



Priorities for Early Revascularization or Introduction of Mechanical Circulatory Support in Patients With Acute Coronary Syndrome Complicated by Cardiogenic Shock

— A Systematic Review and Meta-Analysis —

Aya Katasako-Yabumoto, MD, PhD; Kazuo Sakamoto, MD, PhD; Katsutaka Hashiba, MD; Takeshi Yamamoto, MD, PhD; Naoki Nakayama, MD, PhD; Hiroyuki Hanada, MD, PhD; Takahiro Nakashima, MD, PhD; Jin Kirigaya, MD; Tomoko Ishizu, MD, PhD; Yumiko Hosoya, MD, PhD; Toru Kondo, MD, PhD; Yusuke Okazaki, MD; Masahiro Yamamoto, MD, PhD; Takumi Osawa, MD; Marina Arai, MD, PhD; Yoshio Tahara, MD, PhD; Hiroshi Nonogi, MD, PhD; Teruo Noguchi, MD, PhD; Yasushi Tsujimoto, MD, PhD, MPH; Migaku Kikuchi, MD, PhD; Tetsuya Matoba, MD, PhD; for the Japan Resuscitation Council (JRC) Cardiogenic Shock (CS) Task Force and the Guideline Editorial Committee on behalf of the Japanese Circulation Society (JCS) Emergency and Critical Care Committee

Background: The optimal timing for mechanical circulatory support (MCS) initiation in patients with acute myocardial infarction complicated by cardiogenic shock (CS) is unknown, so in this study we analyzed whether MCS implementation before percutaneous coronary intervention (PCI) is associated with better outcomes compared to after PCI.

Methods and Results: We conducted a systematic review and meta-analysis using a random-effects model to account for potential heterogeneity. Risk ratios and 95% confidence intervals were used for dichotomous outcomes. PubMed, Web of Science, and CENTRAL were searched up to April 30, 2023. Certainty of evidence was evaluated according to the Risk of Bias in Non-Randomized Studies of Interventions-I tool. A total of 14 observational studies met the inclusion criteria. We found that venoarterial-extracorporeal membrane oxygenation (VA-ECMO) may have little to no positive effect on short-term survival, but the evidence was very uncertain. Impella use probably increases short-term survival (moderate certainty of evidence), whereas the timing of intra-aortic balloon pump (IABP) insertion improves outcomes (very low certainty of evidence). Pre- and post-PCI MCS implementation may result in little to no difference in bleeding complications or stroke incidence across all device types (low to very low certainty of evidence).

Conclusions: Early Impella implementation before PCI may increase short-term survival, whereas the timing of ECMO or IABP implementation may have little to no effect on outcomes; however, the evidence is very uncertain.

Key Words: Cardiogenic shock; Coronary revascularization; Mechanical circulatory support

Approximately 10% of patients with acute myocardial infarction (AMI) have cardiogenic shock (CS) despite appropriate management.¹⁻⁴ Despite the widespread adoption of early reperfusion therapy and advancements in mechanical circulatory support (MCS), the mortality rate of AMI complicated by CS remains high

at 30–50%.⁵⁻¹² Therefore, the need for more focused and specific interventions for these patients is crucial.¹³

CS secondary to AMI is characterized by a state of low cardiac output due to cardiac ischemia, leading to hypotension and generalized multiple organ failure. Furthermore, a progressive negative cycle of inflammation, ischemia,

Received May 21, 2025; accepted May 21, 2025; J-STAGE Advance Publication released online July 23, 2025 Time for primary review: 1 day

Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Osaka (A.K.-Y., Y. Tahara, T. Noguchi); Department of Cardiovascular Medicine, Kyushu University Graduate School of Medical Sciences, Fukuoka (K.S., T.M.); Department of Cardiology, Yokosuka General Medical Center, Kanagawa (K.H.); Department of Cardiovascular Intensive Care, Nippon Medical School Hospital, Tokyo (T.Y.); Department of Cardiology, Kanagawa Cardiovascular and Respiratory Center, Yokohama (N.N.); Graduate School of Medicine Medical Science Course Emergency and Disaster Medicine, Hirosaki University, Aomori (H.H.); Department of Cardiovascular Medicine Graduate School of Medical Sciences, Kumamoto University, Kumamoto (T. Nakashima, M.Y.); Division of Cardiology, Yokohama City University Medical Center, Yokohama (J.K.);

(Footnote continued the next page.)

vasoconstriction, and cardiac overload often persists and ultimately leads to death.^{14,15} To break this negative cycle, early reperfusion therapy to resolve myocardial ischemia¹⁶ and early initiation of MCS to stabilize hemodynamic instability is essential.^{12,17–19} However, the optimal sequence of interventions (i.e., whether early revascularization or MCS should be initiated first) remains controversial.

To clarify this issue, we analyzed whether MCS before revascularization is associated with better outcomes in patients with AMI-related CS.

Methods

The Japan Resuscitation Council (JRC) CS Task Force for the 2025 JRC guidelines was established by the Japanese Circulation Society and the Japanese Society of Internal Medicine. The JRC CS Task Force established 10 clinically relevant questions for systematic reviews.²⁰ In this study, we examined the research question regarding the effect of timing of MCS initiation for patients with CS.

We aimed to assess all available studies to resolve the following research question: “In patients with acute coronary syndromes complicated by CS, what should be prioritized: early revascularization or introduction of MCS first (ECMO, Impella, or IABP)?”

P (patients): Patients with AMI-related CS

I (intervention): Revascularization before MCS

C (comparisons, controls): Revascularization after MCS

O (outcomes): Short-term survival (survival to discharge and 1 or 3-month survival), bleeding and stroke as critical outcomes

S (study designs): Observational studies (there were no randomized controlled trials)

T (timeframe): All literature published up to April 30, 2023.

In clinical studies that included various causes of CS, patients with non-MI causes were excluded, as were studies that did not assess timing. This study protocol was pre-registered in the Open Science Framework (OSF registry; doi:10.17605/OSF.IO/69XQF). The systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²¹

Search Strategies

We identified relevant research trials by searching electronic databases, including PubMed, Web of Science Core Collection (Science Citation Index Expanded, since 1973), and the Cochrane Library (CENTRAL). Using terms determined by the review team, the search was conducted up to April 30, 2023. Articles published in English and Japanese were included; however, Japanese articles with-

out English abstracts were excluded.

Study Selection

After removing duplicates, the title and abstract were screened and sequentially excluded based on the eligibility criteria by 2 investigators (A.K.-Y. and K.S.). When uncertainty remained after screening the title and abstract, full-text articles were independently reviewed by both investigators. After excluding case reports, case series, reviews, guidelines, animal studies, and studies that did not clearly report original clinical data in humans relevant to the primary review question, the 2 reviewers independently assessed the full-text of potentially eligible studies to confirm the inclusion and exclusion criteria (second screening). Any disagreements were resolved through discussions involving a third reviewer (K.H.) until a consensus was reached.

The primary objective was to investigate the effect of the timing of MCS introduction before or after percutaneous coronary intervention (PCI) in patients with AMI-related CS.

Risk of Bias Assessment

The risk of bias in all included studies was centrally assessed by 2 reviewers (A.K.-Y. and K.H.) using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool.²² Each study was evaluated across 7 domains, and the overall risk of bias was categorized as low, moderate, serious, or critical or classified as no information based on these assessments. Disagreements between the reviewers regarding the risk of bias in specific studies were resolved through discussion.

