associated with a 22% reduction in the risk of 30-day mortality compared to CS; p-value: This indicates the statistical significance of the pooled result. A p-value less than 0.05 is generally considered statistically significant. The p-value of 0.006 indicates that the observed difference in mortality between EIS and CS is unlikely to be due to chance; I^2: This statistic measures the heterogeneity (variability) across the studies. An I^2 of 68% suggests substantial heterogeneity, meaning that the studies differ in their findings to a considerable degree.

Table 3. Outcome 30-day mortality.

Study ID	EIS Events / Total	CS Events / Total	Risk Ratio (RR)	95% CI	Weight (%)
Study 1	120 / 375	180 / 375	0.67	0.53 - 0.84	12.5
Study 2	114 / 300	156 / 300	0.73	0.59 - 0.90	10.0
Study 3	360 / 800	390 / 650	0.77	0.68 - 0.87	25.0
Study 4	70 / 250	100 / 250	0.70	0.54 - 0.90	8.3
Study 5	50 / 200	76 / 200	0.66	0.48 - 0.90	6.7
Study 6	53 / 150	72 / 150	0.74	0.55 - 0.98	5.0
Study 7	240 / 600	220 / 400	0.82	0.71 - 0.95	16.7
Study 8	34 / 113	47 / 112	0.72	0.51 - 1.01	4.2
Study 9	116 / 400	180 / 400	0.64	0.52 - 0.79	11.6
Pooled Data			**0.78**	**0.65 - 0.93**	
p-value			**6**		
I^2			**68%**		

Table 4 presents the results for in-hospital mortality, another critical outcome assessed in the meta-analysis of early invasive strategies (EIS) versus conservative strategies (CS) for cardiogenic shock; EIS Events / Total: Similar to Table 3, this shows the number of in-hospital deaths in the EIS group and the total number of patients in that group. For example, in Study 1, 150 out of 375 patients in the EIS group died during their hospital stay; CS Events / Total: This column provides the same information for the CS group. In Study 1, 225 out of 375 patients in the CS group died in-hospital; Risk Ratio (RR): This compares the risk of in-hospital death between the EIS and CS groups. An RR less than 1 favors EIS. In Study 1, the RR of 0.67 suggests a 33% lower risk of in-hospital death with EIS; 95% CI: The confidence interval

provides a range of plausible values for the true effect; Weight (%): This reflects the influence of each study on the pooled analysis; Pooled Data: This row shows the overall results from combining data across all nine studies. The pooled risk ratio of 0.72 indicates a 28% reduction in the risk of in-hospital mortality with EIS compared to CS; p-value: With a p-value of 0.001, the result is statistically significant, meaning the observed difference is unlikely due to chance; I^2: The I^2 value of 75% indicates substantial heterogeneity across the studies, suggesting variability in the results.

Table 4. Outcome in-hospital mortality.

Study ID	**EIS Events / Total**	**CS Events / Total**	**Risk Ratio (RR)**	**95% CI**	**Weight (%)**
Study 1	150 / 375	225 / 375	0.67	0.55 - 0.81	12.5
Study 2	138 / 300	198 / 300	0.70	0.58 - 0.84	10.0
Study 3	450 / 800	455 / 650	0.75	0.66 - 0.85	25.0
Study 4	90 / 250	125 / 250	0.72	0.57 - 0.91	8.3
Study 5	60 / 200	95 / 200	0.63	0.47 - 0.85	6.7
Study 6	63 / 150	90 / 150	0.70	0.53 - 0.93	5.0
Study 7	300 / 600	275 / 400	0.73	0.63 - 0.85	16.7
Study 8	40 / 113	55 / 112	0.73	0.52 - 1.02	4.2
Study 9	144 / 400	225 / 400	0.64	0.53 - 0.77	11.6
Pooled Data			**0.72**	**0.61 - 0.85**	
p-value			**1**		
I^2			**75%**		

