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Comparative Analysis of Patient Characteristics in Cardiogenic Shock Studies: Differences Between Trials and Registries

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Comparative Analysis of Patient Characteristics in Cardiogenic Shock Studies

Differences Between Trials and Registries

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ABSTRACT

OBJECTIVES This study sought to evaluate the differences in cardiogenic shock patient characteristics in trial patients and real-life patients.

BACKGROUND Cardiogenic shock (CS) is a leading cause of mortality in patients presenting with acute myocardial infarction (AMI). However, the enrollment of patients into clinical trials is challenging and may not be representative of real-world patients.

METHODS We performed a systematic review of studies in patients presenting with AMI-related CS and compared patient characteristics of those enrolled into randomized controlled trials (RCTs) with those in registries.

RESULTS We included 14 RCTs (n = 2,154) and 12 registries (n = 133,617). RCTs included more men (73% vs 67.7%, $P < 0.001$) compared with registries. Patients enrolled in RCTs had fewer comorbidities, including less hypertension (61.6% vs 65.9%, $P < 0.001$), dyslipidemia (36.4% vs 53.6%, $P < 0.001$), a history of stroke or transient ischemic attack (7.1% vs 10.7%, $P < 0.001$), and prior coronary artery bypass graft surgery (5.4% vs 7.5%, $P < 0.001$). Patients enrolled in RCTs also had lower lactate levels (4.7 ± 2.3 mmol/L vs 5.9 ± 1.9 mmol/L, $P < 0.001$) and higher mean arterial pressure (73.0 ± 8.8 mm Hg vs 62.5 ± 12.2 mm Hg, $P < 0.001$). Percutaneous coronary intervention (97.5% vs 58.4%, $P < 0.001$) and extracorporeal membrane oxygenation (11.6% vs 3.4%, $P < 0.001$) were used more often in RCTs. The in-hospital mortality (23.9% vs 38.4%, $P < 0.001$) and 30-day mortality (39.9% vs 45.9%, $P < 0.001$) were lower in RCT patients.

CONCLUSIONS RCTs in AMI-related CS tend to enroll fewer women and lower-risk patients compared with registries. Patients enrolled in RCTs are more likely to receive aggressive treatment with percutaneous coronary intervention and extracorporeal membrane oxygenation and have lower in-hospital and 30-day mortality.
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Cardiogenic shock (CS) is a leading cause of mortality in patients presenting with acute myocardial infarction (AMI). The incidence of AMI-related CS (AMICS) is 5% to 15%.[1,2] Despite a substantial risk of death, nearing 50%,[3] AMICS remains understudied, particularly in randomized controlled trials (RCTs). Difficulties encountered during recruitment into RCTs stem from challenges with

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

AMICS = acute myocardial infarction–related cardiogenic shock

CS = cardiogenic shock

ECMO = extracorporeal membrane oxygenation

MCS = mechanical circulatory support

PCI = percutaneous coronary intervention

RCT = randomized controlled trial

informed consent in hemodynamically compromised patients and investigators' beliefs and biases about a potential lack of equipoise between treatment modalities.[4] With only a small number of RCTs having been performed, varying inclusion criteria, and heterogeneity in shock severity, it may be challenging to generalize the results of such trials to all comers. We sought to evaluate the differences between patients enrolled in RCTs compared with patients enrolled in contemporary registries.

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METHODS

SEARCH STRATEGY. We conducted a systematic review of studies that included patients with AMICS. We performed a computerized search according to the proposal for conducting and reporting Meta-analysis of Observational Studies in Epidemiology[5] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[6] We performed a systematic search limited to the English language through the MEDLINE, Embase, and Cochrane databases from January 2005 to July 2021 using the following search terms separately and in combination: "cardiogenic shock," "randomized controlled trial," "registry," "CS," and "shock." We screened the retrieved studies' bibliographies and previous reviews for any relevant studies not found through the initial search. The search was performed by 2 independent investigators (K.B. and M.M.) who are both physicians. We included all RCTs that included patients with AMICS during our study period. Our strategy was to compare patients enrolled in RCTs, of which the data are used to form current clinical practice guidelines to contemporary real-world patients. To ensure that we included a representative sample of contemporary patients in the comparison, we opted to include only recent large registries. We included registries published in 2012 onward that enrolled >1,000 patients. The rationale for choosing large registries was that they would better represent patients than smaller registries that might originate from a single or a few regional centers, introducing selection bias. The data were extracted by 2 independent investigators (K.B. and M.M.). We did not include registries with duplicate or overlapping cohorts. The detailed search strategy and flowchart of the study are shown in **Figure 1**. The study is a meta-analysis, and Institutional Review Board approval was not required.

