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Cangrelor in critically ill patients with cardiogenic shock or post-cardiac arrest undergoing percutaneous coronary intervention: a systematic review and meta-analysis

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Abstract

Background Evidence for cangrelor in critically ill patients remains extremely limited, despite heightened thrombotic risk from delayed oral P2Y₁₂ inhibitor effects post- percutaneous coronary intervention (PCI). We aim to assess intravenous (IV) cangrelor's efficacy and safety in patients with cardiogenic shock (CS) or post-cardiac arrest (CA) undergoing PCI.

Methods This systematic review and meta-analysis (PROSPERO number: CRD420251126926) searched PubMed, Embase, and the Cochrane library to identify studies comparing adjunctive cangrelor with oral P2Y₁₂ inhibitor during PCI in patients with CS or CA, published up until August 31, 2025. Efficacy endpoints included all-cause mortality, cardiovascular (CV) mortality, stent thrombosis, myocardial infarction (MI), stroke, and TIMI 3 flow achievement; safety endpoints were major and minor bleeding episodes.

Results A total of 12 studies including 4,537 patients were identified. Compared with the conventional treatment, adjunctive cangrelor reduced all-cause mortality overall (RR, 0.90; 95% CI, 0.82–0.98); the effect was significant in CS (RR, 0.86; 95% CI, 0.78–0.96) but not in CA (RR, 0.94; 95% CI, 0.74–1.18). No significant differences were observed in CV mortality (RR, 0.96; 95% CI, 0.76–1.22), stent thrombosis (RR, 0.72; 95% CI, 0.34–1.53), MI (RR, 0.83; 95% CI, 0.44–1.57), or stroke (RR, 1.83; 95% CI, 0.89–3.74). In addition, cangrelor was associated with higher rates of post-PCI TIMI 3 flow (RR, 1.14; 95% CI, 1.01–1.29). Major bleeding was not significantly increased overall (RR, 1.37; 95% CI, 0.95–1.97), but in controlled studies the risk was relatively increased (RR, 1.50; 95% CI, 1.10–2.05). Subgroup analyses of patients with CS supported by mechanical circulatory support, out-of-hospital CA, and CA managed with targeted temperature management showed no significant differences in clinical outcomes across all endpoints.

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Conclusions IV cangrelor was associated with reduced mortality following PCI in hemodynamically unstable patients, with the most pronounced benefit observed in those with CS, alongside improved coronary flow. These findings support its role as a valuable alternative when oral P2Y₁₂ inhibitor administration is not feasible, pending confirmation of overall clinical benefit in large-scale randomized trials.

Keywords Cangrelor, Cardiogenic shock, Cardiac arrest, Percutaneous coronary intervention, P2Y₁₂ inhibitor

Introduction

Oral P2Y₁₂ inhibitors—clopidogrel, prasugrel, and ticagrelor—form a cornerstone of dual antiplatelet therapy (DAPT) in patients with coronary artery disease (CAD) [1]. However, their pharmacokinetic profiles present significant clinical limitations. In critically ill patients, oral administration has a delayed onset; several hours may be needed to achieve effective platelet inhibition, leaving patients vulnerable to early ischemic events. Furthermore, these agents have prolonged offset times, ranging from 3–5 days for ticagrelor to 5–10 days for clopidogrel and prasugrel, which can complicate management in the event of bleeding or urgent surgery [2].

Cangrelor, an intravenous (IV) P2Y₁₂ inhibitor, offers a distinct pharmacodynamic advantage. It provides immediate, potent platelet inhibition within two minutes of administration, with a rapid offset and recovery of platelet function within approximately one hour of discontinuation [3]. This characteristic makes it ideally suited for patients undergoing percutaneous coronary intervention (PCI) for acute thrombotic conditions, especially when oral absorption may be delayed or where immediate antiplatelet effect is crucial and quick reversibility may be needed for procedural complications. These advantages become particularly vital in high-acuity scenarios such as cardiogenic shock (CS) or cardiac arrest (CA), where gut hypoperfusion, mucosal edema, and vasopressor use severely compromise enteral absorption [4, 5], rendering oral P2Y₁₂ inhibitors unreliable and potentially ineffective at the most critical time. Moreover, patients with CS or CA face a substantially higher risk of stent thrombosis due to low-flow states, heightened inflammatory responses, and increased platelet activation, making reliable peri-procedural platelet inhibition particularly crucial in these populations [6].

Despite a strong physiologic rationale, high-quality evidence supporting cangrelor in these populations remains scarce. While the large-scale randomized clinical trials (RCTs) established the efficacy and safety of cangrelor across broad PCI populations, these trials systematically excluded hemodynamically unstable patients in the protocol [7–9]. Consequently, the evidence base is predominantly observational, with inconsistent findings that indicate treatment-effect heterogeneity and a possible signal of increased bleeding [10]. Most recently, the DAPT-SHOCK-AMI (Dual Antiplatelet Therapy for Shock Patients With Acute Myocardial Infarction)

trial—the first randomized evaluation of antiplatelet therapy in AMI patients complicated by CS—found that cangrelor did not demonstrate superiority to crushed ticagrelor for its primary composite endpoint, though without a significant increase in major bleeding [11].

Given the profound clinical vulnerability of these patient cohorts and the ongoing uncertainty regarding optimal antiplatelet strategy, we conducted a systematic review and meta-analysis to evaluate the clinical efficacy and safety of cangrelor in patients with CS or CA undergoing PCI.

Methods

This systematic review and meta-analysis was conducted in accordance with the Cochrane Collaboration recommendations and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table 1) [12]. The study protocol was registered prospectively with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420251126926.

Literature search and study selection

We performed a systematic search of PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to August 31, 2025, restricting results to English-language publications. Search terms encompassed relevant keywords related to acute coronary syndrome (ACS) (e.g., infarction, coronary, angina), critical states (e.g., shock, hypotension, arrest, coma, resuscitation), and the intervention (e.g., cangrelor) (Supplementary Table 2). To maximize sensitivity, the search strategy intentionally omitted terms related to outcomes. Two authors (HH and JJ) independently conducted the literature search, screening of abstracts, and selection of the included trials. Any discrepancies were resolved through discussion, and if consensus could not be reached, a third reviewer was consulted (YHJ). Additionally, we manually screened the reference lists of all included articles and monitored presentations from major cardiology congresses to identify further potentially eligible studies. Full-text review and assessment of supplementary materials were performed for all studies meeting initial screening criteria. An updated search conducted on October 19, 2025, using the original strategy identified no additional eligible studies.

Eligibility criteria

No restrictions were applied regarding publication date or status. We included RCTs and observational studies that met the following criteria: (1) compared cangrelor with either an oral P2Y₁₂ inhibitor or a control group not receiving cangrelor; (2) enrolled patients with CS or CA undergoing PCI; and (3) reported at least one predefined clinical outcome of interest. Studies were excluded in cases of overlapping populations, crossover designs, absence of a control group, or lack of relevant outcome variables. To avoid duplication, publications from overlapping patient data or time frames were excluded; only the most recent or comprehensive study reporting the outcomes of interest was retained.

Data extraction

Data extraction was performed independently by two authors (HH and JJ). One reviewer (HH) conducted the initial data extraction, which was subsequently verified for accuracy and completeness by the second reviewer (JJ). Any discrepancies were resolved through discussion, with consultation of a third reviewer (YHJ) when consensus could not be reached. Extracted information included study characteristics, baseline patient demographics, antithrombotic treatment details, and clinical outcomes. The available clinical outcomes are summarized in Supplementary Table 3. For studies identified through conference presentations, data were extracted directly from the presented slides, abstracts, and accompanying press materials. Potential disagreements in the review and selection of studies were discussed and resolved through consensus.

Quality assessment

The methodological quality of the included RCT was evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool, which assesses risk of bias across key domains and classifies it as low, high, or presenting some concerns [13]. Observational studies were appraised using the Newcastle–Ottawa Scale (NOS), which assigns a maximum score of nine stars across three domains: selection of study groups, comparability of groups, and outcome ascertainment [14]. Publication bias was evaluated visually using funnel plots of study weights versus point estimates for outcomes where at least 10 studies were available.

