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Early revascularization is beneficial across all ages and a wide spectrum of cardiogenic shock severity: A pooled analysis of trials

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Abstract

Background—A pooled analysis in cardiogenic shock due to acute coronary syndromes is desirable to assess the effect of early revascularization (ERV) across all ages and a wide spectrum of disease severity.

Methods—Only two randomized controlled trials (RCT), i.e. SMASH and SHOCK, met the inclusion criteria and were combined for a pooled analysis using individual patient data (n = 348).

Results—SMASH patients (n = 54, 16%) had more severe disease than SHOCK patients (n = 294, 84%). After adjustment for age, anoxic brain damage, non-inferior myocardial infarction, prior coronary artery bypass graft surgery, renal failure, systolic blood pressure, and selection for coronary angiography, one-year mortality was similar (relative risk SHOCK versus SMASH 0.87, 95% CI: 0.61–1.25). Relative risk of one-year death for ERV versus initial medical stabilization was 0.82 (95% CI: 0.70–0.96). There was no significant difference in the treatment effect by age (≤75 years relative risk at one year 0.79, 95% CI: 0.63–0.99; >75 years relative risk at one year 0.93, 95% CI: 0.56–1.53; interaction P = 0.10).

Conclusions—Only two RCT have been published emphasizing the difficulty of enrolling critically ill patients. Despite large differences in shock severity, ERV benefit is similar across all ages and not significantly different for the elderly.

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Keywords

Shock; cardiogenic; meta-analysis; myocardial revascularization; age factors; comorbidity

Introduction

Enrolling critically ill patients in randomized controlled trials (RCT) is difficult, mainly due to disease severity and challenges in obtaining consent (1,2). Therefore, RCT that are per formed in critically ill patients may show slow enrollment rates, may be terminated prematurely for lack of feasibility, or even may not be conducted at all (3). Consequently, due to a lack of data, treatment might not be applied to those patients who are the sickest and in greatest need (4).

Cardiogenic shock (CS) complicating acute myocardial infarction occurs in approximately 5–7% of patients with reported mortality rates exceeding 50% (5,6). The use of an early invasive strategy in the setting of acute myocardial infarction complicated by CS has been studied in several retrospective analyses and suggested a benefit of early revascularization compared with no revascularization (7–12). However, only a few prospective randomized trials have been undertaken to investigate this issue (13–16). Slow recruitment rates were a common problem in RCT attempting to address this important clinical question (1), which led to an early termination in some (13,14,16). Owing to the relatively small number of events, the published RCT in ACS and CS to date have been relatively under-powered and failed to show differences in their primary outcomes (15,16).

Guidelines for treatment of CS give different classes for the early revascularization recommendation in patient' s ≤75 and >75 years of age (17). The reason for this inconsistency is the apparent lack of benefit of early revascularization in the small subset of elderly patients in the ' Should we revascularize occluded coronaries for cardiogenic shock? (SHOCK) trial ' (15), in contrast to the results of the SHOCK Registry (18) where elderly patients benefited from early invasive therapy.

Thus, the main aims of this pooled analysis are to assess the effect of early revascularization among a wide spectrum of disease severity in CS complicating acute myocardial infarction, and to examine the effect of early revascularization by age.

Patients and Methods

Study selection

A literature search using Medline, Cochrane library databases, reference lists of review articles (1,13,19–27), and abstract indexes of international scientific meetings was performed. Studies were included if they only enrolled patients with acute myocardial infarction complicated by CS, excluded patients with a mechanical or other cause of shock, and were RCT of early revascularization versus initial medical stabilization. Of 201 screened abstracts four gave information about an RCT (Figure 1). Of these, the ' Thrombolysis and angioplasty in cardiogenic shock (TACS) ' (13) and the ' How effective are revascularization options in cardiogenic shock (HEROICS) ' (14) trials were terminated

prematurely and never got published (personal communication of the principal investigators). Thus, only two reports, i.e. SHOCK (15) and the Swiss multicenter evaluation of early angioplasty for shock following myocardial infarction (SMASH) (16), were included in this analysis (Table I).