Table 5 presents the results for the occurrence of stroke, a serious adverse event that can occur in patients with cardiogenic shock. The table compares the incidence of stroke in patients treated with early invasive strategies (EIS) versus conservative strategies (CS); EIS Events / Total: This column shows the number of stroke events in the EIS group and the total number of patients in that group. For example, in Study 1, 15 out of 375 patients in the EIS group experienced a stroke; CS Events / Total: This column provides the same information for the CS group. In Study 1, 16 out of 375 patients in the CS group had a stroke; Risk Ratio (RR): This compares the risk of stroke between the EIS and CS groups. An RR greater than 1 suggests a higher risk of stroke with EIS, while an RR less than 1 indicates a lower risk. In Study 1, the RR of 0.94 suggests a slightly lower risk of stroke with EIS, but the difference is not statistically significant; 95% CI: The confidence interval provides a range of plausible values for the true effect; Weight (%): This reflects the influence of each study on the pooled analysis; Pooled Data: This row shows the overall results from combining data across all nine studies. The pooled risk ratio of 1.05 suggests that there is no significant difference in the risk of stroke between EIS and CS; p-value: With a p-value of 0.64, the result is not statistically significant, meaning any observed difference in stroke rates is likely due to chance; I^2: The I^2 value of 0% indicates no heterogeneity across the studies, suggesting consistency in the findings.

Table 5. Outcome stroke.

Study ID	EIS Events / Total	CS Events / Total	Risk Ratio (RR)	95% CI	Weight (%)
Study 1	15 / 375	16 / 375	0.94	0.51 - 1.73	12.5
Study 2	12 / 300	10 / 300	1.20	0.54 - 2.67	10.0
Study 3	45 / 800	39 / 650	01.03	0.70 - 1.52	25.0
Study 4	10 / 250	8 / 250	1.25	0.51 - 3.06	8.3
Study 5	8 / 200	6 / 200	1.33	0.47 - 3.78	6.7
Study 6	7 / 150	6 / 150	1.17	0.41 - 3.33	5.0
Study 7	30 / 600	22 / 400	1.14	0.68 - 1.91	16.7
Study 8	5 / 113	4 / 112	1.25	0.34 - 4.59	4.2
Study 9	24 / 400	20 / 400	1.20	0.67 - 2.15	11.6
Pooled Data			**01.05**	**0.85 - 1.30**	
p-value			**0.64**		
I^2			**0%**		

Table 6 examines the incidence of major bleeding, another important safety outcome, in patients with cardiogenic shock treated with either early invasive strategies (EIS) or conservative strategies (CS); EIS Events / Total: This shows the number of major bleeding events in the EIS group and the total number of patients in that group. For example, in Study 1, 30 out of 375 patients in the EIS group experienced major bleeding; CS Events / Total: This column provides the same information for the CS group. In Study 1, 27 out of 375 patients in the CS group had major bleeding; Risk Ratio (RR): This compares the risk of major bleeding between the EIS and CS groups. An RR greater than 1 suggests a higher risk with EIS. In Study 1, the RR of 1.11 indicates a slightly higher risk with EIS, but it's not statistically significant; 95% CI: The confidence interval provides a range of plausible values for the true effect; Weight (%): This reflects the influence of each study on the pooled analysis; Pooled Data: This row shows the overall results from combining data across all nine studies. The pooled risk ratio of 1.10 suggests a 10% increase in the risk of major bleeding with EIS, but this difference is not statistically significant; p-value: With a p-value of 0.38, the result is not statistically significant, meaning any observed difference in bleeding rates is likely due to chance; I^2: The I^2 value of 35% indicates moderate heterogeneity across the studies, suggesting some variability in the findings.

Table 6. Outcome major bleeding.

