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Early Invasive Strategy in Non-ST-Elevation Acute Coronary Syndrome With Congestive Heart Failure

— A Systematic Review and Meta-Analysis —

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Background: Congestive heart failure (CHF) is associated with worse clinical outcomes in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS); however, the optimal timing of invasive intervention in NSTE-ACS with CHF remains unclear. In this study, we assessed the impact of early vs. delayed invasive strategies on mortality and cardiac events by synthesizing a systematic review of randomized controlled trials of patients with NSTE-ACS.

Methods and Results: We searched MEDLINE, CENTRAL, and the Web of Science for randomized controlled trials comparing early and delayed invasive strategies in patients with NSTE-ACS and CHF, published before February 2023. Observational studies were excluded. The primary endpoint was a composite of all-cause mortality and myocardial infarction at 2 years. Two eligible studies, including 310 participants, were identified. The primary endpoint occurred in 40 (24.5%) of 163 patients in the early invasive strategy group, compared with 39 (26.5%) of 147 patients in the delayed invasive strategy group, and the effect of an early invasive strategy on the primary outcome was uncertain (risk ratio 0.95 [95% confidence interval 0.66–1.37]). The certainty of the evidence was rated very low.

Conclusions: The effects of an early invasive strategy in patients with NSTE-ACS and CHF remains uncertain, with no clear reduction in composite outcome of mortality and myocardial infarction at 2 years compared with delayed intervention.

Key Words: Congestive heart failure; Early invasive strategy; Non-ST-elevation acute coronary syndrome

Several meta-analyses indicate that a routine invasive strategy with coronary angiography and revascularization for patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) reduces the risk of cardiovascular events.[1–3] Accordingly, current guidelines recommend a routine invasive strategy for most patients with NSTE-ACS.[4–6] However, the optimal timing of an invasive strategy in NSTE-ACS remains unclear. Meta-analyses have failed to show any overall benefit of an early invasive strategy for mortality or non-fatal myocardial infarction

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(MI) among patients with NSTE-ACS,[7–9] whereas there is some evidence of reduced cardiovascular events among high-risk patients.[8,10] Therefore, current guidelines recommend an early invasive strategy within 24 h of hospital admission for patients at high-risk, such as those with a Global Registry of Acute Coronary Events (GRACE) risk score >140, dynamic ST-segment or T-wave changes, or transient ST-segment elevation.[4–6,11,12]

In patients with NSTE-ACS, the presence of congestive heart failure (CHF) is commonly observed and is strongly associated with worse short- and long-term outcomes.[13–19] The presence of CHF evaluated by Killip class on hospital admission is one of the components of the GRACE risk score, as well as 7 other factors (i.e., age, heart rate, systolic blood pressure, serum creatinine concentration, cardiac arrest, presence of ST-segment deviation, and elevated cardiac enzymes/markers).[4,6,20] Despite its prognostic significance, the optimal timing of an invasive strategy in patients with NSTE-ACS and CHF remains unclear. In this study, we performed a systematic review to investigate the effect of an early invasive strategy in patients with NSTE-ACS and CHF.

Methods

The Japan Resuscitation Council (JRC) ACS Task Force for the 2025 JRC Guidelines was established by the Japanese Circulation Society, the Japanese Association of Acute Medicine, and the Japanese Society of Internal Medicine. The JRC ACS Task Force formulated 10 clinically relevant questions. After discussion between the JRC ACS Task Force and the Guidelines Editorial Committee, the population intervention comparator outcome study design and time frame (PICOST) were used to guide the systematic review as follows: P (population) – patients admitted to the hospital with NSTE-ACS complicated by heart failure; I (interventions) – early invasive strategy, including invasive coronary angiography with or without further revascularization; C (comparators, controls) – strategies other than an early invasive strategy; O (outcomes) – composite of all-cause mortality and recurrent MI at 2 years; S (study design) – randomized control trials (RCTs) published in English, excluding review papers; T (timeframe) – all literature published until February 14, 2023.

This systematic review and meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement, registered with the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42023399585), and performed according to the PRISMA guidelines.[21,22] The procedures followed were in accordance with the Declaration of Helsinki.