Our main objective was to describe and compare baseline characteristics of patients in RCTs and registries. All baseline variables were compared between both groups. When analyzing specific treatment variables that were reported as outcomes (eg, multivessel percutaneous coronary intervention [PCI]), we excluded RCTs dedicated to investigating that specific treatment to avoid bias. For example, we excluded the CULPRIT-SHOCK (Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock) trial when reporting multivessel PCI as an outcome.[7] Categoric variables were compared using the chi-square test, whereas continuous variables were compared using the 2-sample *t*-test. For mortality outcomes, we performed a pooled analysis using the following meta-analysis method. We first input the total clinical setting percentage for the main outcome and the number of participants of each study and then calculated the corresponding 95% CIs using the normal approximation to the Poisson distribution. Then, we pooled effect sizes, which denoted median "rates" and the 95% CIs using the inverse variance method with random effects. We performed the analysis to estimate the 95% CIs of mortality rates. However, we still compared both groups using the chi-square test for proportions given the invalidity of comparing 2 medians with the 95% CIs without patient-level data. The characteristics and outcomes presented were weighted according to the sample size. To further evaluate the patients enrolled in the most recent RCTs, we performed a sensitivity analysis including the 6 most recently published RCTs from 2017 onward[8–13] and compared them with registries that enrolled patients within the same time frame.[3,14–18]

We also evaluated the trend of enrolling women in the included RCTs using the first year of enrollment rather than publication year. Trend analysis was performed using the Poisson regression method. A P value ≤0.05 was considered statistically significant. Statistical analysis was performed using STATA software for Windows version 17.0 (StataCorp LLC).

RESULTS

We included 14 RCTs and 12 registries in our study. Details on the included RCTs are shown in Supplemental Table S1. RCTs included a total of 2,154 patients, and their publication dates ranged from 2005 to 2020. Most of the trials were performed in Europe, except 1 study that included centers in North America.[19] Of the 14 RCTs, 7 aimed to evaluate mechanical circulatory support (MCS) devices.[8,11,20–24] The

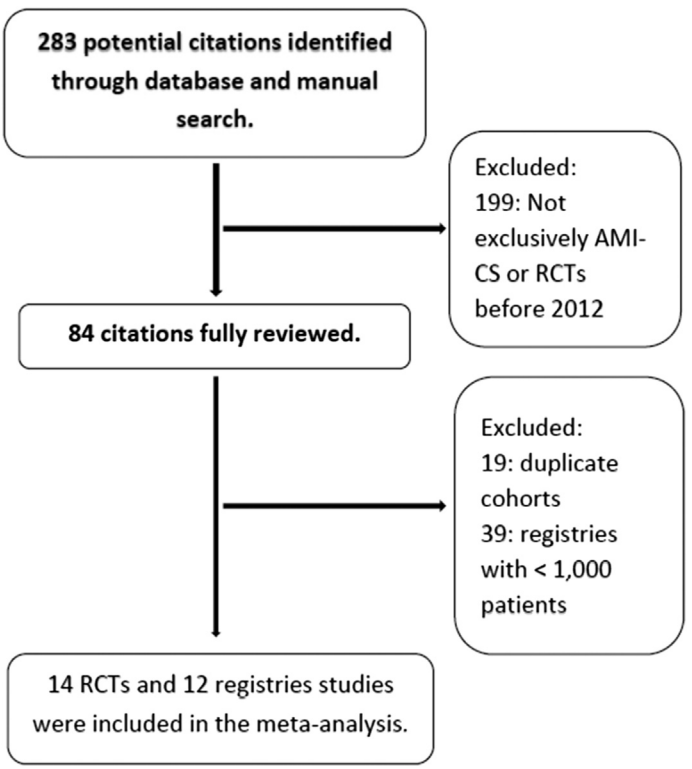
revascularization strategy in the included RCTs was predominantly PCI with a small percentage of coronary artery bypass graft surgeries. The exclusion criteria of RCTs are also shown in Supplemental Table S1. Most studies excluded patients who were determined to be moribund due to prolonged resuscitation or severe comorbid conditions. Most of the left ventricular assist device trials excluded patients with right ventricular failure. Studies in which 1 randomization arm included intra-aortic balloon pumps also excluded patients with severe aortic regurgitation.

