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META-ANALYSIS

Percutaneous assist devices in acute myocardial infarction with cardiogenic shock: Review, meta-analysis

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Abstract

AIM: To assess the impact of percutaneous cardiac support in cardiogenic shock (CS) complicating acute myocardial infarction (AMI), treated with percutaneous coronary intervention.

METHODS: We selected all of the studies published from January 1st, 1997 to May 15st, 2015 that compared the following percutaneous mechanical support in patients with CS due to AMI undergoing myocardial revascularization: (1) intra-aortic balloon pump (IABP) *vs* Medical therapy; (2) percutaneous left ventricular assist devices (PLVADs) *vs* IABP; (3) complete extracorporeal life support with extracorporeal membrane oxygenation (ECMO) plus IABP *vs* IABP alone; and (4) ECMO plus IABP *vs* ECMO alone, in patients with AMI and CS undergoing myocardial revascularization. We evaluated the impact of the support devices on primary and secondary endpoints. Primary endpoint was the inhospital mortality due to any cause during the same hospital stay and secondary endpoint late mortality at 6-12 mo

of follow-up.

RESULTS: One thousand two hundred and seventy-two studies met the initial screening criteria. After detailed review, only 30 were selected. There were 6 eligible randomized controlled trials and 24 eligible observational studies totaling 15799 patients. We found that the inhospital mortality was: (1) significantly higher with IABP support *vs* medical therapy (RR = +15%, *P* = 0.0002); (2) was higher, although not significantly, with PLVADs compared to IABP (RR = +14%, *P* = 0.21); and (3) significantly lower in patients treated with ECMO plus IABP *vs* IABP (RR = -44%, *P* = 0.0008) or ECMO (RR = -20%, *P* = 0.006) alone. In addition, Trial Sequential Analysis showed that in the comparison of IABP *vs* medical therapy, the sample size was adequate to demonstrate a significant increase in risk due to IABP.

CONCLUSION: Inhospital mortality was significantly higher with IABP *vs* medical therapy. PLVADs did not reduce early mortality. ECMO plus IABP significantly reduced inhospital mortality compared to IABP.

Key words: Intra-aortic balloon pump; Impella; TandemHeart; Extracorporeal membrane oxygenation; Cardiogenic shock; Meta-analysis

Core tip: Meta-analyses from observational studies represent an area of innovation in statistical science. In the present review, we identified only a small number of randomized trials, which by themselves were underpowered to assess the efficacy of the support devices on inhospital mortality. To increase the power of the analysis we included observational data, which enabled us to add 14909 additional patients to the 890 from the randomized controlled trials selected. The results of the analysis showed that: (1) intra-aortic balloon pump (IABP) used alone was associated with significant increase in inhospital mortality compared to Medical therapy; (2) percutaneous left ventricular assist devices increased, although non significantly, the mortality as compared with IABP; and (3) extracorporeal membrane oxygenation (ECMO) plus IABP had significant protective effect compared to IABP or ECMO alone.

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INTRODUCTION

Cardiogenic shock (CS) occurs in 5% to 15% of patients with acute myocardial infarction (AMI). Despite major technical advances the inhospital mortality of these patients continues to remain unacceptably high at over 40%[1-4]. To date immediate myocardial revascularization represents the only intervention of proven benefit. Emergency percutaneous coronary intervention (PCI) is recommended if coronary anatomy is amenable and emergency surgical revascularization is recommended in case coronary anatomy is not amenable for PCI (AHA/ACC and ESC/EACTS indication: Class I, Level B)[5-7]. In order to maintain hemodynamic stabilization before and/or after early revascularization, mechanical support with devices such as intra-aortic balloon pump (IABP), percutaneous left ventricular assist devices (PLVADs) and complete extracorporeal life support with extracorporeal membrane oxygenation (ECMO) are often considered[8]. It is known that IABP support provides significant benefit when used in association with thrombolysis; however, it is of no benefit when used in association with PCI[4,9,10].