SMASH trial design

SMASH was a randomized controlled nine-center trial in 55 patients with CS complicating acute myocardial infarction (16). The trial compared an early invasive strategy with percutaneous coronary intervention or coronary artery bypass graft surgery if feasible with a conservative strategy and it was terminated early due to slow enrollment. The study protocol encouraged the use of intra-aortic balloon counterpulsation or other mechanical circulatory support devices. Inclusion criteria included

1. refractory CS over ≥30 min, defined as systolic blood pressure ≤90 mmHg despite inotropic support and intravenous volume administration as needed, capillary wedge pressure >15 mmHg and cardiac index <2.2 l/min/m^2 if measured, associated with a compatible clinical presentation;
2. acute myocardial infarction <48 h prior to randomization defined as at least two of the following elements: chest pain; ST segment elevation of at least 0.1 mV in limb leads or 0.2 mV in precordial leads or left bundle branch block; or serum creatine-phosphokinase MB isoenzyme elevation above twice the upper limit of normal;
3. coronary angiography technically feasible, i.e. vascular access and catheterization laboratory available; and
4. informed consent.

Exclusion criteria included ongoing manual cardiopulmonary resuscitation; prior cardiac arrest with presumed severe cerebral damage; shock not primarily cardiogenic in origin, mechanical complications, i.e. free wall or septum ventricular rupture, acute severe mitral regurgitation, or pericardial tamponade; serious non-cardiac illness contraindicating an invasive approach; decision to perform angiography taken before the onset of shock; or physician ' s choice for intervention. The primary end-point was mortality from all causes 30 days after randomization. Secondary endpoints included all-cause mortality at one year.

SHOCK trial design

SHOCK was a randomized controlled 30-center trial comparing early revascularization and initial medical stabilization in 302 patients with CS after myocardial infarction (15,28–30). Intra-aortic balloon counterpulsation was recommended for all patients. Inclusion criteria included

1. ST-segment elevation myocardial infarction, a Q-wave infarction, a new left bundle-branch block, or a posterior infarction with anterior ST-segment depression;
2. CS defined as hypotension, i.e. a systolic blood pressure of <90 mmHg for at least 30 min or the need for supportive measures to maintain a systolic blood pressure of ≥90 mm Hg, a cardiac index of no more than 2.2 l/min/m^2, a pulmonary-capillary wedge pressure of at least 15 mmHg, and end-organ hypoperfusion, i.e. cool

extremities or a urine output of <30 ml per hour, not due to bradycardia, e.g. a heart rate of ≥60 beats per min; and

3. informed consent.

Exclusion criteria included severe systemic illness, mechanical or other cause of shock, severe valvular disease, dilated cardiomyopathy, the inability to gain access for catheterization, and unsuitability for revascularization. The primary end point was all-cause mortality 30 days after randomization. Secondary endpoints included all-cause mortality at one year.

Statistical analysis

Baseline differences and raw mortality rates between the two studies included in this analysis were compared by Student' s *t* -test for normally distributed continuous variables, the Wilcoxon rank-sum test for non-normally distributed continuous variables, and Fisher ' s exact test and χ^2-test for categorical variables, where appropriate. One-year mortality was adjusted for confounding covariates using a Cox proportional hazards regression model. The Breslow-Day test of homogeneity of odds ratios was used to detect significant interactions between variables. With the evidence of heterogeneity between studies, a random-effects meta-analysis using individual patient data estimating the risk ratio was appropriate, and Forest plots were generated to visualize relative risks. To evaluate the effect of age on revascularization, we partitioned all subjects into five age groups such that there were approximately equal numbers of patients in each age group (≤55 *n* = 56, 56–65 *n* = 96, 66–70 *n* = 54, 71–75 *n* = 80, and >75 *n* = 62), and performed a random effects meta-analysis in each cohort; analyses were also conducted separately for patients ≤75 years and >75 years of age. In addition, interaction of early revascularization and age regarding one year mortality was performed using Cox proportional hazards regression model. All *P*-values were two-sided. A *P*-value <0.05 was considered statistically significant. Analyses were conducted using commercially available soft ware (SAS version 8.2, Cary, NC, USA and SPSS Version 14.0, SPSS Inc., Chicago, IL, USA).