Details on the included registries are listed in Supplemental Table S2. Registries included 133,617 patients published from 2012 to 2021. MCS use was predominantly intra-aortic balloon pumps in earlier studies but incorporated other devices in later publications, as shown in Supplemental Table S2. The largest registries included were from the CathPCI Registry (accounting for about one-half of the cohort, 56,497 patients from 2005 to 2013)[25] followed by a studies from both the CathPCI Registry and the Chest Pain Registry (28,304 patients from 2015 to 2017),[18] the Japan-PCI Registry (n = 17,549),[15] and the IQ registry (n = 15,259).[26] The most common access site used was the femoral access (91.3%).

COMPARISON BETWEEN RCTs AND REAL-WORLD REGISTRIES. Differences in baseline characteristics between patients included in RCTs and registries are listed in **Table 1**. Patients in RCTs were more likely to be men (73% vs 67.7%, $P < 0.001$). Patients included in RCTs had fewer comorbidities, including less hypertension (61.6% vs 65.9%, $P < 0.001$), dyslipidemia (36.4% vs 53.6%, $P < 0.001$), smoking (32.9% vs 38.8%, $P < 0.001$), history of stroke or transient ischemic attack (7.1% vs 10.7%, $P < 0.001$), and history of coronary artery bypass graft surgery (5.3% vs 7.5%, $P < 0.001$). Patients included in RCTs were less likely to present with ST-segment elevation myocardial infarction (72.4% vs 79.3%, $P < 0.001$) and more likely to have a lower body mass index (26.8 ± 2.0 kg/m^2 vs 28.6 ± 6.3 kg/m^2, $P < 0.001$), lower lactate levels (4.7 ± 2.3 mmol/L vs 5.9 ± 1.9 mmol/L, $P < 0.001$), and higher mean arterial blood pressure at presentation (73.0 ± 8.8 mm Hg vs 62.5 ± 12.2 mm Hg, $P < 0.001$).

The sensitivity analysis results comparing the patients' baseline characteristics between the recently published registries and RCTs are shown in Supplemental Table S3. The differences between both groups were concordant with the overall analysis, with the patients enrolled in RCTs more likely to be men with fewer comorbidities.

FIGURE 1 Flowchart of the Included Studies



AMI-CS = acute myocardial infarction-related cardiogenic shock; RCTs = randomized controlled trials.

The percentage of women enrolled in RCTs was low, ranging between 7.1% and 37% (Supplemental Table S4). There was no significant change in the trend of enrolling women in RCTs over the years from 2000 to 2015 (P trend = 0.156) (Supplemental Figure S1).

DIFFERENCES IN TREATMENT MODALITIES AND MORTALITY. PCI (95.8% vs 58.4%, $P < 0.001$), multivessel PCI (31% vs 27.4%, $P < 0.001$), and extracorporeal membrane oxygenation (ECMO) (11.6% vs 3.4%, $P < 0.001$) were used more often in RCT patients, whereas G2b3a inhibitors were used less often in patients enrolled in RCTs (26.7% vs 41%, $P < 0.001$). The in-hospital mortality (23.9% [95% CI: 18.0%-29.9%] vs 38.4% [95% CI: 29.2%-47.5%], $P < 0.001$) and 30-day mortality (39.9% [95% CI: 33.1%-46.6%] vs 45.9% [95% CI: 33.0%-58.9%], $P < 0.001$) were lower in patients enrolled in RCTs compared with real-life registry patients (**Table 1, Figure 2**). A summary of the study results is shown in the **Central Illustration**.