Outcome measures

The prespecified efficacy outcomes were all-cause mortality, cardiovascular (CV) mortality, stent thrombosis, myocardial infarction (MI), and stroke. Non-clinical outcomes included the incidence of post-PCI Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow. Safety outcomes encompassed major and minor bleeding episodes, with Bleeding Academic Research Consortium (BARC)

criteria preferentially used when available [15]; study-specific definitions were applied otherwise (Supplementary Table 4). All outcomes were assessed over the short term (in-hospital or at 30 days).

Statistical analysis

Dichotomous outcomes are expressed as risk ratios (RRs) with 95% confidence intervals (CIs). The Mantel–Haenszel method was used for binary endpoints, and the inverse-variance method was applied for continuous endpoints. Heterogeneity was evaluated using Cochran's Q test (considered significant at $P < 0.10$) and quantified using the I^2 statistic. A fixed-effect model was employed for analyses with low heterogeneity ($I^2 \leq 25\%$), while a DerSimonian–Laird random-effects model was used in cases of substantial heterogeneity ($I^2 > 25\%$) or when observational studies were included.

To assess the robustness of the findings, a leave-one-out sensitivity analysis was performed by iteratively excluding each study and recalculating the pooled effect size. Predefined subgroup analyses were conducted for controlled studies (RCTs and propensity score-matched), as well as for specific high-risk populations: CS patients supported with mechanical circulatory support (MCS) devices, out-of-hospital CA (OHCA) patients, and those managed with targeted temperature management (TTM).

To investigate specific clinical hypotheses and explore sources of heterogeneity, univariate meta-regression analyses were performed for outcomes including at least 10 studies to ensure sufficient power. All analyses were performed using Review Manager (RevMan, version 5.4.1, The Cochrane Collaboration) and Comprehensive Meta-Analysis software (CMA, version 4, Biostat, Inc.).

Results

Study selection and characteristics

The systematic literature search identified 308 records from 3 databases. After duplicate removal and screening of titles and abstracts, 32 full-text articles and conference abstracts underwent eligibility assessment, with supplementary materials reviewed where available. Eleven studies initially met inclusion criteria. Prospective monitoring of major cardiology congresses subsequently identified one additional eligible RCT (the DAPT-SHOCK-AMI trial) [11]. Ultimately, 12 studies (4,537 patients) [10, 11, 16–25] met the inclusion criteria and were included in the meta-analysis (Fig. 1).

Among these, two were RCTs and ten were observational studies. Key study and baseline characteristics are detailed in Table 1. A total of 2,089 patients (46.0%) received IV cangrelor, typically a 30 µg/kg bolus followed by a 4 µg/kg/min infusion during the periprocedural period. In the control group, ticagrelor was used most

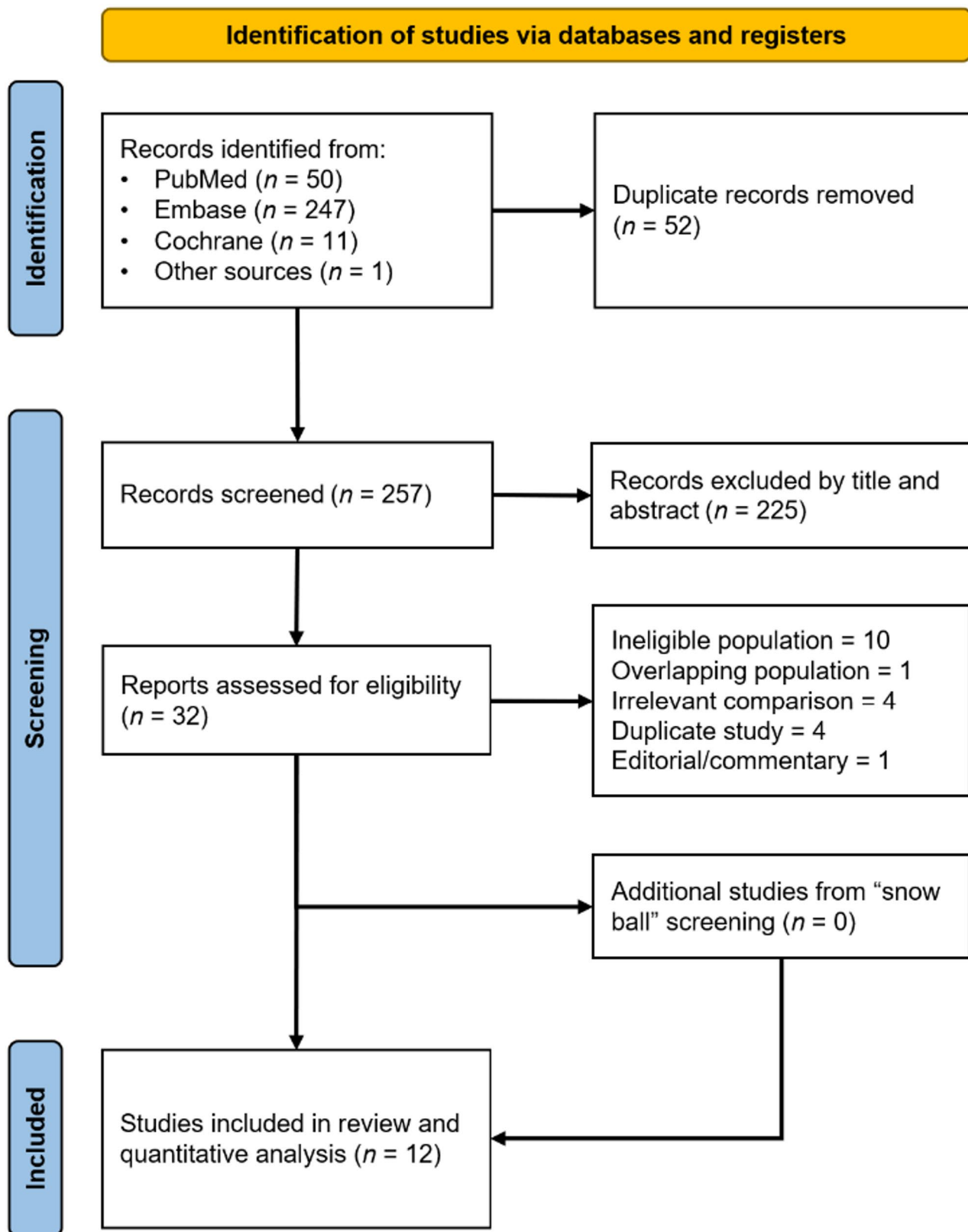


Fig. 1 PRISMA flow diagram of study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Table 1 Baseline characteristics of included studies