It is of note that current guidelines do not recommend routine use of IABP in AMI patients with CS complicating AMI (AHA/ACC and ESC/EACTS indication: Class III, Level A), but IABP use may be considered in these patients when CS is secondary to mechanical complications (AHA/ACC indication: Class IIa, Level C). Further, it is recommended that the use of PLVADs should be restricted for short-term circulatory support (AHA/ACC and ESC/EACTS indication: Class IIb, Level C)[5-7].

Because the sickest patients are often excluded from randomized controlled trials (RCTs), only few RCTs of circulatory assist devices have been conducted thus far. On the other hand, there are some data from clinical observational studies[11-15].

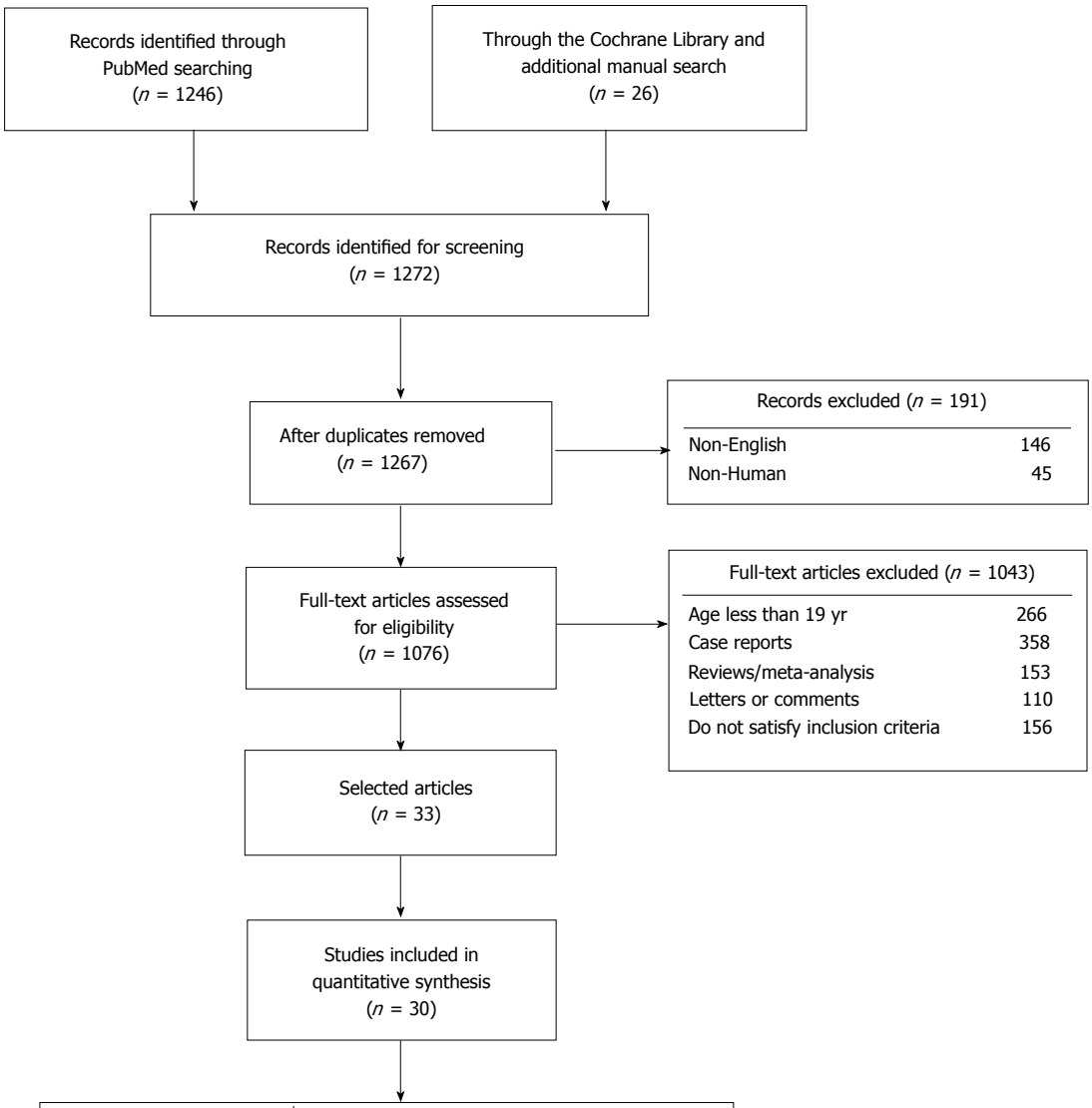
We present here a meta-analysis of available data, based on RCTs and observational studies, on the use of support devices in AMI patients with CS undergoing PCI with regard to inhospital and late mortality.