Search Strategies

Literature search strategies were developed using medical subject headings and key words related to NSTE-ACS and (heart failure or high risk). The full search strategy is described in the **Supplementary Appendix**. A systematic search of published reports was conducted in MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science databases to retrieve relevant articles published from their inception to February 14, 2023. We searched for full-text manuscripts of human studies published before February 14, 2023.

Study Selection and Inclusion Criteria

The study population included adult patients with NSTE-ACS and CHF admitted in an emergency setting. We did not restrict our analysis by country. However, only studies published in English were included. Eligible studies met the following criteria: (1) RCT; (2) included patients diagnosed with NSTE-ACS; (3) compared early vs. delayed invasive strategies (an invasive strategy was defined as coronary angiography and percutaneous coronary intervention [PCI]); and (4) whether patients had CHF at hospital admission. CHF was defined as follows: (1) Killip class 2 or 3; or (2) elevated serum B-type natriuretic peptide (BNP), proBNP, or N-terminal pro BNP (NT-proBNP) levels.[23,24] Studies were ineligible if they were: (1) observational trials; (2) ongoing trials; (3) pilot or single-arm studies and studies with irretrievable full-text reports; or (4) trials that compared a routine invasive strategy with a conservative strategy. If there were no RCTs focusing on patients with NSTE-ACS complicated by CHF, we included the RCTs of patients with NSTE-ACS and examined the impact of complicated CHF on prognosis in a subanalysis.

Data Extraction and Management

We extracted the following data: author name(s), title, journal name, publication year, website (URL), and abstract. Once duplicates were removed, full study titles and abstracts were independently screened by 2 authors (K. Hao, T.T.) according to the study inclusion criteria. In instances of uncertainty, full-text articles were screened independently (K. Hao, T.T.). Any disagreements regarding inclusion or exclusion were resolved through discussion and final adjudication by a third independent author (S.K.).

Assessment of the Risk of Bias

The biases of each study and outcome were evaluated

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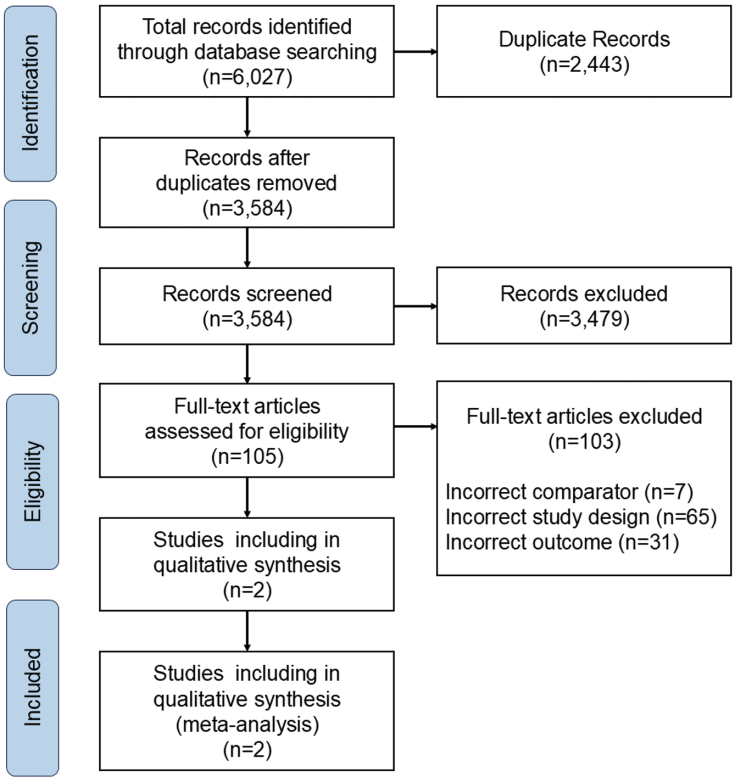

Figure 1. Flow diagram summarizing the evidence search and study selection.

using the Cochrane Risk of Bias 2 (RoB2) tool.[25] RoB2 assesses biases across 5 domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each identified bias is then categorized as 'low risk', 'high risk', or 'some concerns'. Two reviewers (K. Hao, T.T.) independently appraised the risk of bias in all the included studies. Studies were categorized as having a 'low', 'unclear', or 'high' risk of bias in each domain. The risk of bias for each element was considered 'high' when bias was present and likely to affect the outcomes, and 'low' when bias was not present or present but unlikely to affect the outcomes.