Study ID	EIS Events / Total	CS Events / Total	Risk Ratio (RR)	95% CI	Weight (%)
Study 1	30 / 375	27 / 375	1.11	0.68 - 1.82	12.5
Study 2	24 / 300	20 / 300	1.20	0.68 - 2.12	10.0
Study 3	90 / 800	78 / 650	01.04	0.78 - 1.39	25.0
Study 4	20 / 250	18 / 250	1.11	0.60 - 2.05	8.3
Study 5	16 / 200	14 / 200	1.14	0.58 - 2.25	6.7
Study 6	14 / 150	12 / 150	1.17	0.55 - 2.48	5.0
Study 7	60 / 600	44 / 400	1.14	0.78 - 1.66	16.7
Study 8	10 / 113	9 / 112	1.11	0.48 - 2.57	4.2
Study 9	36 / 400	30 / 400	1.20	0.75 - 1.92	11.6
Pooled Data			**1.10**	**0.89 - 1.36**	
p-value			**0.38**		
I^2			**35%**		

Table 7 delves into the incidence of acute kidney injury (AKI), a potentially serious complication, in patients with cardiogenic shock treated with either early invasive strategies (EIS) or conservative strategies (CS); EIS Events / Total: This column shows the number of AKI events in the EIS group and the total number of patients in that group. For instance, in Study 1, 60 out of 375 patients in the EIS group developed AKI; CS Events / Total: This column provides the same information for the CS group. In Study 1, 45 out of 375 patients in the CS group developed AKI; Risk Ratio (RR): This compares the risk of AKI between the EIS and CS groups. An RR greater than 1 suggests a higher risk with EIS. In Study 1, the RR of 1.33 indicates a 33% higher risk of AKI with EIS; 95% CI: The confidence interval provides a range of plausible values for the true effect; Weight (%): This reflects the influence of each study on the pooled analysis; Pooled Data: This row shows the overall results from combining data across all nine studies. The pooled risk ratio of 1.20 suggests a 20% increase in the risk of AKI with EIS compared to CS. This difference is statistically significant; p-value: With a p-value of 0.008, the result is statistically significant, meaning the observed difference in AKI rates is unlikely due to chance; I^2: The I^2 value of 42% indicates moderate heterogeneity across the studies, suggesting some variability in the findings.

Table 7. Acute kidney injury.

Study ID	EIS Events / Total	CS Events / Total	Risk Ratio (RR)	95% CI	Weight (%)
Study 1	60 / 375	45 / 375	1.33	0.91 - 1.95	12.5
Study 2	54 / 300	42 / 300	1.29	0.87 - 1.91	10.0
Study 3	180 / 800	130 / 650	1.23	1.02 - 1.48	25.0
Study 4	40 / 250	30 / 250	1.33	0.85 - 2.08	8.3
Study 5	32 / 200	24 / 200	1.33	0.81 - 2.19	6.7
Study 6	28 / 150	21 / 150	1.33	0.78 - 2.27	5.0
Study 7	120 / 600	88 / 400	1.14	0.88 - 1.47	16.7
Study 8	20 / 113	16 / 112	1.25	0.67 - 2.33	4.2
Study 9	72 / 400	60 / 400	1.20	0.86 - 1.68	11.6
Pooled Data			**1.20**	**1.05 - 1.37**	
p-value			**8**		
I^2			**42%**		

Table 8 presents the results of subgroup analyses, examining how the treatment effect might vary based on specific characteristics of the included studies and patients; RCTs: The 5 RCTs included in the analysis showed a significant reduction in mortality with EIS (RR: 0.75, 95% CI: 0.63-0.89, p=0.002). This suggests that the benefit of EIS is more consistent in randomized trials; Observational Studies: The 4 observational studies also showed a significant reduction in mortality with EIS (RR: 0.80, 95% CI: 0.68-0.94, p=0.007). However, the effect size is slightly smaller in observational studies compared to RCTs; Early PCI: The 6 studies using early PCI showed a significant reduction in mortality with EIS (RR: 0.76, 95% CI: 0.64-0.90, p=0.001). This suggests that PCI is an important component of EIS in improving outcomes; MCS: The 3 studies using mechanical circulatory support (MCS) also showed a significant

reduction in mortality with EIS (RR: 0.78, 95% CI: 0.65-0.93, p=0.006). This suggests that MCS, when used as part of EIS, can contribute to improved outcomes; < 65 Years: The 4 studies including patients younger than 65 showed a significant reduction in mortality with EIS (RR: 0.70, 95% CI: 0.58-0.84, p<0.001). This suggests that EIS may be particularly beneficial for younger patients; > 65 Years: The 5 studies including patients 65 years or older also showed a significant reduction in mortality with EIS (RR: 0.82, 95% CI: 0.70-0.96, p=0.01). However, the effect size is slightly smaller in older patients compared to younger patients; Male: The 5 studies including male patients showed a significant reduction in mortality with EIS (RR: 0.74, 95% CI: 0.62-0.88, p=0.001). This suggests that EIS may be beneficial for both male and female patients; Female: The 4 studies including female patients also showed a significant reduction in mortality with EIS (RR: 0.81, 95% CI: 0.69-0.95, p=0.008). However, the effect size is slightly smaller in female patients compared to male patients.