Rating the Certainty of Evidence

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool to rate the certainty of the evidence on the effect of the timing of MCS introduction before or after PCI in patients with AMI-related CS. The certainty of the evidence was classified as “high”, “moderate”, “low”, or “very low” by evaluating the risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Statistical Analysis

The meta-analysis was conducted using unadjusted results from retrospective studies, including risk ratios (RR) with 95% confidence intervals (CI). Pooled estimates were calculated using a random-effects model to account for potential heterogeneity. RRs and 95% CIs were used for dichotomous outcomes. $P < 0.05$ indicated a statistically significant difference. Statistical heterogeneity was assessed based on the I^2 value to quantify inconsistency: an I^2 value

Department of Cardiology, Institute of Medicine, University of Tsukuba, Ibaraki (T.I., T.O.); Department of Cardiology, Sakakibara Heart Institute, Tokyo (Y.H.); Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya (T.K.); Department of Internal Medicine, Cardiology and Diabetology, Steel Memorial Muroran Hospital, Hokkaido (Y.O.); Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai (M.A.); Pharmaceutical Sciences, University of Shizuoka, Shizuoka (H.N.); Scientific Research WorkS Peer Support Group (SRWS-PSG), Osaka (Y. Tsujimoto); Oku Medical Clinic, Osaka (Y. Tsujimoto); and Department of Cardiovascular Medicine, Emergency and Critical Care Center, Dokkyo Medical University, Tochigi (M.K.), Japan

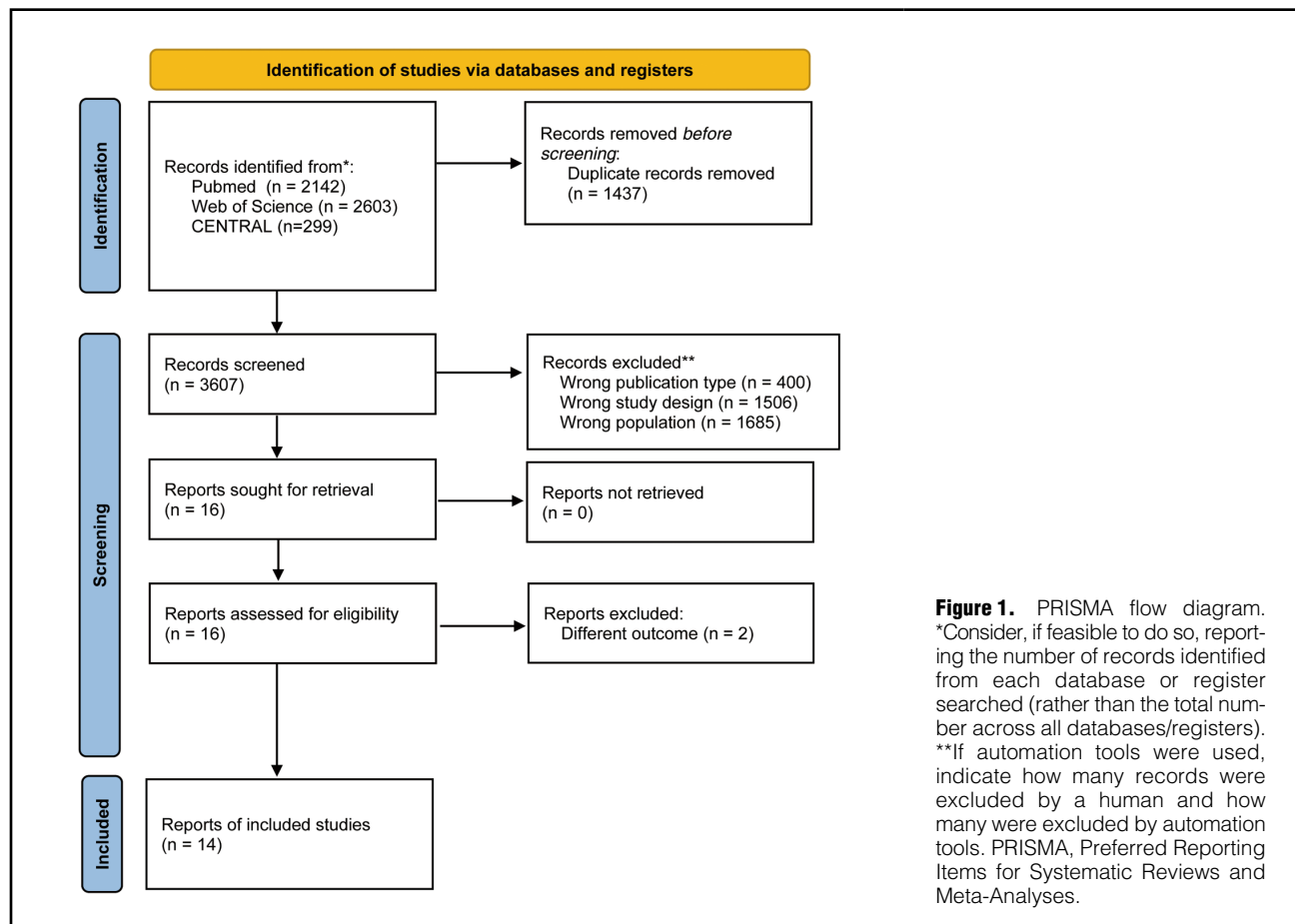
T.M. is a member of *Circulation Reports* Editorial Team.

Mailing address: Katsutaka Hashiba, MD, Department of Cardiology, Yokosuka General Medical Center, 1-8 Shimmeicho, Yokosuka, Kanagawa 239-8567, Japan. email: hsb.sgt.ktstk@gmail.com

All rights are reserved to the Japanese Circulation Society. For permissions, please email: cr@j-circ.or.jp

ISSN-2434-0790





>50% was considered indicative of substantial heterogeneity.²³ Additionally, Cochran's Q test was performed to assess the statistical significance of heterogeneity. Potential publication bias was examined using funnel plots. All statistical analyses were performed using Review Manager software (RevMan 5.4.1).

Results

Study Selection

Our search retrieved 2,142 items from PubMed, 2,603 items from the Web of Science and 299 items from CENTRAL, of which 1,437 were duplicates. After screening for content, wrong publication type, wrong study design, wrong population and different outcome, 3,593 items were excluded. Finally, 14 studies were evaluated (Figure 1).

Study Characteristics

All 14 included studies were observational in design. Regarding MCS types, 3 studies evaluated venoarterial-extracorporeal membrane oxygenation (VA-ECMO), 7 examined Impella, and 5 investigated intra-aortic balloon pump (IABP); 1 study (Helgestad et al.⁴⁰) included both Impella and IABP groups. All studies focused on CS caused by AMI, with 4 studies specifically examining patients with acute ST-segment elevation myocardial infarction (STEMI). Detailed characteristics of the individual studies are presented in Table 1.

Risk of Bias

Figure 2 illustrates the short-term survival outcomes, Figure 3 shows the bleeding outcomes and Figure 4 presents the stroke outcomes for all MCS devices with risk of bias tables. A visual assessment of funnel plots did not indicate evidence of publication bias (Supplementary Figures 1–3).