Rating Certainty of Evidence

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool to rate the certainty of the evidence as to whether an early invasive strategy is effective for patients with NSTE-ACS and CHF.[26,27] The certainty of evidence was assessed as 'high', 'moderate', 'low', or 'very low' according to the risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Statistical Analysis

Results were summarized using a random-effects model to facilitate pooling of the estimated treatment effects. Dichotomous outcomes are described as risk ratios (RRs) and 95% confidence intervals (CIs). Heterogeneity between trials for each outcome was evaluated using the I^2 statistic to quantify inconsistencies,[28] which were considered significant if the reason for heterogeneity could not be explained and the I^2 value was ≥50%. We generated a funnel plot to investigate potential publication bias. All analyses were performed using Review Manager software (RevMan 5.4).

Difference Between the Protocol and Review

After selecting 2 eligible studies,[29,30] to evaluate the effect of an early invasive strategy on the outcome during the same follow-up period from the 2 trials, the number of events at 2 years was provided by the Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography (VERDICT) trial investigators,[29] and the composite outcome of all-cause death and recurrent MI at 2-years in this systematic review. However, several outcomes such as all-cause death, cardiovascular death, and MI could not be evaluated because of data unavailability.

Results

Literature Search

Figure 1 shows a flow diagram of the study adapted from the PRISMA statement.[21,22] We identified 6,027 studies in the PubMed, Web of Science, and Cochrane Library databases. In total, 105 studies were assessed for eligibility based on title and abstract screening. The full-text review excluded 103 studies because of incorrect comparators (n=7), study designs (n=65), and outcomes (n=31). Two RCTs met the inclusion criteria and reported outcomes for patients with NSTE-ACS complicated by CHF.[29,30]

Study Characteristics

The characteristics of the included studies are summarized

Table 1. Characteristics of the Included Study

Study	Study design	Overall patients, Early vs. Delayed (n)	Timing of ICA, Early vs. Delayed, median (h)	Mode of revascularization, Early vs. Delayed, n (%)
ELISA-3 (Badings et al. 2017)[30]	Multicenter RCT	269 vs. 265	2.6 vs. 54.9	PCI: 180 (66.7) vs. 164 (61.9) CABG: 62 (23.2) vs. 68 (12.4)
VERDICT (Butt et al. 2021)[29]	Multicenter RCT	1,075 vs. 1,072	4.7 vs. 61.6	PCI: 498 (46.3) vs. 442 (41.2) CABG: 132 (12.2) vs. 132 (12.3)

Study	Definition of CHF	Patients with CHF, Early vs. Delayed (n)	Primary endpoint	Follow up
ELISA-3 (Badings et al. 2017)[30]	ProBNP ≥659 pg/mL	119 vs. 103	Death, MI, or recurrent ischemia	2 years
VERDICT (Butt et al. 2021)[29]	Killip class 2 or 3	Killip 2: 33 vs. 37 Killip 3: 11 vs. 7	Death, MI, admission for heart failure, or admission for refractory ischemia	Median 4.3 years

CABG, coronary artery bypass graft; CHF, congestive heart failure; ICA, invasive coronary angiography; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomized control trial; VERDICT, Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography.