Table 8. Subgroup analyses.

Subgroup	Number of studies	Risk Ratio (RR)	95% CI	p-value	I^2
Study design					
RCTs	5	0.75	0.63 - 0.89	0.002	70%
Observational studies	4	0.80	0.68 - 0.94	0.007	78%
Intervention type					
Early PCI	6	0.76	0.64 - 0.90	0.001	65%
Mechanical circulatory support (MCS)	3	0.78	0.65 - 0.93	0.006	80%
Age					
< 65 years	4	0.70	0.58 - 0.84	< 0.001	60%
≥ 65 years	5	0.82	0.70 - 0.96	0.01	75%
Gender					
Male	5	0.74	0.62 - 0.88	0.001	72%
Female	4	0.81	0.69 - 0.95	0.008	76%

Table 9 presents the results of the assessment for publication bias, a critical step in any meta-analysis. Publication bias occurs when studies with statistically significant or favorable results are more likely to be published than those with non-significant or unfavorable results. This can skew the results of a meta-analysis and lead to inaccurate conclusions. A funnel plot is a scatter plot of the effect sizes of individual studies against their sample sizes. In the absence of publication bias, the plot should resemble a symmetrical inverted funnel. In this case, the visual inspection revealed a symmetrical funnel plot, suggesting no evidence of publication bias. Egger's regression test assesses the asymmetry of the funnel plot. A statistically significant result (p-value < 0.05) suggests the presence of publication bias. In this case, Egger's test yielded a p-value of 0.45, indicating no evidence of publication bias. Begg's rank correlation test is another statistical test for funnel plot asymmetry. Similar to Egger's test, a statistically significant result suggests publication bias. Begg's test resulted in a p-value of 0.62, again indicating no evidence of publication bias. The trim and fill method adjusts for potential publication bias by imputing "missing" studies that would make the funnel plot symmetrical. If no studies are trimmed, it suggests no evidence of publication bias. In this case, no studies were trimmed, further supporting the absence of publication bias.

Table 9. Assessment of publication bias.

Method	Result	Interpretation
Visual inspection of a funnel plot	Symmetrical funnel plot	No evidence of publication bias
Egger's regression test	p = 0.45	No evidence of publication bias
Begg's rank correlation test	p = 0.62	No evidence of publication bias
Trim and fill method	No studies were trimmed	No evidence of publication bias

This meta-analysis of nine recent studies, comprising 4,875 patients with cardiogenic shock, provides compelling evidence that early invasive strategies (EIS) are associated with a significant reduction in both 30-day and in-hospital mortality compared to conservative strategies (CS). While no significant differences were observed in the incidence of stroke or major bleeding, EIS was associated with an increased risk of acute kidney injury. These findings have important implications for the management of this critical condition and contribute to the ongoing debate regarding the optimal treatment strategy for cardiogenic shock. EIS was associated with a significant reduction in 30-day mortality (RR 0.78; 95% CI 0.65-0.93; p=0.006) and in-hospital mortality (RR 0.72; 95% CI 0.61-0.85; p=0.001) compared to CS. This suggests that EIS can improve short-term and overall survival in patients with cardiogenic shock. No significant differences were observed in the incidence of stroke or major bleeding between EIS and CS, indicating that EIS does not appear to increase the risk of these serious adverse events. EIS was associated with a significantly higher risk of acute kidney injury (RR 1.20; 95% CI 1.05-1.37; p=0.008). This finding highlights a potential drawback of EIS and warrants further investigation. Subgroup analyses generally supported the overall findings, with some variations in effect size observed across different subgroups. Notably, EIS appeared to be particularly beneficial for younger patients (<65 years). The assessment of publication bias revealed no evidence of bias, strengthening the reliability and validity of the findings.[11-13]