Study	Design	Population	Patients can- grelor /control	Cangrelor dose & duration	Timing of cangrelor	Control group	Transi- tion: oral P2Y12i agent	Male, % /control	Aget, y cangrelor /control	DM, % cangrelor /control	STEMI, % cangrelor /control	Bleed- ing criteria	Follow-up duration
Kordis 2024 [16]	RCT	CA+TTM	15/15	30 µg/kg bolus+4 µg/ kg/min infusion (4 h)	Start of PCI	No cangrelor	Ticagrelor	93/100	56/58	20/13	60/80	BARC	In- hospital, 30 days
DAPT- SHOCK- AMI 2025 [11]	RCT	CS	298/307	30 µg/kg bolus+4 µg/ kg/min infusion	Peri-PCI	Ticagrelor	Ticagrelor	77/78	65/66	28/28	89/88	BARC	In- hospital, 30 days, 12 months
Emils- son 2025 [10]	Non-RCT, PSM	CS CA	497/497 569/569	NA	Before or dur- ing PCI	Predomi- nantly ticagrelor	Unspecified	67/67 80/79	72/71 67/67	17/15 12/15	87/88 78/77	NA	In- hospital, 30 days
Dropa 2019 [17]	Non-RCT, PSM	CS	88/88	30 µg/kg bolus+4 µg/ kg/min infusion (≥ 2 h), or no bolus+ 0.75 µg/ kg/min for bridging	During PCI	Oral P2Y12i (unspeci- fied)*	Unspecified	72/72	69/71	30/24	71/71	GUSTO	In- hospital, 30 days, 12 months
Zeymer 2023 [18]	Non-RCT, PSM	CA/CS	118/118	Duration: <2 h [67%], 2–4 h [25%], and > 4 h [7%]	13% before PCI	Oral P2Y12i (unspeci- fied)#	NA	NA	NA	NA	NA	BARC	In-hospital
Abus- nina 2025 [19]	Non-RCT, PSM	CS	99/99	NA	NA	Oral P2Y12i (unspecified)	NA	NA	NA	NA	NA	NA	In-hospital
Cohan 2023 [20]	Non-RCT	CS+VA-ECMO	19/18	0.75 µg/kg/ min while on VA–ECMO	11% during PCI	Oral P2Y12i (unspecified)	NA	53/72	64/61	32/56	63/61	BARC	In-hospital
Ferlini 2025 [25]	Non-RCT	CA	34/380	30 µg/kg bolus+4 µg/ kg/min infusion (median 2 h)	Before PCI	Oral P2Y12i (unspecified)	Unspecified	68/78	64/65	15/17	44/40	BARC	In-hospital
Fiore 2018 [21]	Non-RCT	CA	13/9	30 µg/kg bolus+4 µg/ kg/min infusion (4 h)	Before PCI	Ticagrelor	Ticagrelor	NA	NA	NA	NA	NA	In-hospital

Table 1 (continued)

Study	Design	Population	Patients can- grelor /control	Cangrelor dose & duration	Timing of cangrelor	Control group	Transi- tion: oral P2Y12i agent	Male, % cangrelor /control	Age†, y cangrelor /control	DM, % cangrelor /control	STEMI, % cangrelor /control	Bleed- ing criteria	Follow-up duration
Gel- beneg- ger 2025 [22]	Non-RCT	CA + TTM	267/147	30 µg/kg bolus + 4 µg/ kg/min infusion	Peri-PCI	Predomi- nantly ticagrelor	Predomi- nantly Ticagrelor	88/93	57/59	19/16	71/74	BARC, TIMI	In- hospital, 30 days
Prüller 2018 [23]	Non-RCT	CA + TTM	25/17	30 µg/kg bolus + infusion (0.75–4 µg/kg/ min, 2–4 h)	In cath lab	47% ticagrelor, 29% prasu- grel, 24% clopidogrel	NA	84/82	61/65	20/18	60/53	BARC, TIMI	In-hospital
Spahr 2023 [24]	Non-RCT	CS + MCS	47/184	NA	NA	Oral P2Y12i (unspecified)	NA	77/83	66/68	NA	60/60	BARC	In-hospital

†mean or median

*control group from the IABP-SHOCK trial

#control group from the CULPRIT-SHOCK trial

BARC, Bleeding Academic Research Consortium; CA, cardiac arrest; CS, cardiogenic shock; DAPT-SHOCK-AMI, Dual Antiplatelet Therapy For Shock Patients With Acute Myocardial Infarction; DM, diabetes mellitus; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; MCS, mechanical circulatory support device; NA, not available/applicable; PSM, propensity score matching; P2Y12i, P2Y₁₂ inhibitor; RCT, randomized controlled trial; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; TTM, targeted temperature management; VA-ECMO, venoarterial extracorporeal membrane oxygenation

frequently, with clopidogrel and prasugrel also employed. Key baseline characteristics, including age, sex, and prevalence of diabetes and ST-segment elevation myocardial infarction (STEMI), were generally well-balanced between the groups when reported. Bleeding events were defined by Bleeding Academic Research Consortium (BARC) [15], TIMI [26], or Global Utilization of Streptokinase and T-PA for Occluded Coronary Arteries (GUSTO) [27] criteria.

Quality assessment and risk of bias

Risk of bias was assessed using the Cochrane Rob 2.0 tool for RCTs (Supplementary Table 5) and the NOS for observational studies (Supplementary Table 6). One recently published RCT demonstrated low risk of bias according to predefined methodological criteria [11]. Among non-randomized studies, four used propensity-score matching to balance baseline characteristics [10, 17–19]; in two, matched controls were drawn from external trial populations [16, 17]. Three observational studies lost credit in the NOS comparability domain because they did not employ matching or statistical adjustment [20, 21, 23]. Two studies were available only as conference abstracts and were therefore excluded from full appraisal [19, 24]. No study was rated as high risk of bias. Funnel plots for all-cause mortality and major bleeding were symmetrical, indicating a low likelihood of publication bias (Supplementary Fig. 1).

Efficacy outcomes

Compared with the conventional treatment, cangrelor was associated with reduced all-cause mortality overall (RR, 0.90; 95% CI, 0.82–0.98; $P=0.01$; $I^2=0\%$). Subgroup analysis demonstrated significant mortality reduction in patients with CS (RR, 0.86; 95% CI, 0.78–0.96; $P=0.008$; $I^2=0\%$), but not in those with CA (RR, 0.94; 95% CI, 0.74–1.18; $P=0.59$; $I^2=13\%$) (Fig. 2A). This mortality benefit remained consistent in the analyses restricted to the controlled studies (RR, 0.90; 95% CI, 0.82–0.98; $P=0.02$; $I^2=0\%$) (Fig. 2B).

No significant differences were observed between groups for CV mortality (RR, 0.96; 95% CI, 0.76–1.22; $P=0.76$; $I^2=47\%$) (Fig. 3), stent thrombosis (RR, 0.72; 95% CI, 0.34–1.53; $P=0.40$; $I^2=3\%$) (Fig. 4A), MI (RR, 0.83; 95% CI, 0.44–1.57; $P=0.56$; $I^2=22\%$) (Fig. 4B), and stroke (RR, 1.83; 95% CI, 0.89–3.74; $P=0.10$; $I^2=0\%$) (Fig. 4C). Findings for these endpoints were consistent across the CS and CA subgroups.

Post-PCI coronary flow

Four studies including the DAPT-SHOCK-AMI trial [11, 17, 18, 25] reported post-PCI TIMI flow. The pooled analysis showed a significantly higher rate of post-PCI TIMI grade 3 flow with cangrelor versus oral P2Y₁₂ inhibitor

(RR, 1.14; 95% CI, 1.01–1.29; $P=0.03$), with substantial heterogeneity ($I^2=83\%$) (Supplementary Fig. 2).

Safety outcomes

Cangrelor was not associated with increased risk of major bleeding overall (RR, 1.37; 95% CI, 0.95–1.97; $P=0.10$; $I^2=67\%$), with neutral findings in patients presented with CS (RR, 1.18; 95% CI, 0.89–1.56; $P=0.24$; $I^2=0\%$) or CA (RR, 1.62; 95% CI, 0.71–3.73; $P=0.25$; $I^2=85\%$) (Fig. 5A). By contrast, analyses restricted to controlled studies demonstrated a significantly increased risk of major bleeding with cangrelor (RR, 1.50; 95% CI, 1.10–2.05; $P=0.010$; $I^2=8\%$) (Fig. 5B). No significant difference in minor bleeding was observed between the groups (RR, 0.91; 95% CI, 0.55–1.51; $P=0.72$; $I^2=0\%$) (Supplementary Fig. 3). Given variability in bleeding definitions across studies, we conducted a sensitivity analysis restricted to studies using BARC criteria [15], which showed no significant between-group differences (Fig. 6).

Subgroup analyses in selected cohorts

Subgroup analyses of high-risk populations showed no significant treatment effects. In CS patients requiring MCS ($n=268$; 2 studies) [20, 24], cangrelor showed no significant differences in all-cause mortality, access-site bleeding, or major bleeding (BARC type 3 or 5) (Supplementary Fig. S4). Among patients with OHCA ($n=880$; 4 studies) [15, 20, 21, 24], cangrelor demonstrated no significant differences in all-cause mortality, stent thrombosis, or major bleeding (Supplementary Fig. 5). Similarly, in CA patients managed with TTM ($n=486$; 3 studies) [15, 21, 22], no significant differences were observed in these endpoints (Supplementary Fig. 6).