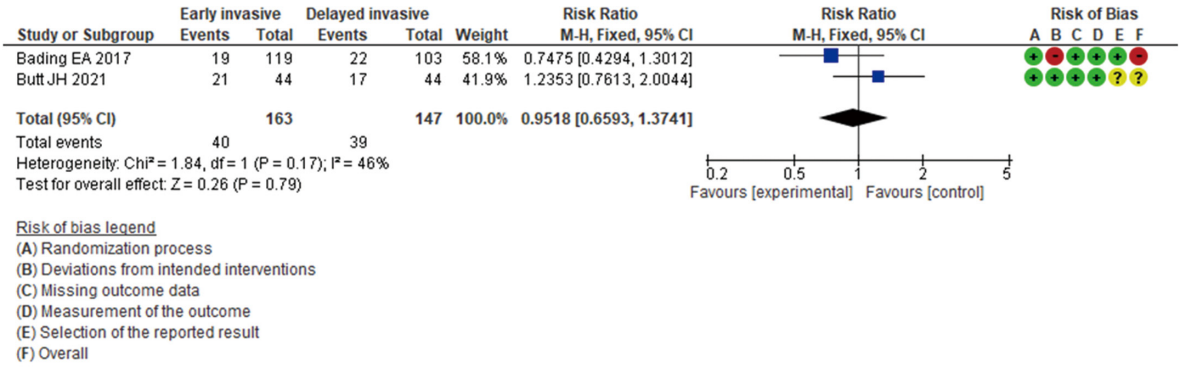

Figure 2. Forest plots of the incidence of 2-year composite outcome of all-cause death and recurrent myocardial infarction and risk of bias summaries in patients with non-ST-elevation acute coronary syndrome and congestive heart failure. CI, confidence interval.

in **Table 1**. In the ELISA-3 trial,[30] patients with NSTE-ACS were randomized to receive an early invasive strategy within 12 h or a delayed invasive strategy after 48 h, whereas in the VERDICT trial,[29] patients were randomized to receive an early invasive strategy within 12 h or a delayed invasive strategy within 48–72 h. Two hundred and twenty-two patients with NSTE-ACS and serum proBNP ≥659 pg/mL among a total of 534 patients from the study of the ELISA-3 trial, and 88 patients with NSTE-ACS and Killip 2 or 3 among a total of 2,147 patients from the study of the VERDICT trial were included in this meta-analysis. Patients with cardiac shock were excluded from both studies. In the ELISA-3 trial, the median timing of invasive coronary angiography (ICA) were 2.6 h and 54.9 h in the early and delayed strategy groups, respectively, whereas in the VERDICT trial, those were 4.7 h and 61.6 h in the early and delayed strategy groups, respectively. PCI rates in the ELISA-3 trial were 66.7% and 61.9% in the early and delayed strategy groups, respectively, whereas PCI rates in the VERDICT trial were 46.3% and 41.2% in the early and delayed strategy groups, respectively.

Risk of Bias

The risks of bias, namely, the randomization process, deviation from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result, and overall outcome, were evaluated for each study (**Figure 2**). The out-of-balance protocol deviation in the ELISA-3 trial was considered to have a high risk of bias due to concerns regarding deviations from the intended interventions. In the VERDICT trial, we obtained a 2-year outcome that was not predefined to match other studies. Therefore, bias in the selection of the reported results was considered a concern.

Outcomes

To evaluate the effect of an early invasive strategy on the outcome during the same follow-up period in the 2 trials, the 2-year composite outcome of all-cause death and recurrent MI were examined in this systematic review. **Figure 2**

Table 2. Evidence Profile

No. studies	Study design	Certainty assessment				
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
2-year all-cause death and recurrent MI, 2	RCT	Serious[A]	Not serious	Serious[B]	Serious[C]	None

No. studies	No. patients		Effect		Certainty	Importance
	Early invasive	Delayed invasive	Relative (95% CI)	Absolute (95% CI)		
2-year all-cause death and recurrent MI, 2	40/163 (24.5%)	39/147 (26.5%)	RR 0.95 (0.66–1.37)	10 fewer per 1,000 (from 110 fewer to 80 more)	Very low	Critical

[A]Bias due to deviations from intended interventions was serious. [B]Definition of CHF was different between the studies. [C]The risk ratio (RR) varies widely. CI, confidence interval. Other abbreviations as in Table 1.

shows a forest plot of the primary outcomes. The primary endpoint, all-cause death or recurrent MI, occurred in 40 (24.5%) of 163 patients in the early invasive strategy group compared with 39 (26.5%) of 147 patients in the delayed invasive strategy group. The effect of an invasive strategy on the incidence of the primary endpoint compared with a delayed invasive strategy remains unclear (RR 0.95 [95% CI 0.66–1.37]; 10 fewer per 1,000 [95% CI 110 fewer to 80 more]; **Table 2**).

Publication Bias and Quality of Evidence

Statistical testing for publication bias could not be performed because only 2 RCTs were included in the analysis. Visual inspection of the funnel plot revealed no asymmetry in the primary endpoint (**Figure 3**).