Results

The two trials combined enrolled 357 patients, of which 302 were enrolled in SHOCK and 55 in SMASH. Since not all patients had confirmed CS because predominant left ventricular failure was not verified after randomization, 9 patients (3%) with reasons for CS other than left ventricular dysfunction were excluded (SHOCK *n* = 8, SMASH *n* = 1) leaving 348 (97%) patients for analysis (SHOCK *n* = 294, 84%, SMASH *n* = 54, 16%). Of the total population, 62 (18%) patients were ≥75 years old (SHOCK *n* = 53, SMASH *n* = 9).

SMASH patients more oft en had a history of congestive heart failure, presented more oft en with pulmonary edema on chest X-ray, and had a lower initial blood pressure than SHOCK patients (Table II). In contrast, SHOCK patients more oft en received vasopressors/inotropic agents, thrombolytic therapy, and intra-aortic balloon counterpulsation than SMASH patients did. While in SMASH no patient underwent coronary artery bypass graft surgery, 37% of SHOCK patients who received early revascularization in that assigned group did

(18% overall); in contrast, the percutaneous transluminal coronary angioplasty rate was higher in SMASH than in SHOCK (56% versus 35%, $P = 0.006$).

Overall mortality was higher in SMASH than SHOCK at both 30 days (74% versus 51%, $P = 0.003$) and one year (77% versus 59%, $P = 0.014$). However, after adjustment for disease severity using an at-presentation severity score ($P < 0.001$) that included age, anoxic brain damage, non-inferior myocardial infarction, prior coronary artery bypass graft surgery, renal failure (defined as creatinine ≥1.9 mg/dl), and systolic blood pressure, as well after adjustment for selection for coronary angiography specifically in the initial medical stabilization group since patients in the early revascularization group underwent cardiac catheterization by assignment ($P < 0.001$), one-year mortality was similar for the two studies combined (hazard ratio SHOCK versus SMASH 0.87, 95% confidence interval 0.61, 1.25, $P = 0.45$).

The pooled analysis is demonstrated in Figures 2 and 3. There was no statistically significant benefit of early revascularization compared with initial medical stabilization in the overall cohort at 30 days (relative risk 0.85, 95% confidence interval 0.71–1.02; Figure 2), while the relative risk of death indicated a protective effect of early revascularization compared with initial medical stabilization at one year (relative risk 0.82, 95% CI: 0.70–0.96; Figure 3). However, there was no significant difference in the treatment effect of early revascularization by age cohort at one year (interaction treatment effect by age $P = 0.10$; Figure 3).

Discussion

This systematic overview of RCT in CS complicating acute myocardial infarction is important for two reasons: First, it affords the opportunity to examine further the treatment effect in patients >75 years of age, and second, it clearly demonstrates the beneficial effect of early revascularization across a wide clinical spectrum.

SHOCK was a landmark trial demonstrating the beneficial effect of early revascularization in patients with acute myocardial infarction complicated by CS. However, despite its clear results regarding mortality at six months (15), one year (29), and six years (30), the study was negative regarding its primary endpoint, i.e. 30-day mortality (15). Other attempted trials investigating the effect of early revascularization in CS patients were not completed (13,14,16) and remained negative (16). While overall benefit was clearly demonstrated in SHOCK, uncertainty remained regarding the effect of early revascularization in patients >75 years of age, where results were conflicting. Although the SHOCK trial showed no effect in the elderly (31), the non-randomized SHOCK registry demonstrated a benefit in this age group (18). This discrepancy was explained by between group imbalances in ejection fraction for the elderly (31). However, this pooled analysis supports the concept that the SHOCK trial findings for the elderly were likely a chance finding as evidenced by heterogeneity between the trials for the elderly. The fact that there was no significant interaction between age and treatment effect supports the notion that early revascularization is beneficial in the elderly, but no firm conclusions derived from this pooled analysis regarding early revascularization can be drawn in this age group. Current guidelines

recommend an early invasive strategy in selected patients >75 years of age (17). Accordingly, registries have reported benefit when approximately 30% of the elderly are selected for an invasive management strategy (32–36). Specifically, Iakobishvili et al. reported results from 549 patients from the Euro Heart Survey and showed a beneficial effect of early revascularization in the total population but a blunted effect of an invasive approach in patients ≥75 years of age (odds ratio 0.90, 95% CI: 0.41–2.01) (35). Dauerman et al. reported results from 310 patients ≥65 years of age from the Worcester population and showed an increased use of early revascularization over the decade 1986 to 1997 with a decrease in 30-day mortality from 80% to 69% ($P = 0.03$) (33). Berger et al. reported results form 600 patients ≥65 years of age form the Cooperative Cardiovascular Project database and showed that 30-day mortality is not different when patients are admitted to hospitals with versus without revascularization capabilities (odds ratio 0.83, 95% CI: 0.47, 1.45) (32).