Primary Outcome: Short-Term Survival

Patients who received any MCS pre-PCI may experience little to no effect on short-term survival compared to those who received MCS post-PCI, but the evidence was very uncertain (RR 1.38, 95% CI: 1.14–1.68, very low certainty of evidence) (Figure 2A, Table 2). Significant heterogeneity was observed among the studies ($I^2=71\%$). Patients who underwent VA-ECMO pre-PCI may have little to no effect on short-term survival compared to those receiving VA-ECMO post-PCI (RR 1.75, 95% CI: 0.99–3.09, very low certainty of evidence) (Figure 2B-i, Table 2). There was moderate heterogeneity ($I^2=66\%$). Impella implementation pre-PCI probably results in an increase in short-term outcomes compared to post-PCI Impella use (RR 1.63, 95% CI: 1.39–1.91, moderate certainty of evidence) (Figure 2B-ii, Table 2). There was no significant heterogeneity observed among the studies ($I^2=0\%$). In contrast, the timing of IABP implementation did not affect short-term outcomes between pre- and post-PCI implementation (RR 1.01, 95% CI: 0.76–1.34, very low certainty of evidence) (Figure 2B-iii, Table 2). Moderate to substantial heteroge-

Table 1. Summary of Included Studies

Authors	Year	Country	Study design	Observation period	Sample size (MCS before/ after PCI)	Type of MCS	Population
Kim et al. ³⁴	2021	Korea	Retrospective study	2013–2016	117/67	VA-ECMO	Nationwide, prospective registry
Choi et al. ³⁵	2020	Korea	Retrospective study	2004–2018	50/97	VA-ECMO	Single-center registry
Huang et al. ³⁶	2018	Taiwan	Retrospective study	2005–2014	12/34	VA-ECMO	Single-center prospective registry
Chatzis et al. ³⁷	2021	Germany	Retrospective study	2014–2019	35/46	Impella 2.5	Single-center registry
Hemradj et al. ³⁸	2020	The Netherlands	Retrospective study	2006–2016	21/67	Impella 2.5, CP or 5.0	Single-center cohort
Schäfer et al. ³⁹	2020	Germany	Retrospective study	2013–2017	68/98	Impella 2.5 or CP	Prospective cohort of 4 institutes
Helgestad et al. ⁴⁰	2020	Denmark	Retrospective cohort study with PS matching	2010–2017	40/40	Impella CP	Retrospective registry of 2 institutes (RETROSHOCK registry)
Loehn et al. ⁴¹	2020	Germany	Retrospective study	2014–2016	34/39	Impella CP	Single-center registry (Dresden Impella Registry)
Meraj et al. ⁴²	2017	USA and Europe	Retrospective study	2009–2015	20/16	Impella 2.5	Multicenter retrospective registry (cVAD registry)
O'Neill et al. ⁴³	2014	USA	Retrospective study	2009–2012	63/91	Impella 2.5	Multicenter retrospective registry of 47 institutes USpella Registry
Fuernau et al. ⁴⁴	2021	Germany	Retrospective study	2009–2012	33/242	IABP	IABP-SHOCK II trial
Helgestad et al. ⁴⁰	2020	Denmark	Retrospective cohort study with PS matching	2010–2017	40/40	IABP	Retrospective registry of 2 institutes (RETROSHOCK registry)
Bergh et al. ⁴⁵	2014	Sweden	Retrospective study	2004–2008	72/67	IABP	The SCAAR registry
Sjaauw et al. ⁴⁶	2012	The Netherlands	Retrospective study	1997–2005	59/140	IABP	Single-center prospective cohort
Abdel-Wahab et al. ⁴⁷	2010	Germany	Retrospective study	2005–2008	26/22	IABP	Single-center retrospective study

(Table 1 continued the next page.)

neity was observed between these studies ($I^2=73\%$).

Safety Outcomes

Bleeding Complications The evidence was very uncertain about the effect on bleeding complications between pre-PCI and post-PCI MCS implementation, regardless of device type (RR for overall MCS: 0.93, 95% CI: 0.62–1.40; ECMO: RR 0.76, 95% CI: 0.42–1.37, low certainty of evidence; Impella: RR 0.84, 95% CI: 0.41–1.73, very low certainty of evidence; IABP: RR 1.34, 95% CI: 0.69–2.62, low certainty of evidence, respectively) (Figure 3, Table 2). Considerable heterogeneity was identified in the overall MCS and Impella analyses ($I^2=47\%$ and 68% , respectively).

Stroke Pre- and post-PCI MCS implementation appeared to have uncertain effects on stroke incidence across all device types (RR for overall MCS: 0.84, 95% CI: 0.42–1.69; ECMO: RR 0.64, 95% CI: 0.15–2.67, very low certainty of evidence; Impella: RR 0.72, 95% CI: 0.15–3.32, low certainty of evidence; IABP: RR 1.96, 95% CI: 0.25–15.66, very low certainty of evidence) (Figure 4, Table 2). ECMO and IABP analyses exhibited low to moderate and

moderate or high heterogeneity, respectively ($I^2=57\%$ and 39% , respectively).

Discussion

This systematic review and meta-analysis demonstrated that the introduction of Impella before PCI probably improves clinical outcomes compared to after PCI in patients with AMI-related CS. This survival benefit may not or only be mildly observed with either IABP or ECMO, but the evidence was very uncertain. Regarding safety outcomes, the timing of MCS introduction, whether before or after PCI, did not reduce the risk of major bleeding or stroke. These findings suggest that the timing of Impella introduction may be a critical factor in optimizing outcomes for patients with AMI-related CS, whereas the introduction timing for other support devices may have less effect on patient prognosis. Previous reports were mainly based on meta-analyses of retrospectively collected data from post-hoc subgroup analyses. However, our study distinctively includes patients who were enrolled in trials with research protocols that specifically designated

Authors	Cause of CS	MCS pre-PCI vs. MCS post-PCI				
		Age (years)	Men (%)	Primary outcome (%)	Secondary outcome	
					Bleeding (%)	Stroke (%)
Kim et al. ³⁴	AMI	59.9 vs. 61.5	103 (88.0) vs. 69 (88.1)	30/117 (25.6) vs. 6/67 (8.9)	N/A	N/A
Choi et al. ³⁵	STEMI 61% NSTEMI 39%	66.9 vs. 63.8	37 (74.0) vs. 78 (80.4)	36/50 (72.0) vs. 56/97 (57.7)	7/50 (14.0) vs. 17/97 (17.5)	2/50 (4.0) vs. 13/97 (13.4)
Huang et al. ³⁶	STEMI	57.5 vs. 56.9	11 (91.7) vs. 29 (85.3)	7/12 (58.3) vs. 10/34 (29.4)	4/12 (33.3) vs. 16/34 (47.1)	3/12 (25.0) vs. 7/34 (20.6)
Chatzis et al. ³⁷	AMI	66.0 vs. 70.2	28 (80.0) vs. 40 (87.0)	19/35 (54.3) vs. 14/46 (30.4)	12/35 (34.3) vs. 6/46 (13.0)	0/35 (0) vs. 0/46 (0)
Hemradj et al. ³⁸	STEMI	60.0 vs. 61.2	18 (85.7) vs. 54 (80.6)	11/21 (52.4) vs. 26/67 (38.8)	6/21 (28.6) vs. 17/67 (25.4)	0/21 (0) vs. 2/67 (3.0)
Schäfer et al. ³⁹	STEMI 69% NSTEMI 31%	65 vs. 67	NA/NA	49/68 (72.1) vs. 48/98 (49.0)	N/A	N/A
Helgestad et al. ⁴⁰	AMI	64.5 vs. 65.9	34 (85.5) vs. 29 (72.5)	24/40 (60.0) vs. 9/40 (22.5)	N/A	N/A
Loehn et al. ⁴¹	STEMI 66% NSTEMI 34%	72.4 vs. 65.9	30 (76.5) vs. 27 (69.2)	16/33 (48.5) vs. 9/39 (23.1)	8/34 (23.5) vs. 22/39 (56.4)	0/34 (0) vs. 0/39 (0)
Meraj et al. ⁴²	AMI	72.6 vs. 66.3	16 (80.0) vs. 12 (75.0)	11/20 (55.0) vs. 3/16 (18.8)	0/20 (0) vs. 1/16 (6.3)	1/20 (5.0) vs. 1/16 (6.3)
O'Neill et al. ⁴³	STEMI 75% NSTEMI 25%	66 vs. 63	46 (73.0) vs. 64 (70.3)	41/63 (65.1) vs. 37/91 (40.7)	9/63 (14.3) vs. 22/91 (24.2)	1/63 (1.6) vs. 2/91 (2.2)
Fuernaue et al. ⁴⁴	AMI	70 vs. 72	22 (66.7) vs. 167 (69.0)	21/33 (63.6) vs. 152/241 (63.1)	7/33 (21.2) vs. 48/242 (19.8)	1/33 (3.0) vs. 1/242 (0.4)
Helgestad et al. ⁴⁰	AMI	68.8 vs. 69.1	33 (82.5) vs. 28 (70.0)	29/40 (72.5) vs. 25/40 (62.5)	N/A	N/A
Bergh et al. ⁴⁵	STEMI	66 vs. 66	50 (69.4) vs. 51 (76.1)	42/71 (59.2) vs. 44/66 (66.7)	4/72 (5.5) vs. 0/67 (0)	N/A
Sjaauw et al. ⁴⁶	STEMI	65.1 vs. 64.6	47 (79.7) vs. 89 (63.6)	22/59 (37.3) vs. 84/140 (60.0)	N/A	N/A
Abdel-Wahab et al. ⁴⁷	AMI	70 vs. 71	23 (88.5) vs. 16 (72.7)	21/26 (80.8) vs. 9/22 (40.9)	6/26 (23.1) vs. 3/22 (13.6)	2/26 (7.7) vs. 2/22 (9.1)