Sensitivity analysis

In sensitivity analyses stratified by study design, all-cause mortality was not significantly reduced with cangrelor in RCTs (RR, 0.95; 95% CI, 0.79–1.15), whereas observational studies showed a significant mortality benefit (RR, 0.88; 95% CI, 0.79–0.98; Supplementary Fig. 7). No significant differences in major bleeding were observed when stratified by study design (Supplementary Fig. 8).

A separate leave-one-out analysis revealed that the largest cohort study [10], contributing approximately 35% of the analytical weight, substantially influenced the pooled estimates. When excluded, the RR for all-cause mortality shifted from 0.90 (95% CI, 0.82–0.98) to 0.94 (95% CI, 0.85–1.05) in the overall cohort and from 0.86 (95% CI, 0.78–0.96) to 0.93 (95% CI, 0.80–1.09) in the CS subgroup (Supplementary Fig. 9), indicating the overall findings were sensitive to this influential study.

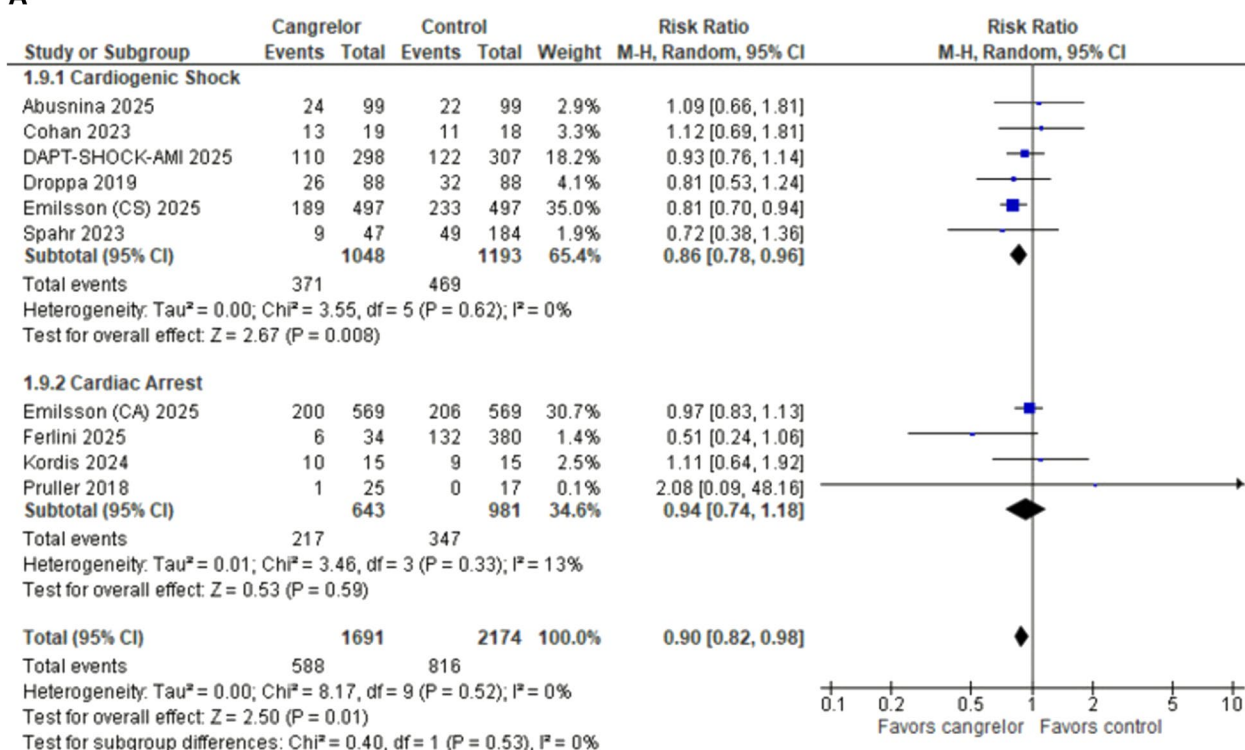
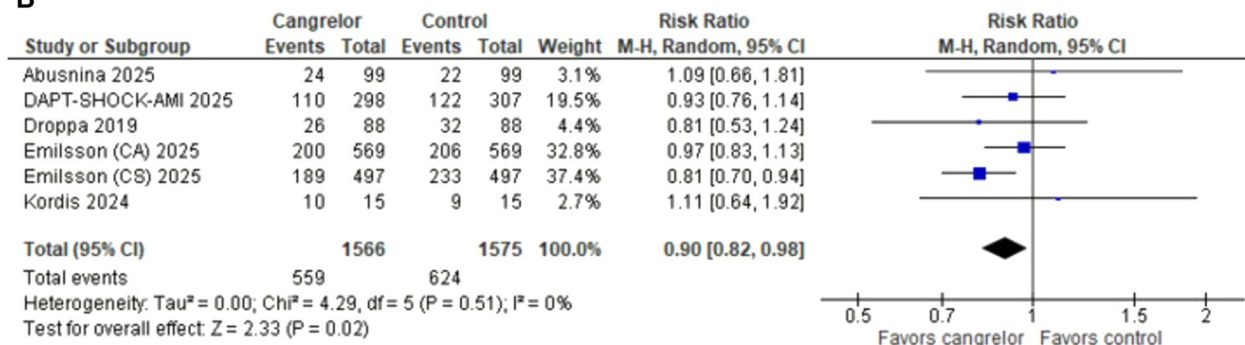
A**B**

Fig. 2 Forest plot of all-cause mortality in **A** overall cohort and **B** controlled studies (randomized controlled trials and propensity score-matched studies). CA, cardiac arrest; CI, confidence interval; CS, cardiogenic shock; DAPT-SHOCK-AMI, Dual Antiplatelet Therapy for Shock Patients with Acute Myocardial Infarction; M-H, Mantel–Haenszel

Meta-regression

To investigate potential sources of heterogeneity and test specific hypotheses, univariate meta-regression analyses were conducted for the primary outcomes of all-cause mortality and major bleeding, for which a sufficient number of studies were available. For all-cause mortality, meta-regression revealed that age ($P = 0.108$), the proportion of patients with STEMI ($P = 0.956$), and the proportion requiring MCS ($P = 0.687$) were not significant effect modifiers (Supplementary Fig. 10). Similarly, for major bleeding—an outcome characterized by substantial heterogeneity—meta-regression found that age ($P = 0.467$), proportion of STEMI ($P = 0.492$) and proportion

requiring MCS ($P = 0.289$) were not significant predictors of the treatment effect (Supplementary Fig. 11).

Discussion

To our knowledge, this analysis represents the first meta-analysis directly comparing IV cangrelor infusion with non-cangrelor-based strategies in patients with CS or post-CA undergoing PCI. Our analysis of 12 studies encompassing 4,537 patients (2,086 receiving cangrelor, 46.0%) demonstrated five key findings: (1) cangrelor was associated with a significant reduction in all-cause mortality overall; the benefit was evident in CS but not in CA; (2) no significant differences were observed in CV