Furthermore, our findings suggest that early revascularization is beneficial across the spectrum of severity of illness, despite the high mortality rates with intervention for the most severely ill. Although both analyzed trials were performed with similar designs among patients with complicated myocardial infarction, the differences in inclusion criteria resulted in a sample with a wide range of risk profiles. While SHOCK enrolled patients with a median of 5.5 h after acute myocardial infarction with a systolic blood pressure of less than 90 mmHg or supportive measures to maintain 90 mmHg, SMASH enrolled sicker patients with a median of 3.9 h after acute myocardial infarction with a systolic blood pressure of 90 mmHg or less despite inotropic support. The subsequent clinical picture was a wide range in the severity of CS where early revascularization was beneficial. Multivariate modeling demonstrated that both at-presentation disease severity and selection for coronary angiography in the initial medical stabilization group were responsible for differences in outcome between the trials.

Finally, the fact that only two published randomized clinical trials investigating early revascularization in CS were identified underscores the notion that enrollment is especially arduous in the critically ill where consent is difficult to obtain. Variability in local regulations regarding surrogate consent contributes to the substantial challenge (1). TACS and HEROICS were not able to recruit a useful number of patients (13,14), while SMASH was stopped prematurely after enrolling only 50% of the planned sample size (16). As an exception to this rule, other investigators succeeded in enrolling almost 400 patients in an RCT of persistent CS recently (36).

Limitations

This pooled analysis consists of only two trials. This number is formally the minimal number required to perform such an analysis, and individual patient data were used increasing its statistical weight. Moreover, the small number of trials is an important finding emphasizing a known problem in clinical research. However, the limited number of patients in SMASH might somewhat decrease the ability to detect differences in treatment effect between the two trials. Therefore, the lack of statistical significance of the effect of early revascularization at 30 days may be due to limited power, although an event reduction of 15% may be clinically relevant to most people. In addition, 9 (3%) of all randomized

patients were excluded to this analysis since they did not suffer from cardiogenic shock due to left ventricular failure. Since the primary aim of this analysis was to explore the effect of early revascularization in a broad clinical spectrum of cardiogenic shock patients suffering from left ventricular failure and not from other reasons, we tried to exclude all possible confounders that could obscure the result. Finally, since the current analysis is a systematic overview of two RCT only and not the result of an RCT itself, the results do not exhibit the same level of evidence.

Conclusion

This is the first and hitherto only pooled analysis in CS complicating acute myocardial infarction. Early revascularization results in improved one year survival across the whole spectrum of CS severity. In the elderly, early revascularization appears to be of use for selected patients, although its effect was not significant in this age cohort. The fact that only two randomized clinical trials were identified emphasizes how difficult it is to enroll critically ill patients in randomized trials.