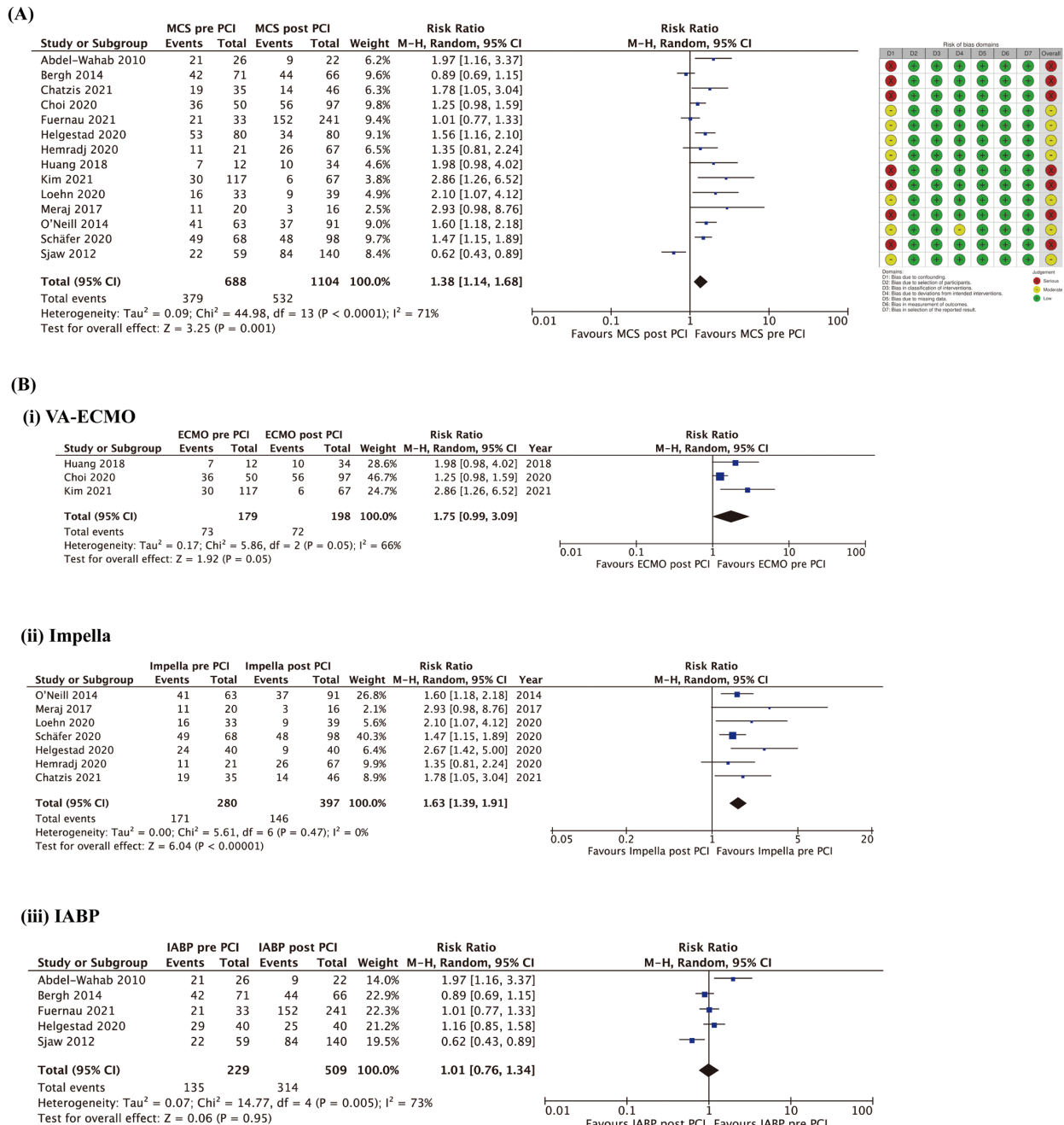
AMI, acute myocardial infarction; CCB, calcium-channel blockade; CCL, cardiac catheterization laboratory; CS, cardiogenic shock; CPR, cardiopulmonary resuscitation; ED, emergency department; HR, hazard ratio; IABP, intra-aortic balloon pump; ICU, intensive care unit; MCS, mechanical circulatory support; OR, odds ratio; PCI, percutaneous coronary intervention; PS, propensity score; ROSC, Return of Spontaneous Circulation; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction; VA-ECMO, venoarterial-extracorporeal membrane oxygenation.

MCS introduction either before or after PCI. Furthermore, our study differs from previous studies in that we excluded reports that included cases where MCS was introduced for high-risk PCI. This methodological difference from prior research leads to a more direct and intentional evaluation of the impact of intervention sequencing. However, all studies included in this meta-analysis were observational, and the certainty of evidence was judged to be very low to moderate.

Left ventricular (LV) unloading before reperfusion reduces LV wall stress and activates signaling pathways that promote myocardial salvage in the non-infarct zone of AMI.^{24,25} In fact, LV unloading using Impella before revascularization reduced LV infarct size in patients with STEMI.²⁶ This pathophysiological benefit suggests that the timing of mechanical support relative to revascularization may be critical for clinical outcomes. However, other than the DanGer Shock trial, no research has proven the prognostic improvement by Impella.¹² This discrepancy

between theoretical benefits and clinical evidence may be explained by differences in study protocols. In the IMPRESS in Severe Shock trial, device introduction before revascularization was limited to just 21% of cases, potentially diminishing any timing-dependent benefits.²⁷ In contrast, in the DanGer Shock trial, Impella placement before PCI was attempted in 89% of patients, implementing the intervention with the optimal pathophysiological phase suggested by preclinical data. Therefore, the ability to demonstrate the prognostic improvement effect of Impella in the DanGer Shock trial might be attributed not only to the characteristics of the eligible patients but also to the strategic timing of MCS introduction.