TABLE 1 Comparison of Baseline Characteristics and Treatment Modalities Based on Study Type

	14 RCTs (n = 2,154)	12 Registries (n = 133,617)	*P* Value
Baseline characteristics and hemodynamic parameters			
Age, y	67.5 ± 7.0 [2,109]	66.1 ± 12.9 [129,951]	<0.001
BMI, kg/m^2	26.8 ± 2.0 [1,633]	28.6 ± 6.3 [86,517]	<0.001
Male, %	73.0	67.7	<0.001
Hypertension, %	61.6 [2,141]	65.9 [118,358]	<0.001
Diabetes, %	32.4	32.2 [118,358]	0.862
Smoking, %	33.3 [2,084]	38.8 [90,054]	<0.001
Dyslipidemia, %	36.4 [1,560]	53.6 [115,366]	<0.001
Previous MI, %	21.3 [2,080]	21.6 [118,358]	0.762
Previous PCI, %	18.8 [1,488]	20.4 [114,889]	0.136
Previous CABG, %	5.3 [1,844]	7.5 [112,799]	<0.001
History of CVA or TIA, %	7.1 [1,861]	10.7 [90,183]	<0.001
Peripheral vascular disease, %	11.4 [1,408]	8.7 [112,614]	<0.001
LVEF	31.8 ± 6.2 [1,912]	38.6 ± 14.4 [32,147]	<0.001
Mean arterial pressure	73.0 ± 8.8 [1,510]	62.5 ± 12.2 [1,716]	<0.001
STEMI, %	72.4 [1,292]	79.3 [112,625]	<0.001
Lactate	4.7 ± 2.3 [760]	5.9 ± 1.9 [1,716]	<0.001
Out-of-hospital arrest/ resuscitation	49.7 [2,008]	32.0 [52,651]	<0.001
Procedural characteristics			
PCI, %	97.5 [2,031]	58.4 [8,551]	<0.001
Thrombolysis, %	6.2 [1,328]	4.1 [91,636]	<0.001
Multivessel PCI	31.0 [805]	27.4 [64,106]	0.025
CABG, %	2.5 [1,927]	2.0 [26,260]	0.156
GP2b3a inhibitor, %	26.7 [1,888]	41.0 [8,885]	<0.001
Mechanical ventilation, %	80.6 [1,394]	54.2 [5,806]	<0.001
ECMO use	11.61 [739]	3.4 [1,716[a]]	<0.001
In-hospital mortality, %	23.9 (18.0-29.9) [279]	38.4 (29.2-47.5) [91,452]	<0.001
30-day mortality, %	39.9 (33.1-46.6) [2,045]	45.9 (33.0-58.9) [6,835]	<0.001

Values are mean ± SD, %, or % (95 CI). Numbers in brackets represent the number of subjects with a reported variable when different from the baseline. [a]Single registry.

BMI = body mass index; CABG = coronary artery bypass graft; CVA = cerebrovascular event; ECMO = extracorporeal membrane oxygenation; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack.