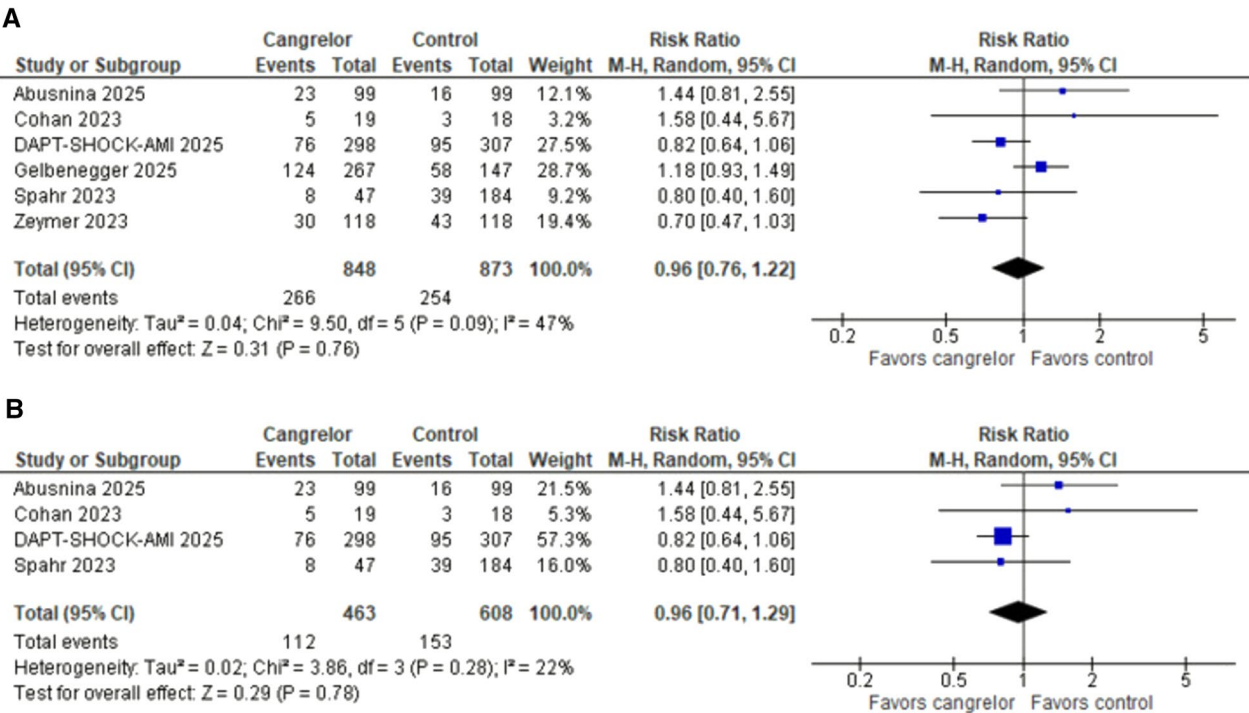


Fig. 3 Forest plot of cardiovascular mortality in **A** overall cohort and **B** cardiogenic shock subgroup. CI, confidence interval; DAPT-SHOCK-AMI, Dual Antiplatelet Therapy for Shock Patients with Acute Myocardial Infarction; M-H, Mantel–Haenszel

mortality, stent thrombosis, MI, or stroke; (3) cangrelor use significantly increased the likelihood of achieving post-PCI TIMI grade 3 flow; (4) while pooled analyses did not show increased risk of serious bleeding, the controlled-study subset indicated a signal toward higher risk of major bleeding; and (5) in high-risk cohorts such as CS with MCS, OHCA, and CA managed with TTM, no significant differences in clinical events were observed.

The results of this analysis provide the most comprehensive synthesis to date for the critically ill patients. Notably, the all-cause mortality reduction observed in our meta-analysis is directionally consistent with the signal reported in DAPT-SHOCK-AMI. Although the trial did not meet its primary composite endpoint, its mortality results suggest a trend favoring cangrelor. Compared with crushed oral ticagrelor ($n = 307$; 180-mg loading dose followed by 90 mg twice daily), IV cangrelor ($n = 298$; 30 $\mu\text{g/kg}$ bolus followed by continuous infusion at 4 $\mu\text{g/kg/min}$) demonstrated non-inferiority for all-cause mortality at both 30 days (36.9% vs. 39.7%; absolute difference, -2.8% ; P for non-inferiority = 0.17) and 1 year (43.6% vs. 49.2%; absolute difference, -5.6% ; P for non-inferiority = 0.044) [11]. This convergence between our pooled results and the directional signal from a randomized trial—although underpowered for rare endpoints—strengthens the hypothesis of a genuine treatment effect and underscores the value of our large-scale synthesis in

a field where landmark cangrelor RCTs have systematically excluded these high-risk patients [7–9].

The observed mortality benefit in CS patients is supported by a compelling biological rationale. Achieving adequate periprocedural platelet inhibition is paramount during PCI to prevent adverse thrombotic events. In CS, impaired gut absorption, splanchnic hypoperfusion, gut edema, and concomitant vasopressor use can significantly delay and diminish the efficacy of oral P2Y₁₂ inhibitors during PCI [28]. Cangrelor, administered intravenously, circumvents these limitations by providing immediate, potent, and predictable platelet inhibition at the time of PCI [29]. This aligns with existing pharmacodynamic data in critically ill patients and underscores the potential value of cangrelor in ensuring reliable antiplatelet effect when enteral absorption is compromised [30].

This theoretical advantage is confirmed by clinical pharmacodynamic evidence, with multiple studies consistently demonstrating cangrelor’s superiority in hemodynamically unstable cohorts. In DAPT-SHOCK-AMI including CS patients, satisfactory platelet inhibition—defined as Vasodilator-Stimulated Phosphoprotein Phosphorylation (VASP-P) platelet reactivity index (PRI) $< 50\%$ —was achieved in 100% of cangrelor-treated patients versus 22.1% with crushed ticagrelor at the end of the procedure [11]. Extending to CA populations, clinical studies in OHCA patients undergoing PCI showed faster and more complete platelet inhibition