Although VA-ECMO enables full circulatory and respiratory support, it has the disadvantage of becoming an afterload for the LV. Our findings suggest that introducing VA-ECMO before PCI might be beneficial despite the very uncertain evidence. This timing-dependent benefit indicates that early hemodynamic support with VA-ECMO

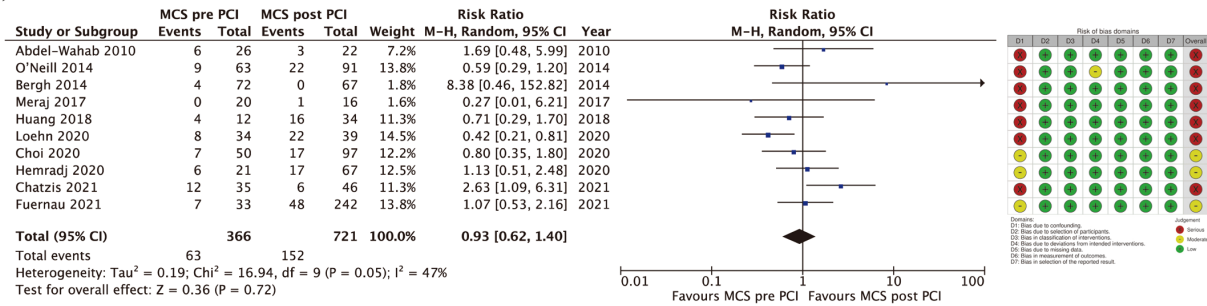


before PCI may create more favorable conditions. However, early hemodynamic support with VA-ECMO may simultaneously increase afterload for the LV from the out-set. These opposing effects might explain why improved prognoses have not been achieved with VA-ECMO. In a retrospective study, Pappalardo et al. demonstrated that concomitant treatment with VA-ECMO and Impella may improve hospital mortality in patients with CS compared

with VA-ECMO only (47% vs. 80%, $P < 0.001$).²⁸ Considering these results, early introduction of VA-ECMO with Impella support could potentially improve outcomes.

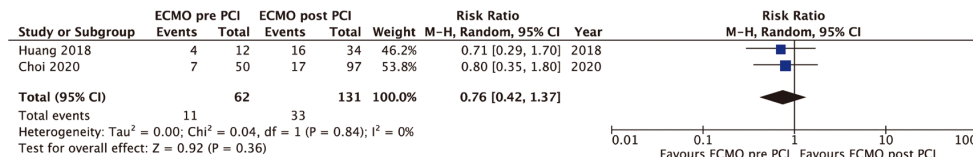
Although IABP is widely used as a convenient LV assist device, the assistive flow rate and LV unloading effect are inferior to those of Impella. Hence, previous research has not been able to identify the effectiveness of IABP in reducing myocardial infarct size,²⁹ and the IABP-SHOCK II

(A)

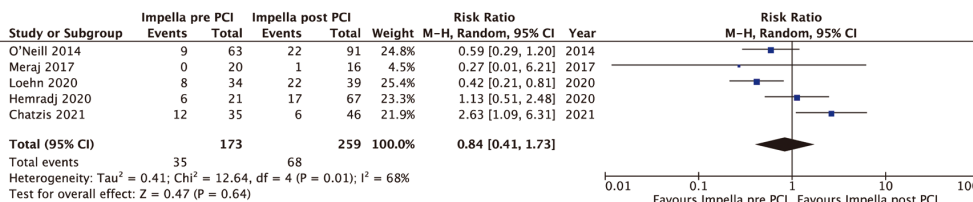


(B)

(i) VA-ECMO



(ii) Impella



(iii) IABP

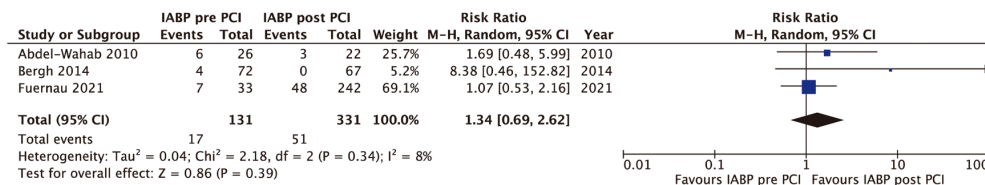


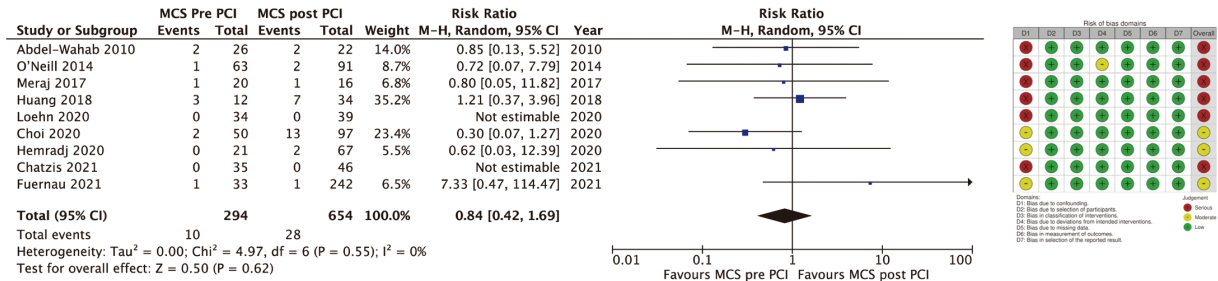
Figure 3. Forest plots for bleeding. (A) Forest plot for bleeding and risk of bias domains for all MCS devices. (B) Forest plots of bleeding for each MCS device: (i) VA-ECMO, (ii) Impella, (iii) IABP. CI, confidence interval; IABP, intra-aortic balloon pump; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention; VA-ECMO, venoarterial-extracorporeal membrane oxygenation.

trial did not find a reduction in the 30-day mortality.⁵ In this study, we investigated the potential for improved outcomes by earlier device introduction before reperfusion therapy. However, similar to previous reports, our findings could not demonstrate the effectiveness of IABP.³⁰ Early introduction of IABP may theoretically contribute to reducing LV afterload and increasing coronary blood flow; however, owing to its limited ability to assist circulation, it likely does not lead to improved prognosis.

Regarding safety endpoints such as major bleeding and

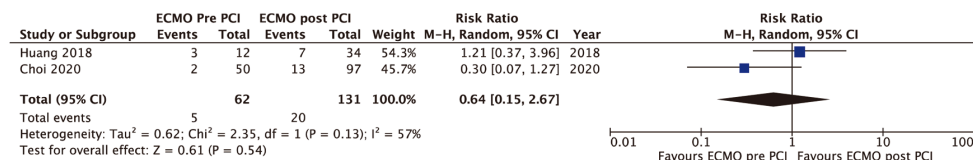
stroke, there was little to no difference between revascularization before or after MCS, similar to previous reports.^{31,32} This suggests that the timing of revascularization relative to MCS introduction may not substantially affect the risk of these major complications. Therefore, the decision regarding the sequence of interventions can potentially be guided primarily by considering hemodynamic stability and myocardial salvage rather than concerns about bleeding or stroke risk.

(A)

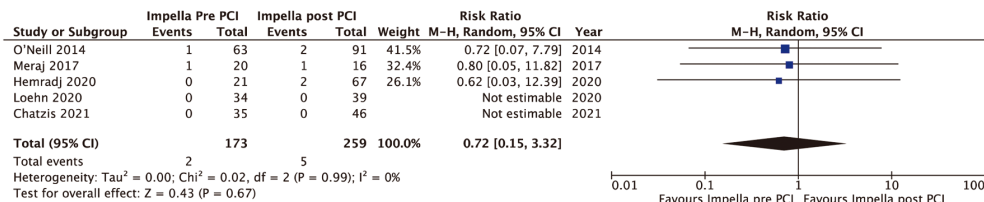


(B)

(i) VA-ECMO



(ii) Impella



(iii) IABP

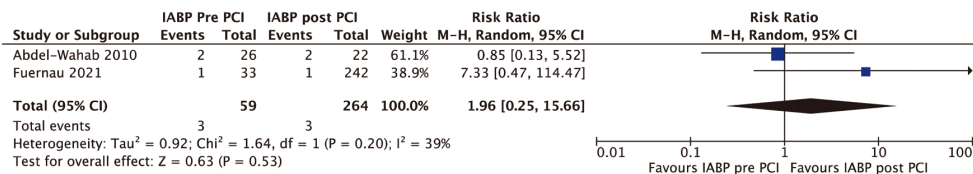


Figure 4. Forest plot for stroke. (A) Forest plot for stroke and risk of bias domains for all MCS devices. (B) Forest plots of stroke for each MCS device: (i) VA-ECMO, (ii) Impella, (iii) IABP. CI, confidence interval; IABP, intra-aortic balloon pump; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention; VA-ECMO, venoarterial-extracorporeal membrane oxygenation.