MATERIALS AND METHODS

Study definition (search and data extraction)

We performed a systematic PubMed and the Cochrane Library literature search using the terms relating to the intervention of interest "IABP" or "IABC", "Impella", "Tandemheart", "PLVADs" "ECMO" or "extracorporeal life support" or "ECLS" or "CPS" in the setting of CS in patients with AMI undergoing percutaneous coronary revascularization. We performed additional manual literature search through: (1) the reference lists of retrieved articles and published reviews; and (2) the abstracts presented at recent (last five years) International Conferences.

Two investigators independently examined the designs, patient populations and interventions used, aiming to include only studies designed to test the effect of the percutaneous support in patients with CS due to AMI and undergoing myocardial revascularization. The



Comparison	No. of studies	Inhospital mortality				Total
		Experimental group		Control group		
		Events	Total	Events	Total	
IABP *vs* medical therapy	13	2016	4360	1783	4431	8791
PLVADs *vs* IABP	6	66	118	73	153	271
ECMO + IABP *vs* IABP	3	32	88	46	76	164
ECMO + IABP *vs* ECMO	6	116	196	72	105	301
Total	28	2230	4762	1974	4765	9527
		Late mortality				
IABP *vs* medical therapy	6	1816	3491	1396	3550	7041
Overall	30	3851	7865	3167	7934	15799

Figure 1 Flow-chart of the study selection process. IABP: Intra-aortic balloon pump; PLVADs: Percutaneous left ventricular assist devices; ECMO: Extracorporeal membrane oxygenation.

search was restricted to English-language journals and excluded studies on non-human subjects as well as articles unrelated to the topic.

The study selection process is outlined in Figure 1. The exclusion criteria were data from registries or studies with lack of a control group, the absence of mortality data, the presence of different timing for the outcome or, more generally, insufficient data for risk estimation. Disagreements were resolved by asking the opinion of a third reviewer to reach consensus at each stage of the screening process. We selected all of the studies published from January 1st, 1997 to May 15st, 2015 that compared the following percutaneous mechanical support in patients with CS due to AMI undergoing myocardial revascularization: (1) IABP *vs* Medical therapy; (2) PLVADs *vs* IABP; and (3) ECMO plus IABP *vs* IABP or ECMO. CS was defined by: (1) a decrease in systolic blood pressure to $\leqslant$ 90 mmHg for more than 30 min, in the absence of hypovolemia, or requiring vasopressor support; (2) a reduction of cardiac

index to 1.8 L/min per square meter without support or to 2.0-2.2 L/min per square meter with support; and (3) elevated left ventricular filling pressures[16,17]. Moreover, profound shock was defined as systolic blood pressure less than 75 mmHg-despite receiving an intravenous inotropic agent that was associated with altered mental status and respiratory failure[18]. The acronym PLVADs included the Impella®2.5 (Abiomed, Danvers, MA, United States) and the TandemHeart (Cardiac Assist Inc., Pittsburgh, PA, United States)[14,15]. The acronym of ECMO included a modified heart-lung machine, generally consisted of a centrifugal pump, a heat exchanger and a membrane oxygenator[15,18-22].

Study outcomes

Primary and secondary endpoints: We evaluated the impact of the support devices on primary and secondary endpoints. Primary endpoint was the inhospital mortality due to any cause during the same hospital stay and secondary endpoint late mortality at 6-12 mo of follow-up.