DISCUSSION

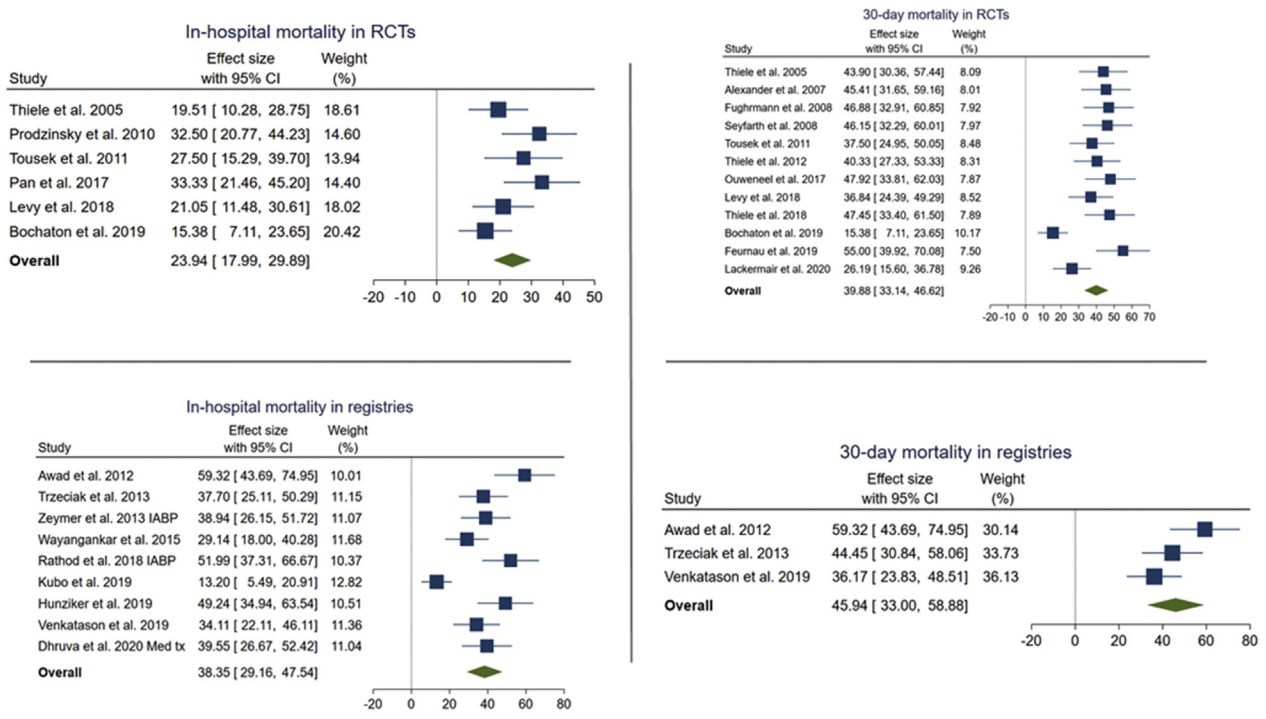
Our study is the first to compare characteristics of patients presenting with CS enrolled in RCTs and registries. The main findings of our study include the following: 1) a limited number of RCTs have been conducted in patients with AMICS (14 since 2005), including just over 2,000 patients; 2) the majority of RCTs were performed in Europe; 3) women remain under-represented in AMICS studies; 4) RCT patients have fewer comorbidities and present with lower risk features; 5) RCT patients are more likely to get aggressive treatment with PCI, multivessel PCI, and ECMO; and 6) RCT patients had lower in-hospital and 30-day mortality.

The major challenge in conducting RCTs in CS is an ethical dilemma when attempting to enroll unstable patients. Physicians must believe in the equipoise of intended treatment and be willing to randomize patients when comparing therapies. They must also be willing to have some treatment delay while consent is obtained from the patient or family. The risk of potential selection bias in the sickest patients can then lead to the enrollment of a lower-risk population. This results in the exclusion of patients who may benefit most from intended therapies and lead to the need for an increased sample size. In our analysis, patients enrolled in RCTs had fewer comorbidities, had lower lactate levels, were less likely to present with ST-segment elevation myocardial infarction, and had lower mortality rates suggestive of a lower-risk cohort.

Patients enrolled in RCTs also received more aggressive treatment with revascularization and ECMO. To date, the only therapy demonstrating efficacy in an AMICS RCT is early revascularization.[27] Our analysis demonstrates a higher rate of revascularization with PCI in RCT compared with registry patients (97.5% vs 58%). Our analysis suggests that RCT patients are less sick and more likely to receive aggressive treatment.

As clinicians relying on evidence-based practices, the gold standard of which are RCTs, we must excerpt tremendous efforts in performing such trials while simultaneously capturing data on all patients in registries. To accomplish this, we must simplify the enrollment process through efforts such as community consent and decreasing the risk of patient exposure by using adaptive clinical trial designs.[28] Our analysis demonstrates most RCT patients were enrolled outside of the United States. Similarly, efforts to improve the inclusion of women and minorities in such trials are paramount. In our analysis, most patients enrolled in RCTs were men, with fewer women than in registries. Our analysis also demonstrated that despite the current efforts, women's enrollment in AMICS trials has not improved since the year 2000. This under-representation poses a challenge to generalizing study results in clinical practice.[29,30] Therefore, investigators and regulatory bodies in the United States must allow an easier care process for such trials, including potentially a waiver or similar streamlining of informed consent, to ensure these trials apply to a broader population. Another potential solution to increasing the generalizability of AMICS studies is to use a standard definition of CS, such as that proposed by the Society for Cardiovascular Angiography and Interventions.[31] In doing so, clinicians may be better equipped to compare

FIGURE 2 **Pooled Analysis of the Effect Sizes of In-Hospital and 30-Day Mortality in RCTs and Registries**



RCT = randomized controlled trial.

outcomes and therapies in a heterogeneous shock cohort. Future RCTs and registries should similarly delineate patients into specific shock phenotypes based on etiology to provide better generalizability to clinicians.