Study Limitations

Several limitations pertaining to our study are worth noting. First, our analysis included only observational studies, which is insufficient to provide definitive evidence supporting our findings. Second, heterogeneity among the included studies regarding patient selection criteria, definitions of CS, and procedural characteristics may have influenced the results. Third, the timing decision between MCS first or PCI first was not randomized but based on clinical judgment, which introduces potential selection bias. Fourth, incomplete reporting of important variables such as door-to-balloon time, time from shock onset to intervention,

and LV function parameters limited our ability to conduct more detailed subgroup analyses. Finally, regarding Impella, management protocols vary across institutions and have been developing over the past few years.³³ Therefore, differences in the time periods during which studies were conducted may have affected the results.

Conclusions

The current findings may support the early implementation of Impella support before coronary revascularization, while the early introduction of ECMO and IABP might

provide little to no benefits in patients with AMI-related CS. However, it should be noted that the quality of evidence for these conclusions ranges from very low to moderate. Further investigations, including RCT analysis, are required in the future.

Acknowledgments

The authors thank Mr. Shunya Suzuki and Ms. Tomoko Nagaoka, librarians at Dokkyo Medical University, Tochigi, Japan, for their assistance with searching the articles.

This work was supported by the Japan Resuscitation Council, Japanese Circulation Society, and the Ministry of Health, Labor, and Welfare (Grant No: JPMH22674927).

Sources of Funding

This study was supported by the Japan Resuscitation Council, the Japanese Circulation Society, and the Ministry of Health, Labor, and Welfare (Grant No: JPMH22674927).

Conflicts of Interest

T.M. reports research grants from Amgen. T.K. received lecture fees from Abbott Japan LLC, AstraZeneca K.K., Boehringer Ingelheim, Ono Pharmaceutical Co., Ltd., Kowa Company Ltd, Kyowa Kirin Co., Ltd. and Novartis Pharma K.K.

Disclosures

T.M. is a member of the Editorial Team of *Circulation Reports*.

IRB Information

Not applicable.

Data Availability Statement

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.

References

- van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, et al. Contemporary management of cardiogenic shock: A Scientific Statement from the American Heart Association. *Circulation* 2017; **136**: e232–e268, doi:10.1161/CIR.0000000000000525.
- Hunziker L, Radovanovic D, Jeger R, Pedrazzini G, Cuculi F, Urban P, et al. Twenty-year trends in the incidence and outcome of cardiogenic shock in AMIS Plus registry. *Circ Cardiovasc Interv* 2019; **12**: e007293, doi:10.1161/CIRCINTERVENTIONS.118.007293.
- Thiele H, Ohman EM, de Waha-Thiele S, Zeymer U, Desch S. Management of cardiogenic shock complicating myocardial infarction: An update 2019. *Eur Heart J* 2019; **40**: 2671–2683, doi:10.1093/eurheartj/ehz363.
- Matoba T, Sakamoto K, Nakai M, Ichimura K, Mohri M, Tsujita Y, et al. Institutional characteristics and prognosis of acute myocardial infarction with cardiogenic shock in Japan: Analysis from the JROAD/JROAD-DPC database. *Circ J* 2021; **85**: 1797–1805, doi:10.1253/circj.CJ-20-0655.
- Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock [Journal Article; Clinical Trial Protocol]. *N Engl J Med* 2012; **367**: 1287–1296, doi:10.1056/NEJMoa1208410.
- Kolte D, Khera S, Aronow WS, Mujib M, Palaniswamy C, Sule S, et al. Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. *J Am Heart Assoc* 2014; **3**: e000590, doi:10.1161/JAHA.113.000590.
- Aissaoui N, Puymirat E, Delmas C, Ortuno S, Durand E, Bataille V, et al. Trends in cardiogenic shock complicating acute myocardial infarction. *Eur J Heart Fail* 2020; **22**: 664–672, doi:10.1002/ehfj.1750.
- Goldberg RJ, Spencer FA, Gore JM, Lessard D, Yarzebski J. Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction: A population-based perspective. *Circulation* 2009; **119**: 1211–1219, doi:10.1161/CIRCULATIONAHA.108.814947.
- Osman M, Syed M, Patibandla S, Sulaiman S, Kheiri B, Shah MK, et al. Fifteen-year trends in incidence of cardiogenic shock hospitalization and in-hospital mortality in the United States. *J Am Heart Assoc* 2021; **10**: e021061, doi:10.1161/JAHA.121.021061.
- Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock [Journal Article; Clinical Trial Protocol]. *N Engl J Med* 2017; **377**: 2419–2432, doi:10.1056/NEJMoa1710261.
- Thiele H, Zeymer U, Akin I, Behnes M, Rassaf T, Mahabadi AA, et al. Extracorporeal life support in infarct-related cardiogenic shock. *N Engl J Med* 2023; **389**: 1286–1297, doi:10.1056/NEJMoa2307227.
- Moller JE, Engstrom T, Jensen LO, Eiskjaer H, Mangner N, Polzin A, et al. Microaxial flow pump or standard care in infarct-related cardiogenic shock. *N Engl J Med* 2024; **390**: 1382–1393, doi:10.1056/NEJMoa2312572.
- Kikuchi M, Tahara Y, Yamaguchi J, Nakashima T, Nomura O, Tanaka A, et al. Executive Summary: Acute coronary syndrome in the Japan Resuscitation Council Guidelines for Resuscitation 2020. *Circ J* 2023; **87**: 866–878, doi:10.1253/circj.CJ-23-0096.
- Tehrani BN, Truesdell AG, Psotka MA, Rosner C, Singh R, Sinha SS, et al. A standardized and comprehensive approach to the management of cardiogenic shock. *JACC Heart Fail* 2020; **8**: 879–891, doi:10.1016/j.jchf.2020.09.005.
- Lusebrink E, Binzenhofer L, Adamo M, Lorusso R, Mebazaa A, Morrow DA, et al. Cardiogenic shock. *Lancet* 2024; **404**: 2006–2020, doi:10.1016/S0140-6736(24)01818-X.
- Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J* 2023, doi:10.1093/eurheartj/ehad191.
- Moller-Helgestad OK, Hyldebrandt JA, Banke A, Rud CS, Udesen NL, Linde L, et al. Impella CP or VA-ECMO in profound cardiogenic shock: Left ventricular unloading and organ perfusion in a large animal model. *EuroIntervention* 2019; **14**: e1585–e1592, doi:10.4244/EIJ-D-18-00684.
- Rihal CS, Naidu SS, Givertz MM, Szeto WY, Burke JA, Kapur NK, et al. 2015 SCAI/ACC/HFSA/STS Clinical Expert Consensus Statement on the use of percutaneous mechanical circulatory support devices in cardiovascular care: Endorsed by the American Heart Association, the Cardiological Society of India, and Sociedad Latino Americana de Cardiologia Intervencion; Affirmation of Value by the Canadian Association of Interventional Cardiology-Association Canadienne de Cardiologie d'intervention. *J Am Coll Cardiol* 2015; **65**: e7–e26, doi:10.1016/j.jacc.2015.03.036.
- Saito Y, Tateishi K, Kobayashi Y. Clinical review of cardiogenic shock after acute myocardial infarction: Revascularization, mechanical circulatory support, and beyond. *Circ Rep* 2025; **7**: 6–14, doi:10.1253/circrep.CR-24-0141.
- Hashiba K, Nakashima T, Kikuchi M, Kojima S, Hanada H, Mano T, et al. Prehospital activation of the catheterization laboratory among patients with suspected ST-elevation myocardial infarction outside of a hospital: Systematic review and meta-analysis. *Circ Rep* 2022; **4**: 393–398, doi:10.1253/circrep.CR-22-0034.
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021; **372**: n71, doi:10.1136/bmj.n71.
- Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; **355**: i4919, doi:10.1136/bmj.i4919.
- Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods* 2006; **11**: 193–206, doi:10.1037/1082-989X.11.2.193.
- Kapur NK, Paruchuri V, Urbano-Morales JA, Mackey EE, Daly GH, Qiao X, et al. Mechanically unloading the left ventricle before coronary reperfusion reduces left ventricular wall stress and myocardial infarct size. *Circulation* 2013; **128**: 328–336, doi:10.1161/CIRCULATIONAHA.112.000029.
- Nakashima T, Kondo T, Nakata J, Saku K, Kawakami S, Kuwabara M, et al. Expert consensus statement on the evaluation, treatment, and transfer of cardiogenic shock using a delphi