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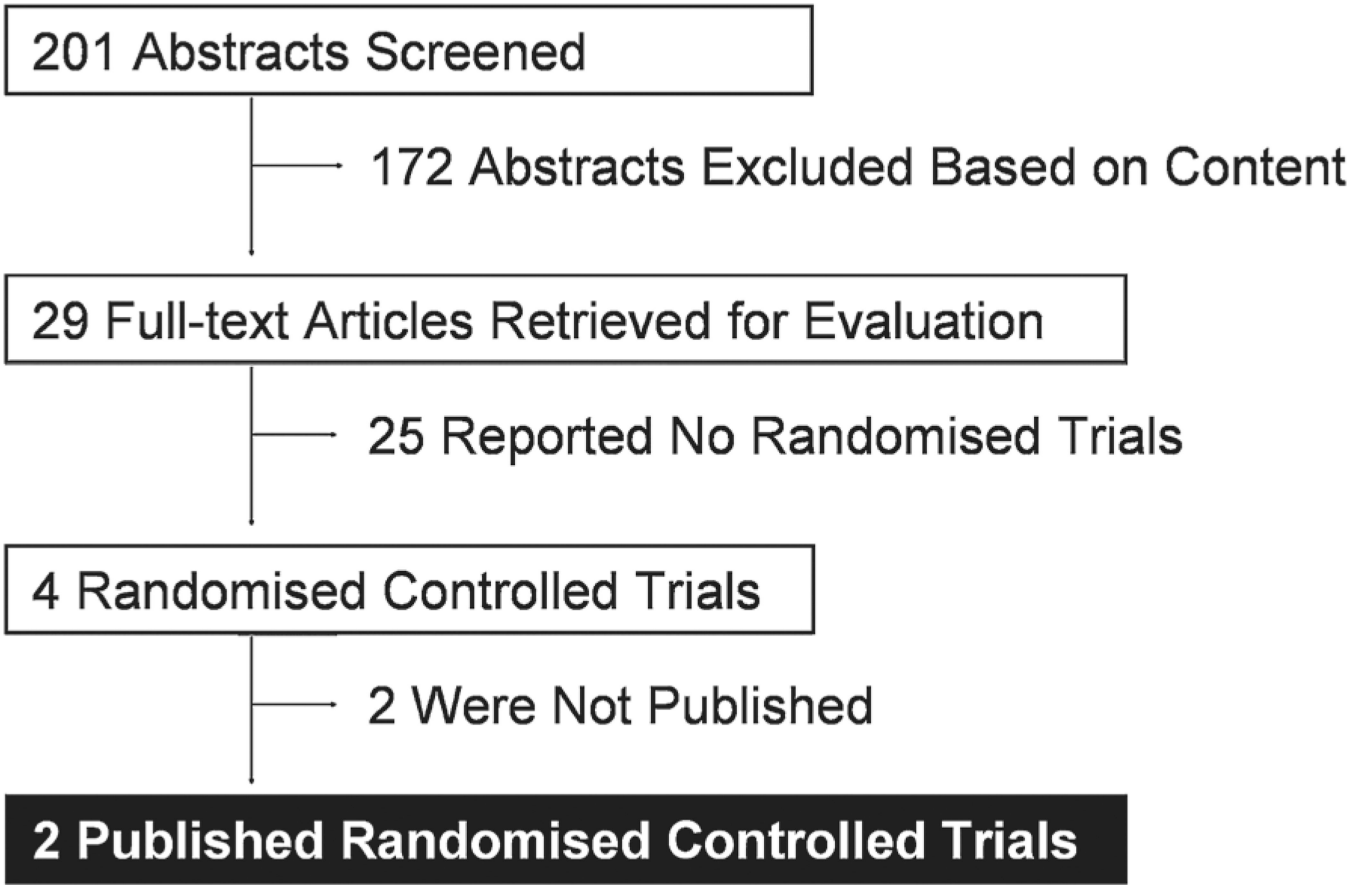

Figure 1.
Study selection for early revascularization versus initial medical stabilization in cardiogenic shock.