Statistical analysis

Meta-analysis was performed separately for observational studies and RCTs comparing the following groups of patients: (1) IABP (experimental) *vs* Medical therapy (control); (2) PLVADs (experimental) *vs* IABP (control); (3) ECMO plus IABP (experimental) *vs* IABP (control); and (4) ECMO plus IABP (experimental) *vs* ECMO (control). We computed the risk ratio (RR) with 95%CI, using the Mantel-Haenszel random-effect model to take into account possible heterogeneity among the individual studies beyond that expected from chance, to point out the relative effect of the mechanical assist devices under study. We used the Forest plot to present the results graphically, to report the effect estimates for the individual studies together with the overall measure of effect. We computed the Cochran's *Q* test and I^2 statistics to quantify the homogeneity/heterogeneity among the selected studies within and between subgroups[23]. A Funnel Plot was designed as visual aid for detecting bias or systematic heterogeneity among the studies included in the meta-analysis (publication bias). A sensitivity analysis was then performed by repeating the meta-analysis after exclusion of the study(ies) falling out the 95%CI.

The meta-analysis was performed using Review Manager (RevMan) (Computer program) Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaborations, 2014[24].

We performed Trial Sequential Analysis using the program provide by "The Copenhagen Trial Unit, Center for Clinical Intervention Research CTU, Denmark; version 0.9 beta; available at www.ctu.dk/tsa" in order to assess if the studies enclosed in the meta-analysis reached the required number of participants (information size), and to construct the monitoring boundaries to detect significance and futility of the primary and secondary endpoints[25,26]. Trial Sequential Analysis was done using the effective difference in risks between the experimental (intervention risk) and control groups (basal risk) with a risk of a type I error of 5% and a power of 80%. The relative risk reductions (RRR) observed were linked to the number of patients to be treated (NNT) or to be harmed (NNH), to assess the clinical benefit or the detrimental effect corresponding to each level of RRR. All statistical tests were two-sided and α error of $\leqslant$ 0.05 was defined as statistically significant.

The statistical methods of this study were reviewed by Flavia Chiarotti, Biostatistician, Research Director from the Italian National Institute of Health.

RESULTS

One thousand two hundred and seventy-two records met the initial screening criteria. After detailed review, only 30 were selected[4,18,21,27-54]. There were 6 eligible RCTs[4,27-31] and 24 eligible observational studies[18,21,32-54] totaling 15799 patients. The main characteristics of the selected studies are reported in Table 1.

IABP vs medical therapy

In the comparison between IABP and Medical therapy, we analysed a total of 15063 patients (14273 from 12 observational studies[32-44] and 790 form 3 RCTs[4,27,31]). The data provided us by French *et al*[31] and Kunadian *et al*[44] contributed only for the analysis of the secondary outcome.

Primary endpoint: Primary endpoint was assessed in 8791 patients (8153 from 11 observational studies[32-43] and 638 from 2 RCTs[4,27]). The inhospital deaths occurred in 46.24% of patients in the experimental group and 40.24% of patients in the control. The NNH was 16 (6 more deaths every 100 patients treated with IABP). The overall analysis showed a significant risk increase (+18%, P = 0.002) in the IABP group (Figure 2). More specifically, we observed a significant risk increase in observational studies (RR = +21%, P = 0.0008) and a nonsignificant risk reduction in RCTs (RR = -3%%, P = 0.78) (Figure 2). The test for subgroup differences showed high heterogeneity among observational studies (I^2 = 63%) and between observational and RCTs (I^2 = 73.9%), providing a significantly different estimate of the IABP effect (Figure 2). In the Funnel plot, the studies by Gu *et al*[37] and by Zeymer *et al*[39] fell out of the 95%CI, thus appearing to be the potential source of bias. After the sensitivity analysis, heterogeneity decreased to a lower level among the observational (I^2 = 19%), but persisted at high levels between observational studies and RCTs (I^2 = 68.2%) (Table 2). Furthermore the overall risk in the experimental group slight decreased (RR = +15%) (Table 2). The NNH was equal to 18 (5 more deaths every 100 patients treated with IABP) (Table 3). Trial Sequential Analysis showed that the required number of participant was reached and the monitoring boundaries,