The certainty of the evidence for outcome was assessed, and a summary of the evidence profile is provided in **Table 2**. Last, we judged the level of evidence to be very low.

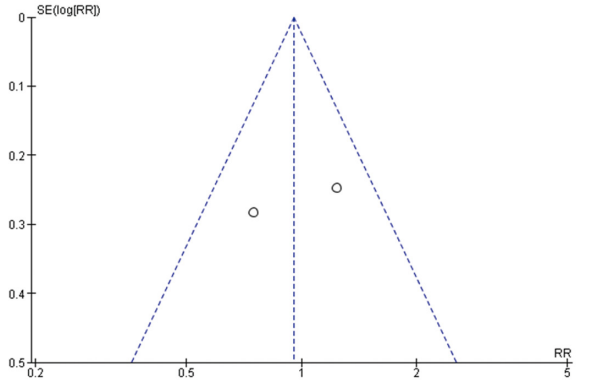

Figure 3. Funnel plots for the incidence of 2-year composite outcome of all-cause death and recurrent myocardial infarction.

Discussion

This meta-analysis found that it remained uncertain whether an early invasive strategy reduces all-cause mortality or MI compared with a delayed strategy in patients with NSTE-ACS complicated by CHF.

A routine invasive strategy with coronary angiography and PCI, if needed for patients with NSTE-ACS, reduced death and MI compared with a selective invasive or conservative strategy.[1–3] Nevertheless, the optimal timing of an invasive strategy is uncertain. Several meta-analyses from RCTs with different timing intervals of invasive angiography among patients with NSTE-ACS have not demonstrated a significant advantage of an early invasive strategy over routine invasive strategies in terms of death or non-fatal MI, although early invasive strategies were associated with reduced recurrent ischemia and shorter hospital stays.[7–9] However, some evidence does suggest a benefit for an early invasive strategy among high-risk patients with NSTE-ACS.[8,10] The VERDICT trial, in which a total of 2,147 patients with NSTE-ACS were randomized to an early invasive strategy within 12 h or a delayed invasive strategy within 48–72 h, demonstrated that among patients with NSTE-ACS with a GRACE risk score >140, an early invasive treatment strategy improved the composite outcome of all-cause death, non-fatal recurrent MI, hospital admission for refractory myocardial ischemia, or hospital admission for heart failure, compared with the delayed invasive treatment. Moreover, a recent meta-analysis comparing early and delayed invasive strategies observed no difference in mortality of the overall population, but a survival benefit in high-risk patients, including those with a GRACE risk score >140 and those with positive troponin, although tests for interaction were inconclusive.[8]

The concomitant CHF evaluated by Killip class is one of the variables in the GRACE risk score,[4,6] and is commonly observed in patients with NSTE-ACS.[13–18,31–33] The presence of CHF is strongly associated with worse short- and long-term outcomes in patients with ACS;[13–18,32–34] however, revascularization is less likely to be performed in patients with ACS complicated by CHF compared with other patients with ACS.[15–17,35,36] In the GRACE registry, only 20% of patients with ACS and CHF were revascularized, compared with 35% of those without CHF, despite that early revascularization remaining as one of the best strategies in this population.[36] Therefore, it remains to be elucidated whether an early invasive strategy is superior to a delayed invasive strategy in patients with NSTE-ACS complicated with CHF. Several retrospective studies have addressed this issue. In the CRUSADE (Can Rapid Risk

Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines) registry that enrolled 3,172 patients with NSTEMI and CHF, an early invasive strategy within 12 h was not associated with reduced 1-year mortality.[37] KAMIR-NIH (Korea Acute Myocardial Infarction Registry–National Institutes of Health) demonstrated that among 1,027 patients with NSTEMI complicated with acute CHF who underwent successful PCI, early PCI within 2 h after admission was not associated with any significant differences in mortality, non-fatal MI, target-vessel revascularization, or re-hospitalization for CHF during the 12-month follow up.[38] In contrast, a Japanese single center study demonstrated that among 160 patients with NSTE-ACS and concomitant CHF who underwent coronary angiography, the early invasive strategy within 24 h was associated with a lower incidence of composite outcome of cardiac mortality, life-threatening arrhythmia, and non-fatal MI during the median follow up of 1,236 days and those findings were confirmed even after propensity matching.[39]