Table 2. Evidence Profile

(A) Primary outcome: Short-term survival						
No. of studies	Certainty assessment					
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
MCS pre-PCI vs. MCS post-PCI for short-term survival of cardiogenic shock						
14	Non-randomized studies	Serious	Serious*	Serious†	Not serious	None
Impella pre-PCI vs. Impella post-PCI for short-term survival of cardiogenic shock						
7	Non-randomized studies	Serious	Not serious	Not serious	Not serious	None
ECMO pre-PCI vs. ECMO post-PCI for short-term survival of cardiogenic shock						
3	Non-randomized studies	Serious	Serious†	Not serious	Serious§	None
IABP pre-PCI vs. IABP post-PCI for short-term survival of cardiogenic shock						
5	Non-randomized studies	Serious	Serious	Not serious	Serious	None
(B) Secondary outcome: Bleeding						
No. of studies	Certainty assessment					
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Impella bleeding						
5	Non-randomized studies	Serious	Serious*	Not serious	Serious†	None
ECMO bleeding						
2	Non-randomized studies	Serious	Not serious	Not serious	Serious†	None
IABP bleeding						
3	Non-randomized studies	Serious	Not serious	Not serious	Serious§	None
(C) Secondary outcome: Stroke						
No. of studies	Certainty assessment					
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations
Impella Stroke						
5	Non-randomized studies	Serious	Not serious	Not serious	Serious*	None
ECMO stroke						
2	Non-randomized studies	Serious	Serious†	Not serious	Serious†	None
IABP stroke						
2	Non-randomized studies	Serious	Serious§	Not serious	Serious	None

(Table 2 continued the next page.)

method approach: A report of the Japan Critical Care Cardiology Committee (J4CS). *Circ J* 2025; **89**: 998–1011, doi:10.1253/circj.CJ-25-0192.

26. Saku K, Kakino T, Arimura T, Sunagawa G, Nishikawa T, Sakamoto T, et al. Left ventricular mechanical unloading by total support of Impella in myocardial infarction reduces infarct size, preserves left ventricular function, and prevents subsequent heart failure in dogs. *Circ Heart Fail* 2018; **11**: e004397, doi:10.1161/CIRCHEARTFAILURE.117.004397.
27. Karami M, Eriksen E, Ouweneel DM, Claessen BE, Vis MM, Baan J, et al. Long-term 5-year outcome of the randomized IMPRESS in severe shock trial: Percutaneous mechanical circulatory support vs. intra-aortic balloon pump in cardiogenic shock after acute myocardial infarction [Journal article]. *Eur Heart J Acute Cardiovasc Care* 2021; **10**: 1009–1015, doi:10.1093/ehjacc/zuab060.
28. Pappalardo F, Schulte C, Pieri M, Schrage B, Contri R, Soeffker G, et al. Concomitant implantation of Impella® on top of veno-arterial extracorporeal membrane oxygenation may improve survival of patients with cardiogenic shock. *Eur J Heart Fail* 2017; **19**: 404–412, doi:10.1002/ehf.668.
29. Mouloupoulos S, Stamatielopoulos S, Petrou P. Intraaortic balloon assistance in intractable cardiogenic shock. *Eur Heart J* 1986; **7**: 396–403, doi:10.1093/oxfordjournals.eurheartj.a062080.
30. Cui K, Lyu S, Liu H, Song X, Yuan F, Xu F, et al. Timing of initiation of intra-aortic balloon pump in patients with acute myocardial infarction complicated by cardiogenic shock: A meta-analysis. *Clin Cardiol* 2019; **42**: 1126–1134, doi:10.1002/clc.23264.
31. Iannaccone M, Franchin L, Hanson ID, Boccuzzi G, Basir MB, Truesdell AG, et al. Timing of impella placement in PCI for acute myocardial infarction complicated by cardiogenic shock: An updated meta-analysis. *Int J Cardiol* 2022; **362**: 47–54, doi:10.1016/j.ijcard.2022.05.011.
32. Miyashita S, Banlengchit R, Marbach JA, Chweich H, Kawabori M, Kimmelstiel CD, et al. Left ventricular unloading before

No. of studies	No. of patients		Effect		Certainty	Importance
	ECMO pre-PCI	ECMO post-PCI	Relative (95% CI)	Absolute (95% CI)		
MCS pre-PCI vs. MCS post-PCI for short-term survival of cardiogenic shock						
15	379/688 (55.1%)	532/1,104 (48.2%)	RR 1.38 (1.14–1.68)	183 more per 1,000 (from 67 more to 328 more)	⊕○○○ Very low	CRITICAL
Impella pre-PCI vs. Impella post-PCI for short-term survival of cardiogenic shock						
7	171/280 (61.1%)	146/397 (36.8%)	RR 1.63 (1.39–1.91)	232 more per 1,000 (from 143 more to 335 more)	⊕⊕⊕○ Moderate	CRITICAL
ECMO pre-PCI vs. ECMO post-PCI for short-term survival of cardiogenic shock						
3	73/179 (40.8%)	72/198 (36.4%)	RR 1.75 (0.99–3.09)	273 more per 1,000 (from 4 fewer to 760 more)	⊕○○○ Very low	CRITICAL
IABP pre-PCI vs. IABP post-PCI for short-term survival of cardiogenic shock						
5	135/229 (59.0%)	314/509 (61.7%)	RR 1.01 (0.76–1.34)	6 more per 1,000 (from 148 fewer to 210 more)	⊕○○○ Very low	CRITICAL
No. of studies	No. of patients		Effect		Certainty	Importance
	ECMO pre-PCI	ECMO post-PCI	Relative (95% CI)	Absolute (95% CI)		
Impella bleeding						
5	35/173 (20.2%)	68/259 (26.3%)	RR 0.84 (0.41–1.73)	42 fewer per 1,000 (from 155 fewer to 192 more)	⊕○○○ Very low	CRITICAL
ECMO bleeding						
2	11/62 (17.7%)	33/131 (25.2%)	RR 0.76 (0.42–1.37)	60 fewer per 1,000 (from 146 fewer to 93 more)	⊕⊕○○ Low	CRITICAL
IABP bleeding						
3	17/131 (13.0%)	51/331 (15.4%)	RR 1.34 (0.69–2.62)	52 more per 1,000 (from 48 fewer to 250 more)	⊕⊕○○ Low	CRITICAL
No. of studies	No. of patients		Effect		Certainty	Importance
	Impella pre-PCI	Impella post-PCI	Relative (95% CI)	Absolute (95% CI)		
Impella Stroke						
5	2/173 (1.2%)	5/259 (1.9%)	RR 0.72 (0.15–3.32)	5 fewer per 1,000 (from 16 fewer to 45 more)	⊕⊕○○ Low	CRITICAL
ECMO stroke						
2	5/62 (8.1%)	20/131 (15.3%)	RR 0.64 (0.15–2.67)	55 fewer per 1,000 (from 130 fewer to 255 more)	⊕○○○ Very low	CRITICAL
IABP stroke						
2	3/59 (5.1%)	3/264 (1.1%)	RR 1.96 (0.25–15.66)	11 more per 1,000 (from 9 fewer to 167 more)	⊕○○○ Very low	CRITICAL

CI, confidence interval; RR, risk ratio.