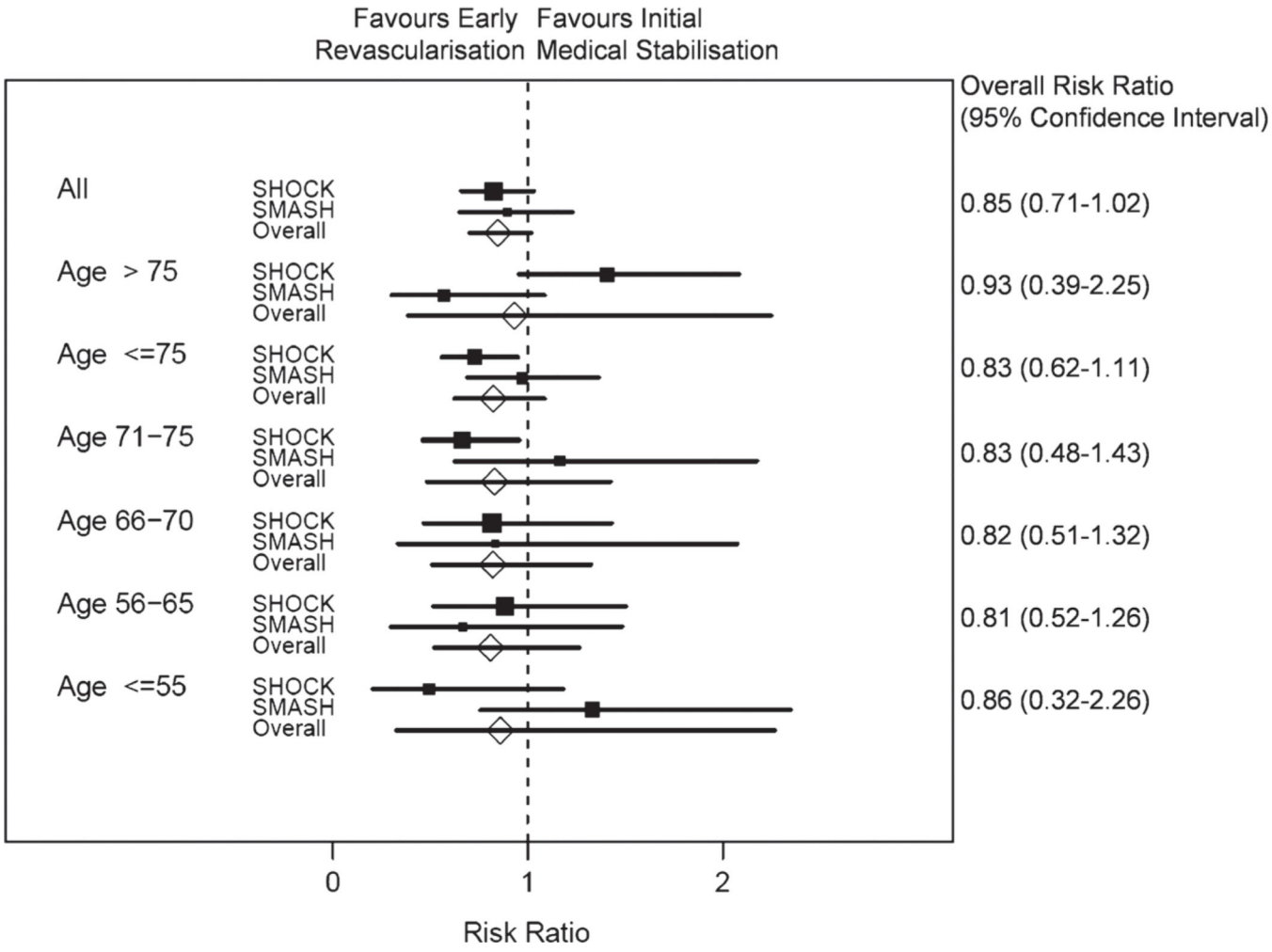

Figure 2.
Forest plots for 30-day mortality.