To date, no RCT has specifically focused on patients with both NSTE-ACS and CHF. Our meta-analysis included 2 RCTs of patients with NSTE-ACS in which a subgroup analysis was performed according to the presence of CHF on admission. Consequently, we did not demonstrate superiority of an early invasive strategy for NSTE-ACS complicated with CHF over a delayed invasive strategy. These findings suggest that CHF is not an important factor in deriving benefits from an early invasive strategy in high-risk patients with NSTE-ACS. The VERDICT trials demonstrated a trend toward a decreased risk of cardiovascular events with the early invasive strategy in patients with new signs of myocardial ischemia on the electrocardiogram, a high heart rate, and low systolic blood pressure, although these trends were not documented in patients with CHF of Killip class 2 and 3.[25] Therefore, hemodynamic and ischemic instabilities might be more important factors than the presence of CHF itself when deciding whether to select the early invasive strategy for NSTE-ACS. Current guidelines recommend an immediate invasive strategy for patients with NSTE-ACS with very high-risk criteria, such as hemodynamic instability, cardiogenic shock, or acute heart failure presumed secondary to ongoing myocardial ischemia. However, it remains unclear whether an immediate invasive strategy improves the outcome of patients with NSTE-ACS with a very high-risk profile or CHF. We could not find a study on an immediate invasive strategy for patients with NSTE-ACS with high-risk profiles, including CHF, in this systematic review, which we wanted to know as a clinical question. To address this important issue, there is the ongoing randomized trial in Korea (KCT0006035)[40] that aims to compare immediate coronary angiography (CAG <2 h after admission) and delayed CAG after stabilization of acute CHF in patients with NSTE-ACS complicated by acute CHF, which may provide a clue.

Study Limitations

This study has some limitations. First, timing of invasive angiography differed between the trials. While invasive angiography was performed within 12 h of randomization in the early invasive strategy groups in both studies, the time from randomization to angiography was different in the delayed invasive groups (48–72 h in the VERDICTS trials,[29] and >48 h in the ELISA-3 trial[30]). Moreover, this systematic review did not examine the impact of an immediate invasive strategy in patients with NSTE-ACS concomitant with CHF. Second, the definition of CHF varied between the trials. In the VERDICT trial, the presence of CHF was evaluated using the Killip class,[29] whereas in the ELISA-3 trial, patients with higher proBNP levels when divided by the median value were enrolled as those with CHF.[30] ProBNP is well known as a useful biomarker for CHF;[23,24] however, the median value of 659 pg/mL in the ELISA-3 trials may be lower as a cut-off value of CHF compared with other studies.[41,42] In several studies for NSTE-ACS, including the VERDICT trial, approximately 5–14% patients with NSTE-ACS had coexisting CHF.[13–15,29] Third, PCI rates may affect the results. Approximately 65% of patients who underwent PCI were in the ELISA-3 trial and 45% were in the VERDICT trial.[25,26] Despite differences between the trials, a few patients did not undergo reperfusion therapy in either trial, which could influence the effect of an early invasive strategy. Fourth, only 2 RCTs with a small number of patients with CHF were included in this systematic review,[29,30] which may not have been sufficient for a meta-analysis. Fifth, we evaluated only the composite endpoints of all-cause death and MI as outcomes, despite some RCTs demonstrating that early invasive strategies for patients with NSTE-ACS were associated with a lower risk of recurrent ischemia and a shorter hospital stay.[7–9]

Conclusions

This meta-analysis demonstrated that it remains uncertain whether an early invasive strategy for NSTE-ACS complicated with CHF reduces the risk of a composite of all-cause mortality and MI within 2 years compared with a delayed invasive strategy. While current evidence does not demonstrate a clear advantage over delayed intervention, the lack of adequately powered RCTs focusing on CHF limits definitive conclusions. Further large-scale trials are needed to determine the optimal timing of intervention in this high-risk population.

Acknowledgments

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Disclosures

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Data Availability

All data used in this analysis are available from PubMed, Web of Science Core Collection (Science Citation Index – Expanded Since 1973), and Cochrane Library (CENTRAL) databases.

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Supplementary Files

Please find supplementary file(s);
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