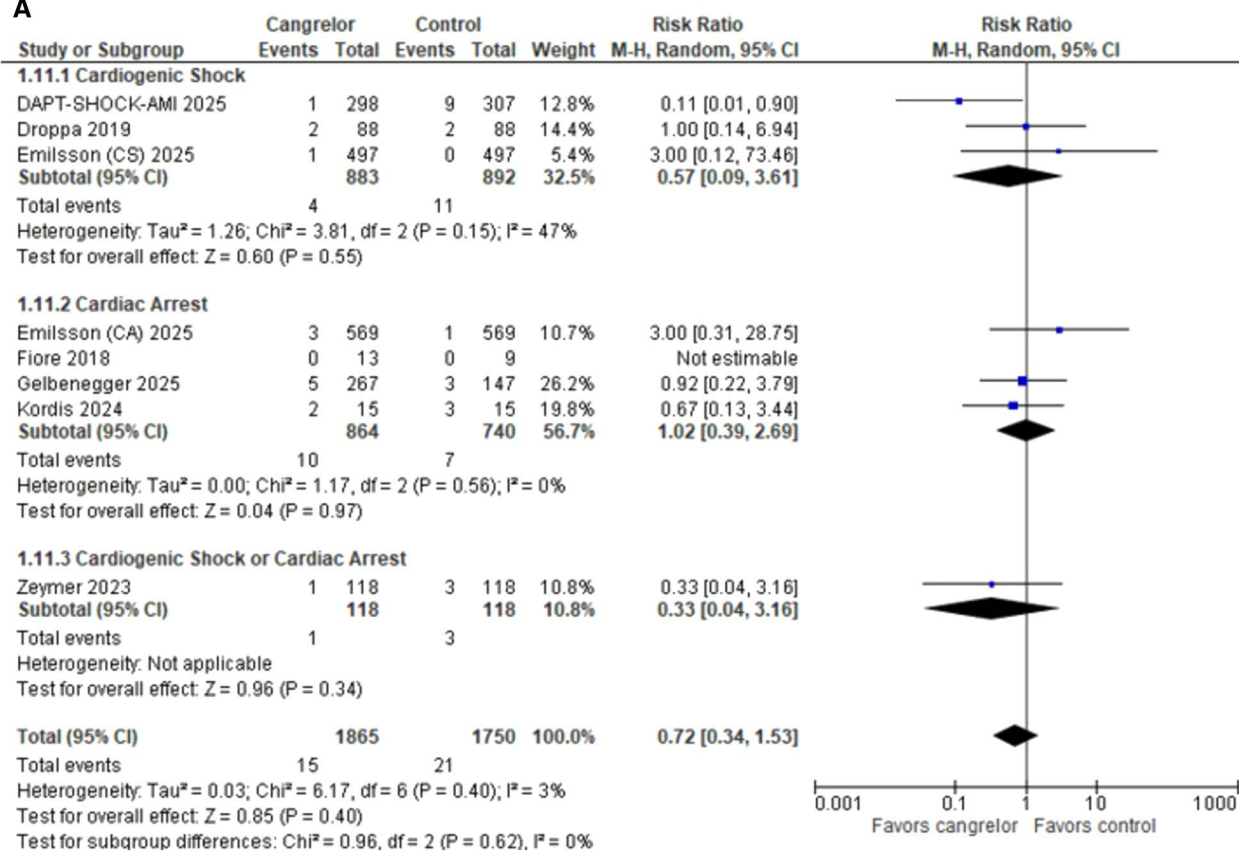
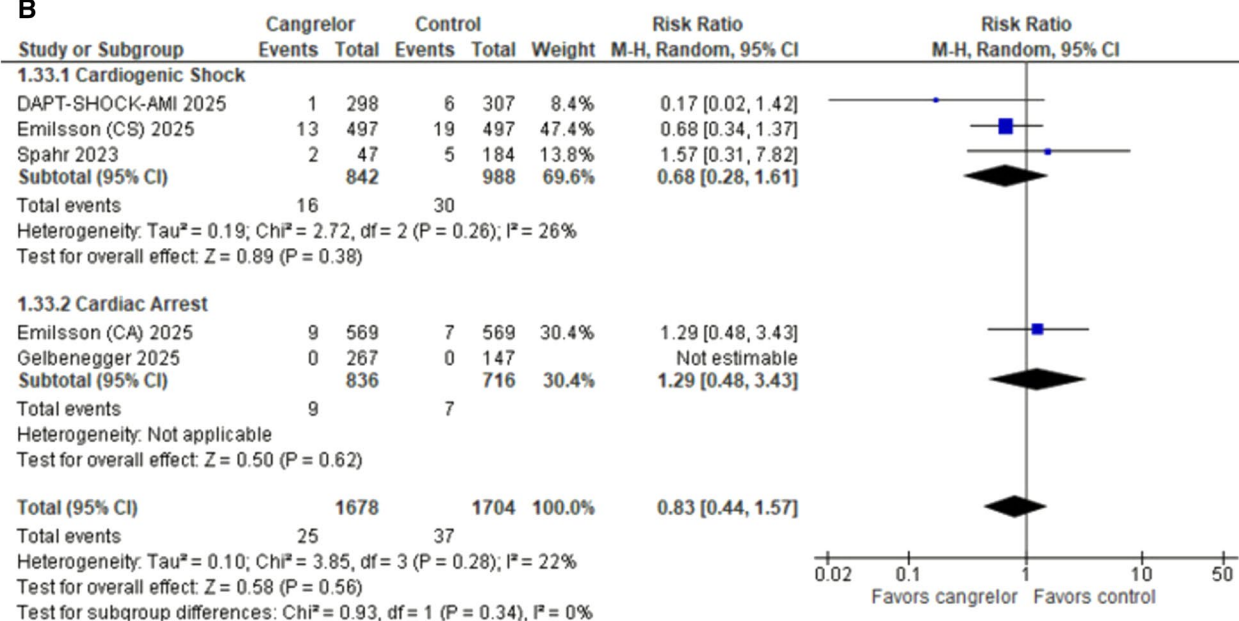
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Fig. 4 Forest plot of **A** stent thrombosis, **B** myocardial infarction and **C** stroke. CA, cardiac arrest; CI, confidence interval; CS, cardiogenic shock; DAPT-SHOCK-AMI, Dual Antiplatelet Therapy for Shock Patients with Acute Myocardial Infarction; M-H, Mantel-Haenszel

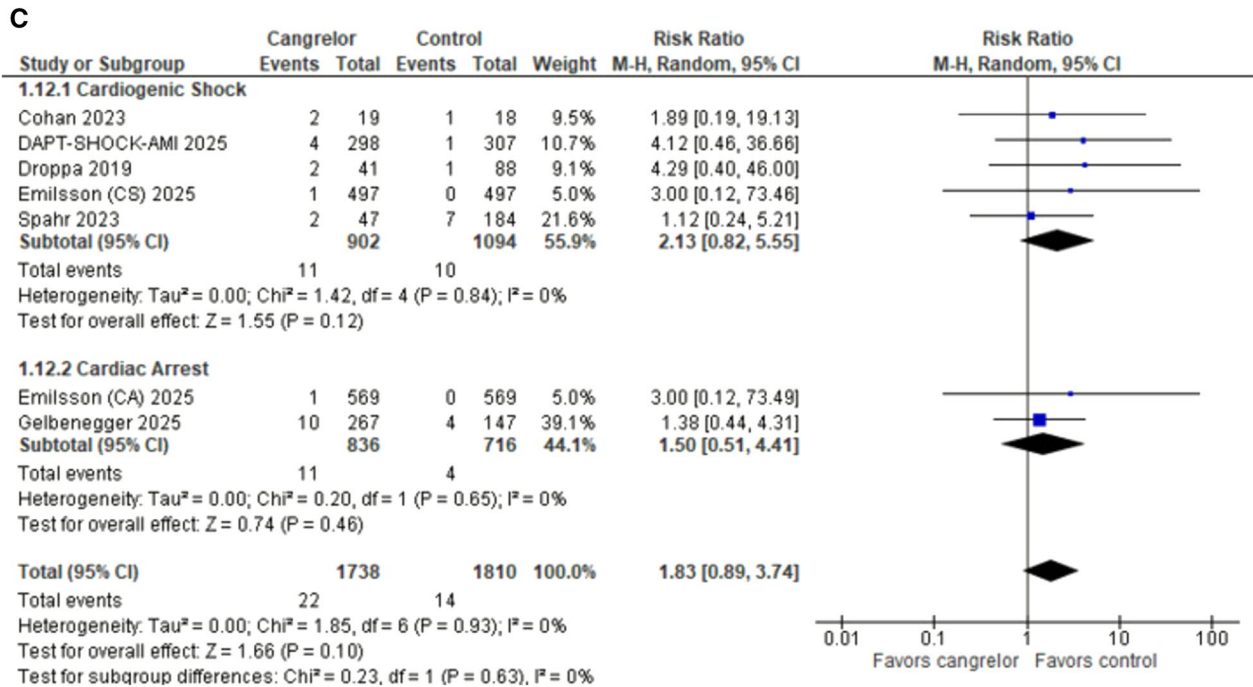


Fig. 4 (continued)

with cangrelor than with oral agents. Fiore et al. reported that 85% of patients receiving cangrelor achieved adequate platelet inhibition (PRI<50%) within one hour post-PCI versus only 11% with ticagrelor alone [21]. Similarly, another study found significantly greater platelet inhibition at 1–3 h with cangrelor in OHCA patients undergoing TTM [16].

This pharmacodynamic advantage appears to translate into procedural benefit: our pooled analysis showed significantly higher rates of post-PCI TIMI 3 flow achievement with cangrelor. The reduction in all-cause mortality without corresponding reductions in CV mortality or thrombotic events may suggest a mechanism beyond prevention of ischemic complications. We hypothesize that improved coronary flow and myocardial perfusion with cangrelor may preserve left ventricular (LV) function, potentially reducing fatalities from pump failure or arrhythmias—deaths that may not be consistently classified as CV in origin. This is supported by DAPT-SHOCK-AMI findings of better LV function with cangrelor, suggesting that securing procedural success may prevent the hemodynamic deterioration that leads to death in CS patients [11]. The consistent link between reliable platelet inhibition and improved coronary flow provides a plausible mechanism for benefit in this high-risk population, especially during the immediate periprocedural window when rapid inhibition is critical to optimize outcomes.