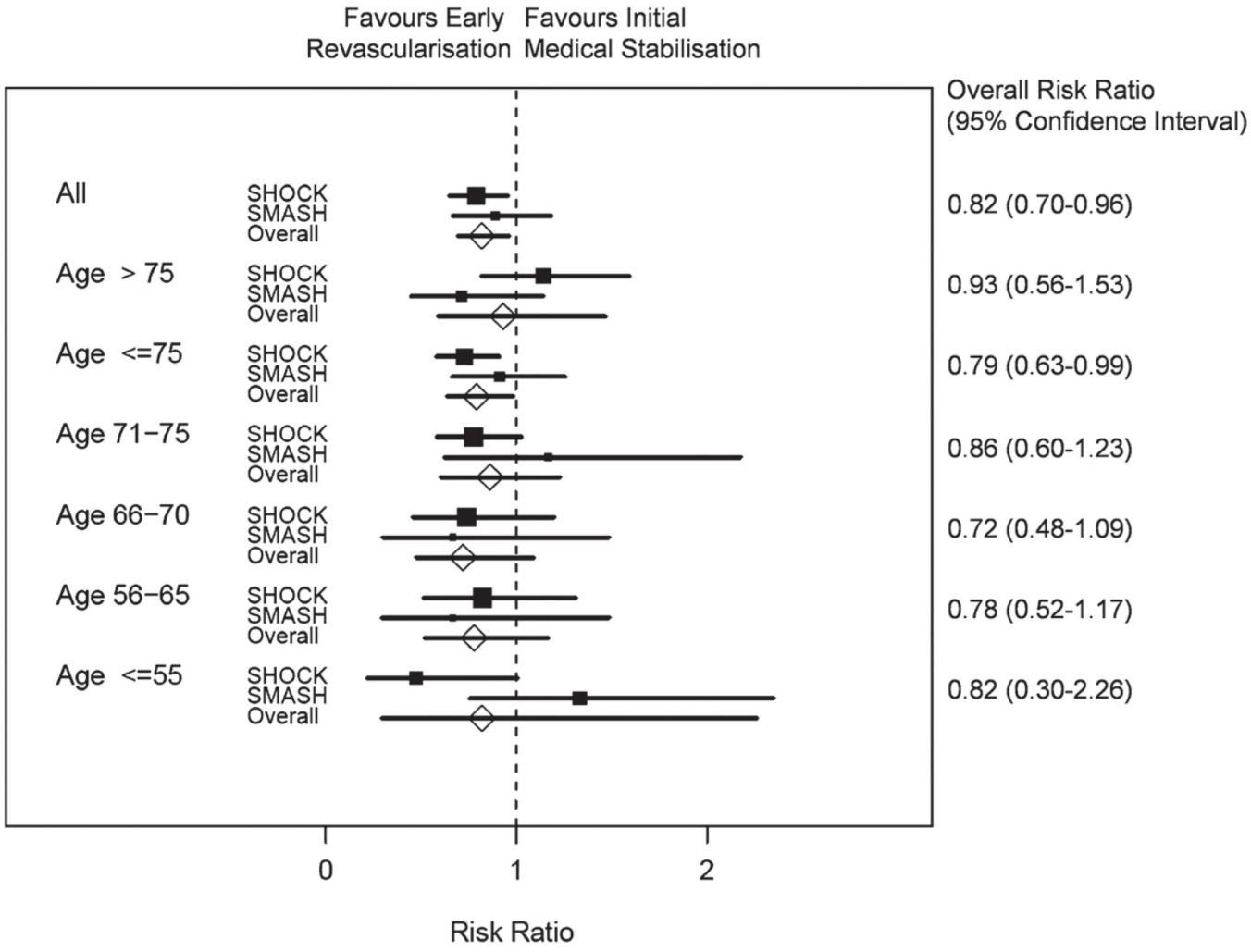

Figure 3.
Forest plots for 1-year mortality.

Table I

Randomized controlled trials in cardiogenic shock.

Acronym	Design	Inclusion criteria	Time requirements	Treatment arms	1° Endpoint	2° Endpoints	*n*
SMASH (24)	Multicenter RCT	Myocardial infarction Systolic blood pressure ≤90 mmHg despite inotropic support and volume therapy PCWP >15 mmHg CI <2.2 L/min/m^2	Shock ≥30 min prior to randomization Myocardial infarction <48 h prior to randomization	Early revascularization Initial medical stabilization	Death at 30 days	Non-emergency PTCA/CABG during hospitalization CCS/ NYHA class at discharge Death, cardiac events and functional status at 1 year	55 (54[a])
SHOCK (23)	Multicenter RCT	Myocardial infarction Systolic blood pressure <90 mmHg or supportive measures to maintain ≥90 mmHg PCWP ≥15 mmHg CI ≤2.2 L/min/m^2 Endorgan hypoperfusion	Shock ≥ 30 min and ≤12 h prior to randomization Myocardial infarction ≤36 h prior to CS	Early revascularization Initial medical stabilization	Death at 30 days	In-hospital death, death at 6 months and 1 year, and extended follow up (up to 11 years, 6 year average) Echocardiograpic parameters Quality of life	302 (294[a])

SMASH, Swiss multicenter evaluation of early angioplasty for shock following myocardial infarction; SHOCK, Should we revascularize occluded coronaries for cardiogenic shock?; RCT, randomized controlled trial; PCWP, pulmonary capillary wedge pressure, CI, cardiac index; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft ; CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association.

[a]Patients with left ventricular dysfunction only

Table II

Baseline, hemodynamic and angiographic characteristics and treatment for SHOCK and SMASH patients.