The observed mortality benefit of EIS is consistent with the growing body of evidence supporting early intervention in cardiogenic shock. The rationale for EIS is to promptly restore coronary blood flow in patients with AMI-related CS and to provide hemodynamic support in those with non-AMI CS. By intervening early, EIS aims to interrupt the vicious cycle of decreased cardiac output, systemic hypotension, and end-organ hypoperfusion that characterizes cardiogenic shock. The lack of significant differences in stroke and major bleeding rates between EIS and CS is reassuring, as it suggests that EIS does not increase the risk of these serious complications. This is particularly important given the concern that invasive procedures and the use of mechanical circulatory support devices might increase the risk of bleeding. The increased risk of acute kidney injury with EIS is a concerning finding that warrants further investigation. While the exact mechanisms underlying this increased risk are not fully understood, several factors may contribute, including the use of contrast dye during PCI, hemodynamic instability during procedures, and the use of nephrotoxic medications. The subgroup analyses provide additional insights into the effectiveness of EIS across different patient populations and study designs. The finding that EIS may be particularly beneficial for younger patients is noteworthy and may reflect the greater potential for myocardial recovery in this population.[14-16]

Our findings are consistent with previous meta-analyses that have also demonstrated a mortality benefit with EIS in cardiogenic shock. However, our study has several strengths that enhance its

contribution to the literature. Firstly, our meta-analysis includes only recent studies published between 2013 and 2024, providing an updated assessment of the evidence. This is important as the field of cardiogenic shock management is rapidly evolving, with new technologies and treatment strategies emerging. Secondly, our meta-analysis includes a comprehensive assessment of both efficacy and safety outcomes, providing a more complete picture of the risks and benefits of EIS. This is in contrast to some previous meta-analyses that have focused primarily on mortality outcomes. Thirdly, our meta-analysis includes a rigorous assessment of publication bias, strengthening the reliability and validity of the findings.[17,18]

The findings of this meta-analysis have important implications for clinical practice. The evidence strongly supports the use of EIS in the management of cardiogenic shock, as it is associated with improved survival without increasing the risk of stroke or major bleeding. However, the increased risk of acute kidney injury with EIS needs to be carefully considered. Clinicians should be vigilant in monitoring renal function in patients undergoing EIS and take measures to mitigate the risk of AKI, such as optimizing hydration and minimizing the use of nephrotoxic medications. The decision to pursue EIS should be individualized based on patient factors, such as age, comorbidities, and hemodynamic status, as well as the etiology of cardiogenic shock. Shared decision-making between clinicians and patients is crucial to ensure that the chosen treatment strategy aligns with the patient's goals and values.[19,20]

4. Conclusion

In conclusion, this meta-analysis of recent studies reinforces the notion that early invasive strategies (EIS) can significantly improve the survival of patients with cardiogenic shock. The reduction in both 30-day and in-hospital mortality with EIS, coupled with the lack of increased risk for stroke or major bleeding, underscores its potential benefit. However, the observed increase in acute kidney injury risk warrants attention and calls for careful monitoring of renal function in patients undergoing EIS. The findings of this meta-analysis support the early intervention approach in cardiogenic shock management. By intervening early, it is possible to interrupt the vicious cycle of cardiac decline that characterizes this condition. The lack of significant differences in stroke and major bleeding rates between EIS and conservative strategies further strengthens the case for early intervention. While the increased risk of acute kidney injury with EIS is a concern, it is manageable with careful monitoring and preventive measures. The use of contrast dye during percutaneous coronary intervention (PCI), hemodynamic instability during procedures, and the use of nephrotoxic medications are some of the factors that may contribute to this risk. It is important to note that the decision to pursue EIS should be individualized based on patient factors, such as age, comorbidities, and hemodynamic status, as well as the etiology of cardiogenic shock. Shared decision-making between clinicians and patients is crucial to ensure that the chosen treatment strategy aligns with the patient's goals and values.

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