However, benefits from enhanced platelet inhibition are not uniform across subgroups. In the CA cohort, no mortality reduction was observed, reflecting the

multifactorial pathophysiology of post-CA syndrome. Outcomes in this heterogeneous population may be driven by hemodynamic instability, arrhythmias, and global hypoxic–ischemic injury; key determinants such as resuscitation duration, anoxic brain injury, and post-arrest shock/multiorgan failure are largely insensitive to antiplatelet intensity. Nonetheless, cangrelor’s immediate onset and rapid offset allow prompt discontinuation if life-threatening bleeding occurs.

Beyond mortality, other efficacy endpoints were largely neutral. Stent thrombosis rates did not differ significantly in pooled or subgroup analyses. Default application of potent P2Y₁₂ inhibitor and newer-generation drug-eluting stents have driven stent thrombosis to historically low levels [31, 32]. The rarity of this outcome renders individual studies underpowered, highlighting the value of pooled analyses for more definitive assessment. Likewise, our OHCA subanalysis—despite wide variability in reported risk [33]—showed no significant differences.

Cangrelor’s safety profile requires careful appraisal in parallel with the observed efficacy. Although pooled analyses across CS and CA showed no overall increase in bleeding, the controlled-study subset suggested a higher risk of major bleeding with cangrelor. This discrepancy may reflect confounding by indication in observational cohorts, wherein clinicians preferentially select cangrelor for patients with fewer comorbidities and lower perceived bleeding risk, thereby attenuating the apparent treatment effect. The Swedish registry illustrates this phenomenon: patients treated with cangrelor had more favorable

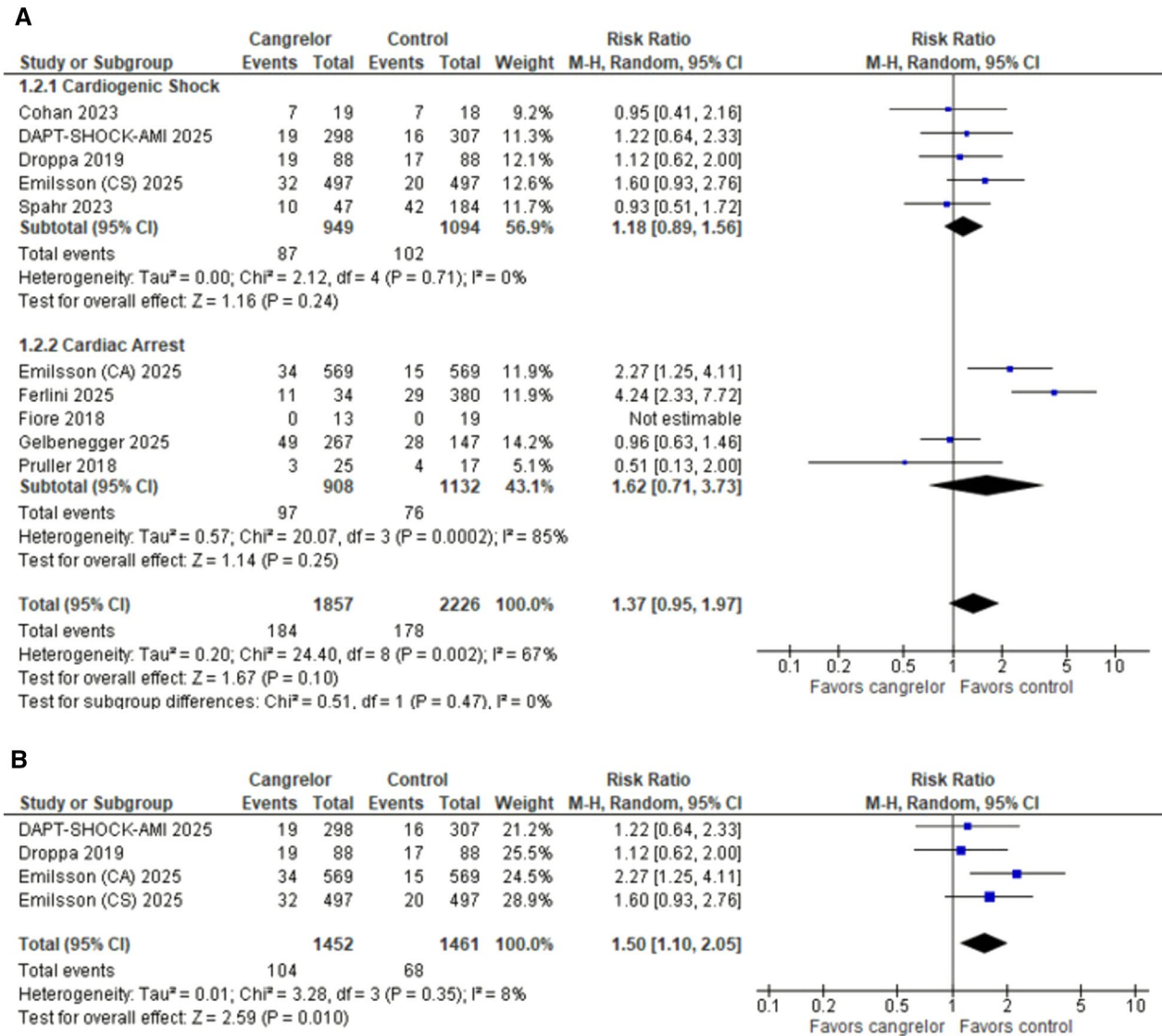


Fig. 5 Forest plots of major bleeding in **A** overall cohort and **B** controlled studies. CA, cardiac arrest; CI, confidence interval; CS, cardiogenic shock; DAPT-SHOCK-AMI, Dual Antiplatelet Therapy for Shock Patients with Acute Myocardial Infarction; M-H, Mantel-Haenszel

baseline characteristics than those receiving oral agents [10]. Clinically, however, the potent and immediate platelet inhibition of cangrelor could heighten bleeding risk, particularly in critically ill patients with shock-induced coagulopathy or hepatic dysfunction. Notably, the DAPT-SHOCK-AMI trial did not demonstrate a significant increase in major bleeding [11], but its controlled design may obscure risks seen in everyday care. Thus, while bleeding with cangrelor appears manageable in trial settings, our findings suggest that the risk may be greater in broader routine practice, underscoring the need for careful patient selection and close monitoring.

These safety considerations are particularly important in critically illness. CS status profoundly alters drug pharmacokinetics and pharmacodynamics [34]. In AMI patients complicated by CS, drug metabolism becomes

erratic, potentially leading to serious adverse events from either under- or over-exposure to the administered agents [35]. Furthermore, these patients are at inherent high bleeding risk (HBR), which occurs in approximately 20% of cases during early hospitalisation [36]. However, because of its rapid offset, cangrelor retains a theoretical safety advantage in this HBR population when urgent discontinuation may be required.

When defining cangrelor’s role in therapy, its profile should be considered alongside other IV antiplatelet agents, particularly glycoprotein IIb/IIIa inhibitors (GPIs). Cangrelor provides rapid blockade of platelet adenosine diphosphate (ADP) P2Y₁₂ receptor, whereas GPIs (e.g., tirofiban) can block the final common pathway of platelet aggregation, offering more potent inhibitory effect on platelet–fibrin clot formation. The