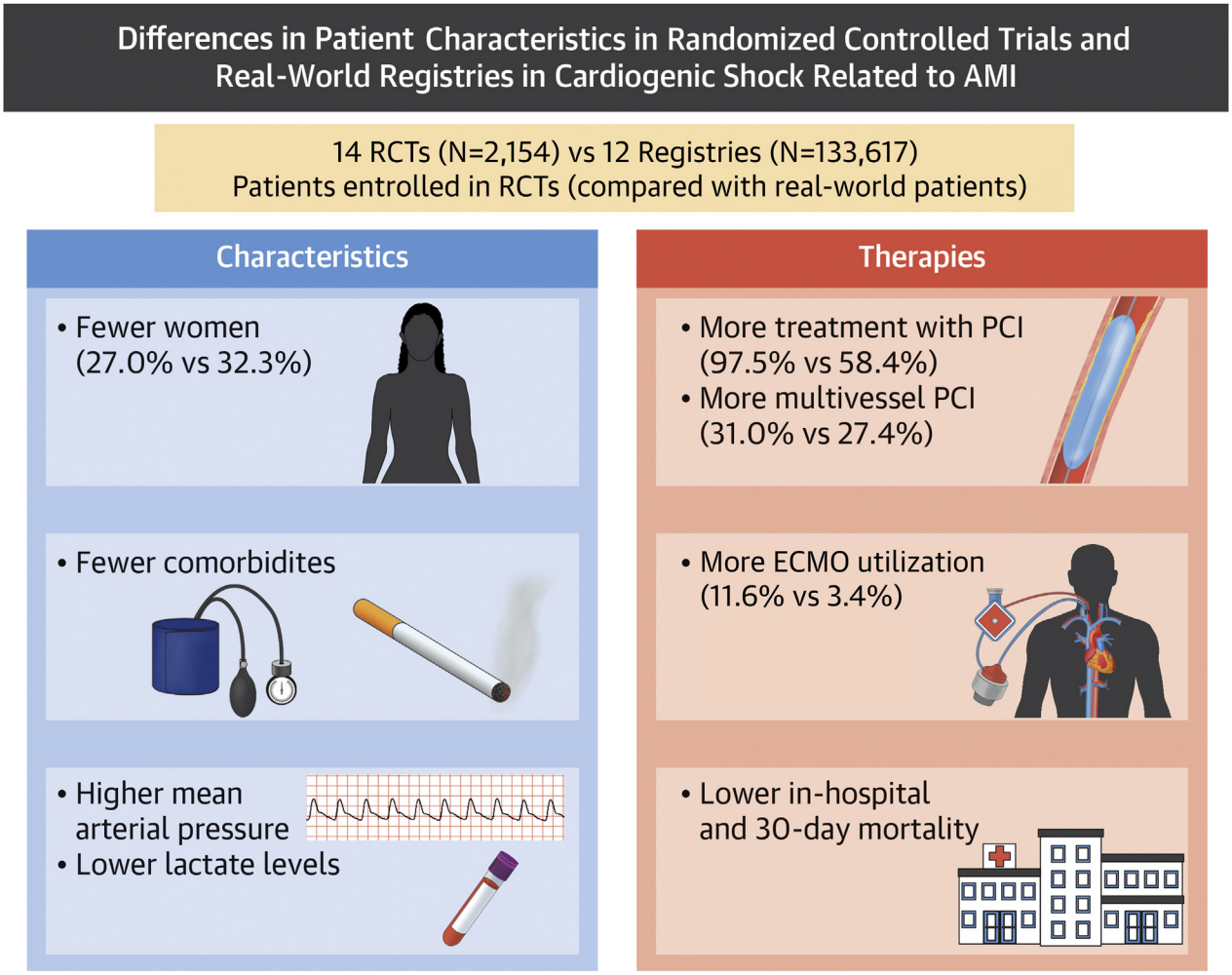
Despite improvement in AMI treatment modalities and systems of care, the incidence of AMICS continues to rise.[3,32] This increased incidence has been attributed to an aging population, more comorbidities, higher rates of multivessel disease, and an increasing rate of CS from non-ST-segment elevation myocardial infarction.[3,33] These temporal changes are important considerations for clinicians to keep in mind as we apply the results of past and future RCTs to current practice. Lastly, it is important to highlight that the current steps leading to the diagnosis, monitoring, and treatment of CS evolved from expert opinion and observational data to help define best practices. These efforts should not be dismissed because they have not been performed in an RCT. There is value in both RCT and registry data in AMICS. Efforts to improve the quality of each and to incorporate newly gained knowledge into future trial designs are needed.