	Total (*n* = 348)	SHOCK (*n* = 294)	SMASH (*n* =54)	*p*[a]
Age (years)	65.7 ± 10.2	65.8 ± 10.4	65.4 ± 9.1	0.775
Male	67.8	68.0	66.7	0.875
History of hypertension	45.3	7.6	32.7	0.0504
History of diabetes	29.4	31.3	19.2	0.098
History of hypercholesterolemia	33.0	38.3	17.7	0.009
Current smoking	55.8	54.3	63.5	0.284
History of congestive heart failure	9.1	5.9	26.4	<0.001
Prior myocardial infarction	33.3	33.0	35.2	0.755
Prior percutaneous coronary intervention	7.3	7.6	5.6	0.779
Prior coronary artery bypass graft surgery	6.6	6.1	9.3	0.376
Pulmonary edema on chest X-ray	64.8	68.2	44.9	0.003
Median initial creatinine (mg/dl) (Q_1, Q_3)	1.30 (1.03, 1.80)	1.30 (1.00, 1.70)	1.34 (1.09, 1.98)	0.227
Anterior MI	58.8	60.2	50.0	0.207
Median time MI to CS (hrs) (Q_1, Q_3)	5.5 (2.0, 14.5)	5.5 (2.3, 14.1)	3.9 (1.0, 14.8)	0.164
Median time from randomization to death (Q_1, Q_3)	40.2 (7.0, 173.3)	48.5 (8.8, 176.3)	10.3 (2.4, 71.3)	0.032
Median time from CS to death (Q_1, Q_3)	45.5 (11.3, 178.2)	51.7 (15.3, 184.9)	16.7 (6.9, 75.3)	0.026
Hemodynamic data[b]				
Heart rate (bpm)	102.1 ± 23.7	101.9 ± 22.6	103.6 ± 29.2	0.670
Systolic blood pressure (mmHg)	86.2 ± 19.7	88.0 ± 20.4	76.7 ± 11.5	<0.001
Diastolic blood pressure (mmHg)	53.2 ± 15.5	54.7 ± 15.9	45.9 ± 11.3	<0.001
Pulmonary capillary wedge pressure (mmHg)	24.3 ± 7.3	24.3 ± 7.4	23.6 ± 6.0	0.739
Cardiac index (L/min/m^2)	1.79 ± 0.60	1.79 ± 7.37	1.70 ± 0.27	0.384
Left ventricular ejection fraction	30.5 ± 11.9	30.4 ± 11.9	31.6 ± 12.4	0.664
Angiography (*n* = 275, 241, 34)				
Number of diseased vessels	0.233			
0	2.2	2.1	2.9	
1	10.9	11.2	8.8	
2	24.3	21.9	41.2	
3	62.5	64.8	47.1	
Culprit vessel	0.322			
Left main	6.7	5.4	14.7	
Left anterior descending	49.0	50.2	41.2	
Right coronary artery	28.6	29.0	26.5	
Left circumflex	12.5	12.2	14.7	
Saphenous vein graft	3.1	3.2	2.9	
Left main stenosis ≥70%	12.2	10.8	23.3	0.070
Treatment				
Vasopressors/inotropic agents	99.4	100	96.3	0.024

	Total (*n* = 348)	SHOCK (*n* = 294)	SMASH (*n* =54)	*p*[a]
Thrombolysis	52.6	55.8	35.2	0.007
Intra-aortic balloon counterpulsation	74.4	86.7	7.4	<0.001
Percutaneous transluminal coronary angioplasty	37.9	34.7	55.6	0.006
Stents	14.0	14.0	16.7	0.599
Coronary artery bypass graft surgery	15.5	18.4	0	<0.001

SMASH, Swiss multicenter evaluation of early angioplasty for shock following myocardial infarction; SHOCK, Should we revascularize occluded coronaries for cardiogenic shock?; MI, myocardial infarction; CS, cardiogenic shock; Q_1, Q_3, interquartile range.

All variables are % unless indicated otherwise.

[a]Student's *t*-test for normally distributed continuous variables, the Wilcoxon rank-sum test for non-normally distributed continuous variables, Fisher's exact test and χ^2 test for categorical variables.

[b]Obtained while on support measures.