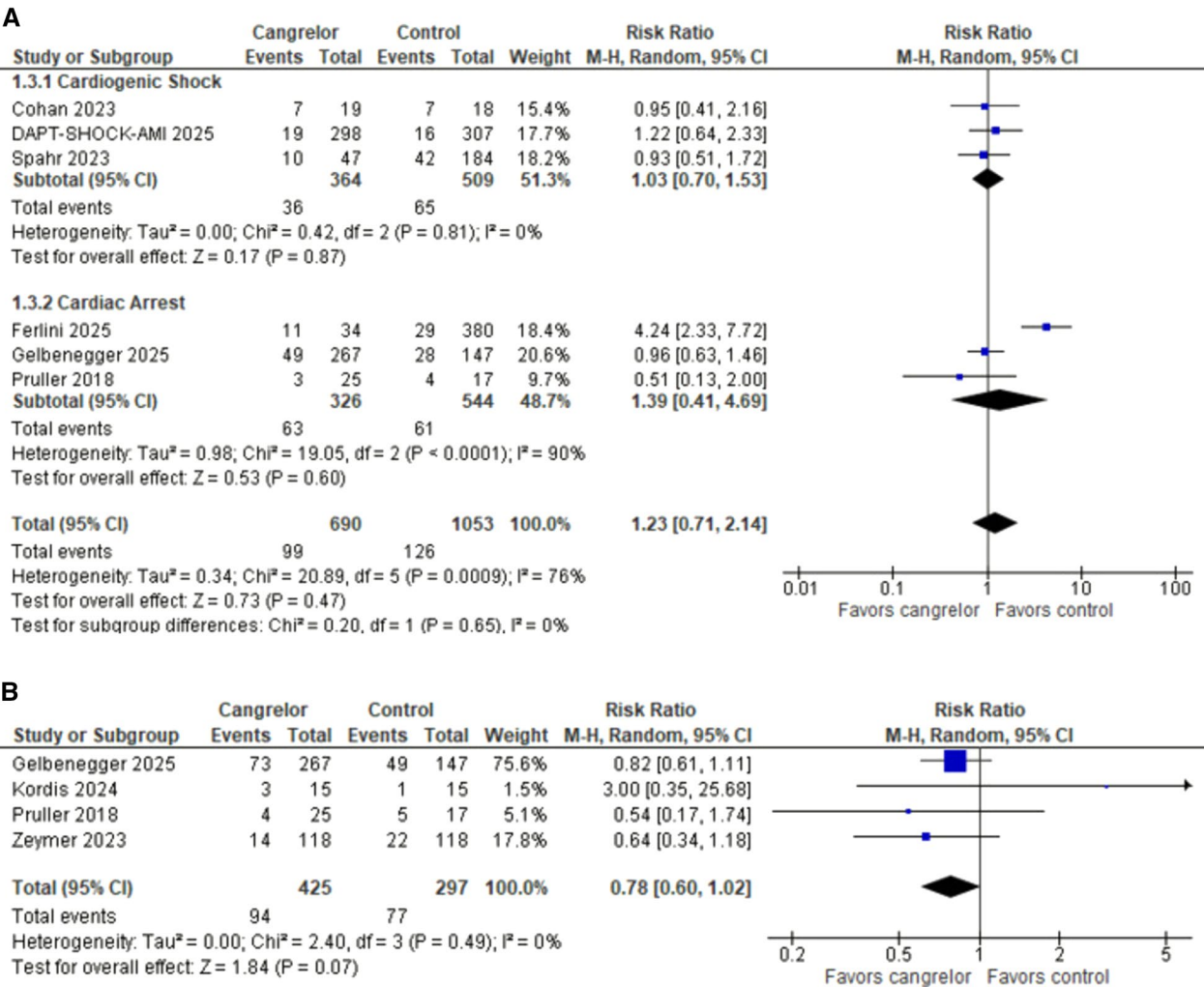


Fig. 6 Forest plots of Bleeding Academic Research Consortium (BARC)-defined events: **A** major bleeding (BARC type 3 or 5); and **B** clinically relevant bleeding (BARC type 2, 3 or 5). CI, confidence interval; DAPT-SHOCK-AMI, Dual Antiplatelet Therapy for Shock Patients with Acute Myocardial Infarction; M-H, Mantel-Haenszel

FABOLUS-FASTER (Facilitation Through Aggrastat or Cangrelor Bolus and Infusion Over Prasugrel) trial reported that IV tirofiban achieved faster and greater ADP-induced platelet inhibition than cangrelor and also suppresses thrombin receptor activating peptide (TRAP)-induced platelet aggregation [37]. This finding may suggest that short-term tirofiban infusion (IV or intracoronary) may provide more comprehensive suppression of platelet–fibrin clot formation in high-thrombotic milieu (e.g., CS patients with high intracoronary thrombus burden). Because of its rapid offset, cangrelor allows prompt discontinuation in bleeding events, a theoretical safety advantage compared with oral agents or GPIs. Choice of agent may therefore hinge on the need for broad-spectrum inhibition versus P2Y₁₂-specific blockade. While our analysis suggests potential benefit of cangrelor in CS, the lack of head-to-head RCTs against

GPIs prevents firm conclusions about the optimal IV antiplatelet agent in this setting.

Limitations

Our results should be interpreted in light of constraints that reflect the current evidence landscape. First, the evidence base remains limited and is largely derived from observational data, as only two randomized trials are available—one small pilot study [16] and another (DAPT-SHOCK-AMI) [11] whose full results have not yet been published. However, the consistency of the mortality benefit for CS across sensitivity analyses restricted to controlled studies strengthens the plausibility of this signal. Second, the pronounced heterogeneity in major bleeding, isolated entirely to the CA subgroup, may be a critical finding. This likely reflects the profound clinical diversity of post-arrest patients, where factors like duration of resuscitation and neurological injury severity may

drastically influence bleeding risk. Our meta-regression found no significant covariates to explain this heterogeneity and represent a key target for future phenotyping research. Third, the overall mortality signal was largely attributable to real-world observational studies, with the point estimate being particularly sensitive to the inclusion of the largest available cohort [10]. Critical appraisal revealed no methodological concerns with this study, and its considerable weight in our analysis suggests its results may more accurately reflect real-world treatment effects. Finally, the strategic inclusion of conference abstracts was necessary to mitigate publication bias and capture the most current data in this rapidly evolving field, acknowledging a trade-off between timeliness and methodological detail.

Conclusions

This meta-analysis provides the first comprehensive synthesis of evidence regarding IV cangrelor in patients with CS or post-CA undergoing PCI. Cangrelor was associated with a potential mortality benefit, most pronounced in patients with CS, and improved procedural success as evidenced by significantly higher rates of post-PCI TIMI grade 3 flow. These findings support its use when immediate platelet inhibition is required and enteral administration is compromised. Future adequately powered, multicenter RCTs are needed to definitively confirm its net clinical benefit and clarify its role relative to GPIs.

Abbreviations

ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
AMI	Acute myocardial infarction
BARC	Bleeding academic research consortium
CA	Cardiac arrest
CAD	Coronary artery disease
CS	Cardiogenic shock
DAPT	Dual antiplatelet therapy
MCSD	Mechanical circulatory support device
MI	Myocardial infarction
OHCA	Out-of-hospital cardiac arrest
PCI	Percutaneous coronary intervention
RCT	Randomized controlled trial
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis in Myocardial Infarction
TTM	Targeted temperature management

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13054-025-05812-x>.

Additional file 1.

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Author contributions

HH, SWK, and YHJ conceived and designed the study. HH and JJ performed the literature search, study selection, and data extraction. HH conducted the quality assessment and statistical analyses, with input from YHJ regarding interpretation of the results. HH wrote the first draft of the manuscript. SWK, YHJ, SYL, JHC, JJ, DAG, JK, UST and PAG critically revised the manuscript, provided substantive intellectual feedback, and reviewed the final version. All authors read and approved the final manuscript.

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Data availability

All data generated during the study are available as Supplementary Information.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

YHJ has received honoraria for lectures from Daiichi Sankyo, Sanofi-Aventis, Han-mi Pharmaceuticals, and Daewoong Pharmaceuticals and research grants or support from Samjin Pharmaceuticals, Hanmi Pharmaceuticals, Yuhan Pharmaceuticals, Biotronik Korea, and U and I Corporation. DAG reports institutional grants from AstraZeneca, and honoraria from BMS, Janssen and Chiesi. JK has been involved in the DAPT-SHOCK-AMI trial as an investigator and received personal fees from AstraZeneca, Ferrer, Adamed and Krka. PAG has received grants and personal fees from Bayer HealthCare, Otitopic, Amgen, and Janssen, US World-Meds; grants from Instrumentation Laboratory, Hikari Dx, Haemonetics, Medicure, and Idorsia Pharmaceuticals; and personal fees from UpToDate and has patents "Detection of Restenosis Risk in Patients Issued" and "Assessment of Cardiac Health and Thrombotic Risk in a Patient."

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