STUDY LIMITATIONS. First, we only aimed to describe differences in patient characteristics between AMICS enrolled in RCTs compared with registries. A robust comparison could not be performed because we lacked patient-level data. Second, data on multiorgan failure, circulatory failure, and other types of shock that could be mixed with CS; the need for vasoactive therapies; and the role of noncardiac organ support were limited and not systematically reported. Therefore, they could not be further analyzed. Finally, data on specific MCS devices could not be analyzed or reported as outcomes because of the high prevalence of dedicated trials and registries that aimed to specifically study those devices.

CONCLUSIONS

RCTs in AMICS tend to enroll fewer women and lower-risk patients compared with registries. Patients enrolled in RCTs are more likely to receive treatment with PCI and ECMO and have lower in-hospital and 30-day mortality. Clinicians must remain practical in incorporating evidence from hard to perform RCTs

CENTRAL ILLUSTRATION **Summary of the Study Results**



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AMI = acute myocardial infarction; ECMO = extracorporeal membrane oxygenation; PCI = percutaneous coronary intervention; RCT = randomized controlled trial.

and broadly applying data to different shock stages and phenotypes. Efforts to synthesize more data in AMICS patients, adopt adaptive clinical trial methods, and resolve ethical dilemmas in the consent process are needed to limit bias and provide a broader application of future RCTs.

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Dr Basir is a consultant/speaker for Abbott Vascular, Abiomed, Cardiovascular Systems, Chiesi, Procyrion, and Zoll. Dr Alaswad has received honoraria for consulting/speaking from Boston Scientific, Cardiovascular Systems Inc, LivaNova, and Teleflex. Dr Brilakis has received honoraria for consulting/speaking from Abbott Vascular, American Heart Association (associate editor *Circulation*), Amgen, Biotronik, Boston Scientific, Cardiovascular Innovations Foundation (Board of Directors), ControlRad, Cardiovascular Systems Inc, Ebix, Elsevier, GE Healthcare, InfraRedx, Medtronic, Siemens, and Teleflex; has received research support from Regeneron and Siemens; and is a shareholder of MHI Ventures. Dr Napp has received honoraria for lecturing/consulting and has received research support from Cytosorbents; has received honoraria for lecturing from Abbott and Maquet; and has received honoraria for lecturing/proctoring/consulting and research funding from Abiomed. Dr O'Neill is a consultant/speaker for Abbott Vascular, Abiomed, Boston Scientific, Edwards, and Zoll. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? CS is a leading cause of in-hospital mortality in patients with AMI. Enrollment of such patients into clinical trials is challenging and may not be representative of real-world patients.

WHAT IS NEW? Patients enrolled in AMICS RCTs have fewer comorbidities and present with lower risk features than those in registries. Patients enrolled in RCTs get more aggressive treatment and have lower in-hospital and 30-day mortality.

WHAT IS NEXT? Clinicians should remain practical when universally applying data from RCTs to clinical practice. Efforts to synthesize more data in AMICS, adopt adaptive clinical trial methods, and resolve ethical dilemmas in the consent process are needed to limit bias and provide a broader application of future RCTs.

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APPENDIX For supplemental tables and a figure, please see the online version of this paper.