(A) *Downgraded by 1 level due to substantial heterogeneity ($I^2=71$). †Downgraded by 1 level due to heterogeneity in study populations. ‡Downgraded by 1 level due to substantial heterogeneity ($I^2=66$). §Downgraded by 1 level due to a low number of events (145) and a 95% CI of the RR below 1.0. ||Downgraded by 1 level due to substantial heterogeneity ($I^2=73$). ¶Downgraded by 1 level due to a 95% CI of the RR below 1.0.

(B) *Downgraded by 1 level due to substantial heterogeneity ($I^2=68$). †Downgraded by 1 level due to a low number of events (103) and a 95% CI of the RR below 1.0. ‡Downgraded by 1 level due to a low number of events (44) and a 95% CI of the RR below 1.0. §Downgraded by 1 level due to a low number of events (68) and a 95% CI of the RR below 1.0.

(C) *Downgraded by 1 level due to a low number of events (7) and a 95% CI of the RR below 1.0. †Downgraded by 1 level due to substantial heterogeneity ($I^2=57$). ‡Downgraded by 1 level due to a low number of events (25) and a 95% CI of the RR below 1.0. §Downgraded by 1 level due to substantial heterogeneity ($I^2=39$). ||Downgraded by 1 level due to a low number of events (6) and a 95% CI of the RR below 1.0.

percutaneous coronary intervention is associated with improved survival in patients with acute myocardial infarction complicated by cardiogenic shock: A systematic review and meta-analysis. *Cardiovasc Revasc Med* 2022; **39**: 28–35, doi:10.1016/j.carrev.2021.10.012.

33. Nakata J, Yamamoto T, Saku K, Ikeda Y, Unoki T, Asai K. Mechanical circulatory support in cardiogenic shock. *J Intensive Care* 2023; **11**: 64, doi:10.1186/s40560-023-00710-2.

34. Kim MC, Ahn Y, Cho KH, Sim DS, Hong YJ, Kim JH, et al. Benefit of extracorporeal membrane oxygenation before revascularization in patients with acute myocardial infarction complicated by profound cardiogenic shock after resuscitated cardiac arrest. *Korean Circ J* 2021; **51**: 533–544, doi:10.4070/kcj.2020.0499.
35. Choi KH, Yang JH, Hong D, Park TK, Lee JM, Song YB, et al. Optimal timing of venoarterial-extracorporeal membrane oxy-

- genation in acute myocardial infarction patients suffering from refractory cardiogenic shock. *Circ J* 2020; **84**: 1502–1510, doi:10.1253/circj.CJ-20-0259.
36. Huang CC, Hsu JC, Wu YW, Ke SR, Huang JH, Chiu KM, et al. Implementation of extracorporeal membrane oxygenation before primary percutaneous coronary intervention may improve the survival of patients with ST-segment elevation myocardial infarction and refractory cardiogenic shock. *Int J Cardiol* 2018; **269**: 45–50, doi:10.1016/j.ijcard.2018.07.023.
 37. Chatzis G, Markus B, Luesebrink U, Ahrens H, Divchev D, Syntila S, et al. Early Impella support in postcardiac arrest cardiogenic shock complicating acute myocardial infarction improves short- and long-term survival. *Crit Care Med* 2021; **49**: 943–955, doi:10.1097/CCM.0000000000004915.
 38. Hemradj VV, Karami M, Sjaauw KD, Engstrom AE, Ouweneel DM, de Brabander J, et al. Pre-PCI versus immediate post-PCI Impella initiation in acute myocardial infarction complicated by cardiogenic shock. *PLoS One* 2020; **15**: e0235762, doi:10.1371/journal.pone.0235762.
 39. Schäfer A, Werner N, Burkhoff D, Sieweke JT, Zietzer A, Masyuk M, et al. Influence of timing and predicted risk on mortality in impella-treated infarct-related cardiogenic shock patients. *Front Cardiovasc Med* 2020; **7**: 74, doi:10.3389/fcvm.2020.00074.
 40. Helgestad OKL, Josiassen J, Hassager C, Jensen LO, Holmvang L, Udesen NLJ, et al. Contemporary trends in use of mechanical circulatory support in patients with acute MI and cardiogenic shock. *Open Heart* 2020; **7**: e001214, doi:10.1136/openhrt-2019-001214.
 41. Loehn T, O'Neill WW, Lange B, Pfluecke C, Schweigler T, Mierke J, et al. Long term survival after early unloading with Impella CP® in acute myocardial infarction complicated by cardiogenic shock. *Eur Heart J Acute Cardiovasc Care* 2020; **9**: 149–157, doi:10.1177/2048872618815063.
 42. Meraj PM, Doshi R, Schreiber T, Maini B, O'Neill WW. Impella 2.5 initiated prior to unprotected left main PCI in acute myocardial infarction complicated by cardiogenic shock improves early survival. *J Interv Cardiol* 2017; **30**: 256–263, doi:10.1111/joic.12377.
 43. O'Neill WW, Schreiber T, Wohns DH, Rihal C, Naidu SS, Civitello AB, et al. The current use of Impella 2.5 in acute myocardial infarction complicated by cardiogenic shock: results from the USpella Registry. *J Interv Cardiol* 2014; **27**: 1–11, doi:10.1111/joic.12080.
 44. Fuernau G, Ledwoch J, Desch S, Eitel I, Thelemann N, Jung C, et al. Impact of timing of intraaortic balloon counterpulsation on mortality in cardiogenic shock: A subanalysis of the IABP-SHOCK II trial. *Eur Heart J Acute Cardiovasc Care* 2021; **10**: 54–61, doi:10.1177/2048872620930509.
 45. Bergh N, Angeras O, Albertsson P, Dworeck C, Matejka G, Haraldsson I, et al. Does the timing of treatment with intra-aortic balloon counterpulsation in cardiogenic shock due to ST-elevation myocardial infarction affect survival? *Acute Card Care* 2014; **16**: 57–62, doi:10.3109/17482941.2014.881504.
 46. Sjaauw KD, Engstrom AE, Vis MM, Boom W, Baan J Jr, de Winter RJ, et al. Efficacy and timing of intra-aortic counterpulsation in patients with ST-elevation myocardial infarction complicated by cardiogenic shock. *Neth Heart J* 2012; **20**: 402–409, doi:10.1007/s12471-012-0312-8.
 47. Abdel-Wahab M, Saad M, Kynast J, Geist V, Sherif MA, Richardt G, et al. Comparison of hospital mortality with intra-aortic balloon counterpulsation insertion before versus after primary percutaneous coronary intervention for cardiogenic shock complicating acute myocardial infarction. *Am J Cardiol* 2010; **105**: 967–971, doi:10.1016/j.amjcard.2009.11.021.

Supplementary Files

Please find supplementary file(s);
<https://doi.org/10.1253/circrep.CR-25-0098>