Table 1 Main characteristics of the selected studies

Ref.	Setting	Study design	Etiology of CS	Cardiac arrest	Treatment	Period	No. of pts
IABP *vs* medical therapy							
Anderson *et al*[32], 1997 (GUSTO-I)	United States, Europe	Obs.; multicenter	STEMI	No	PCI	1990-1993	37
Sanborn *et al*[33], 2000 (SHOCK Registry)	United States, Canada, Europe, New Zealand	Obs.; multicenter registry	AMI	No	PCI or CABG	1993-1997	383
Barron *et al*[34], 2001 (NRMI-2)	United States	Obs.; multicenter registry	AMI	No	PCI	1994- < 2000	2990
French *et al*[31], 2003 (SHOCK Trial 12-mo survival)	United States, Canada, Europe, New Zealand	RCT; multicenter	AMI	No	PCI or CABG	1993-1998	152
Vis *et al*[35,36], 2007 (AMC CS)	Europe	Obs.; single-center	STEMI	No	PCI	1997-2005	292
Gu *et al*[37], 2010	Asia	Obs.; single-center	STEMI	No	PCI	2003-2008	91
Prondzinsky *et al*[27], 2010 (IABP-SHOCK)	Europe	RCT; single-center	AMI	No	PCI	2003-2004	40
Stub *et al*[38], 2011	Europe	Obs.; multicenter registry	ACS	No	PCI	2004-2010	410
Zeymer *et al*[39], 2011 (Euro Heart Survey PCI)	Europe	Obs.; multicenter registry	STEMI or NSTEMI	No	PCI	2005-2008	653
Thiele *et al*[4], 2012 (IABP-SCHOCK II)	Europe	RCT; multicenter	AMI	No	PCI (95.8%), CABG (3.5%), PCI and CABG (0.7%)	2009-2012	598
Zeymer *et al*[40], 2013 (ALKK-PCI)	Europe	Obs.; multicenter registry	STEMI or NSTEMI	No	PCI	2006-2011	1913
Dziewierz *et al*[41], 2014 (EUROTRANSFER registry)	Europe	Obs.; multicenter registry	STEMI	No	PCI (49 pts), CABG (2 pts)	2005-2007	51
Kunadian *et al*[44], 2015 (BCIS registry)	Europe	Obs.; multicenter registry	ACS	No	PCI	2005-2011	6120
Kim *et al*[42], 2015 (KAMIR)	Asia	Obs.; multicenter registry	AMI	Yes	PCI	2005-2014	1214
Suzuki *et al*[43], 2015 (Tokyo CCU Network Scientific Council)	Asia	Obs.; multicenter registry	STEMI	No	PCI	2009-2011	119
PLVADs (TandemHeart, Impella® 2.5) *vs* IABP							
Thiele *et al*[29], 2005[1]	Europe	RCT; single center	AMI	No	PCI (49 pts), CABG (2 pts)	2000-2003	41
Burkoff *et al*[28], 2006[1]	United States, Europe	RCT; multicenter	AMI (70%)	No	PCI (22 pts), CABG (3 pts)	2002-2004	33
Seyfarth *et al*[30], 2008[2] (ISAR-SHOCK)	Europe	RCT; two-center	AMI	No	PCI (22 pts)	2004-2007	26
Schwartz *et al*[46], 2012[1,2]	United States	Obs.; single center	68% STEMI, 11% OHCA	Yes	PCI (63 pts), CABG (5 pts)	2008-2010	76
Shah *et al*[47], 2012[1,2]	United States	Obs.; single center	STEMI or UA/NSTEMI	No	PCI	2007-2009	17
Manzo-Silberman *et al*[45], 2013[2]	Europe	Obs.; single center registry	ACS (mainly), OHCA	Yes	PCI (54 pts)	2007-2010	78
ECMO plus IABP *vs* IABP							
Sheu *et al*[18], 2010	Asia	Obs.; single center	STEMI	No	PCI	1993-2009	71
Tsao *et al*[21], 2012	Asia	Obs.; single center	AMI	No	PCI	2004-2009	58
Perazzolo Marra *et al*[48], 2013	Europe	Obs.; single center	AMI	No	PCI	2010-2012	35
ECMO plus IABP *vs* ECMO							
Yamauchi *et al*[49], 2009	Asia	Obs.; single center	AMI	No	PCI	2000-2007	16
Chung *et al*[50], 2011	Asia	Obs.; multicenter	AMI, INCA (14 pts)	Yes	PCI (7 pts), CABG (13 pts)	2206-2009	20
Kagawa *et al*[51], 2012	Asia	Obs.; multicenter	ACS, INCA, OHCA	Yes	PCI	2004-2011	73
Aoyama *et al*[52], 2014	Asia	Obs.; single center	AMI, INCA (2 pts, OHCA 7 pts)	Yes	PCI (34 pts), CABG (4 pts)	1993-2000	38
Park *et al*[53], 2014	Asia	Obs.; single center	AMI	No	PCI (78 pts), PCI e/o CABG (10 pts), medical treatment (8 pts)	2004-2011	96
Kim *et al*[54], 2014	Asia	Obs.; multicenter	ACS	No	PCI (53 pts), CABG (5 pts)	2010-2013	58

ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; CABG: Coronary artery bypass grafting; CS: Cardiogenic shock; ECMO: Extracorporeal membrane oxygenation; IABP: Intra-aortic balloon pump; INCA: In-of-hospital cardiac arrest; NSTEMI: Non-ST-elevation myocardial infarction; PCI: Percutaneous coronary intervention; PLVADs: Percutaneous left ventricular assist devices with ([1]TandemHeart, or [2]Impella® 2.5); pts: Patients; Obs.: Observational study; OHCA: Out-of-hospital cardiac arrest; RCT: Randomized controlled trial; STEMI: ST-elevation myocardial infarction; UA: Unstable angina.

Table 2 Meta-analysis before and after sensitivity analysis

Comparison/subgroup	RR							
	Before				After			
	n	I^2 (%)	Estimate (95%CI)	*P*	*n*	I^2 (%)	Estimate (95%CI)	*P*
Inhospital mortality								
IABP *vs* medical therapy								
Observational studies	11	63	1.21 (1.08, 1.36)	0.0008	9	19	1.17 (1.09, 1.26)	< 0.0001
RCTs	2	0	0.97 (0.81, 1.18)	0.78	2	0	0.97 (0.81, 1.18)	0.78
Overall effect	13	62	1.18 (1.06, 1.32)	0.002	11	24	1.15 (1.07, 1.24)	0.0002
Test for subgroup differences[1]		χ^2 = 3.83, df = 1 (P = 0.05), I^2 = 73.9%				χ^2 = 3.14, df = 1 (P = 0.08), I^2 = 68.2%		
ECMO plus IABP *vs* ECMO								
Observational studies	6	12	0.78 (0.65, 0.94)	0.008	5	0	0.80 (0.68, 0.94)	0.006
Late mortality								
IABP *vs* medical therapy								
Observational studies	3	90	0.92 (0.51, 1.67)	0.78	2	60	1.16 (0.69, 1.95)	0.57
RCTs	3	32	1.16 (0.86, 1.58)	0.34	2	0	1.56 (0.97, 2.52)	0.07
Overall effect	6	85	1.08 (0.82, 1.41)	0.60	4	0	1.38 (1.30, 1.46)	< 0.00001
Test for subgroup differences[1]		χ^2 = 0.48, df = 1 (P = 0.49), I^2 = 0%				χ^2 = 0.68, df = 1 (P = 0.41), I^2 = 0%		

[1]Between observational studies and RCTs. IABP: Intra-aortic balloon pump; RCT: Randomized controlled trial; ECMO: Extracorporeal membrane oxygenation.

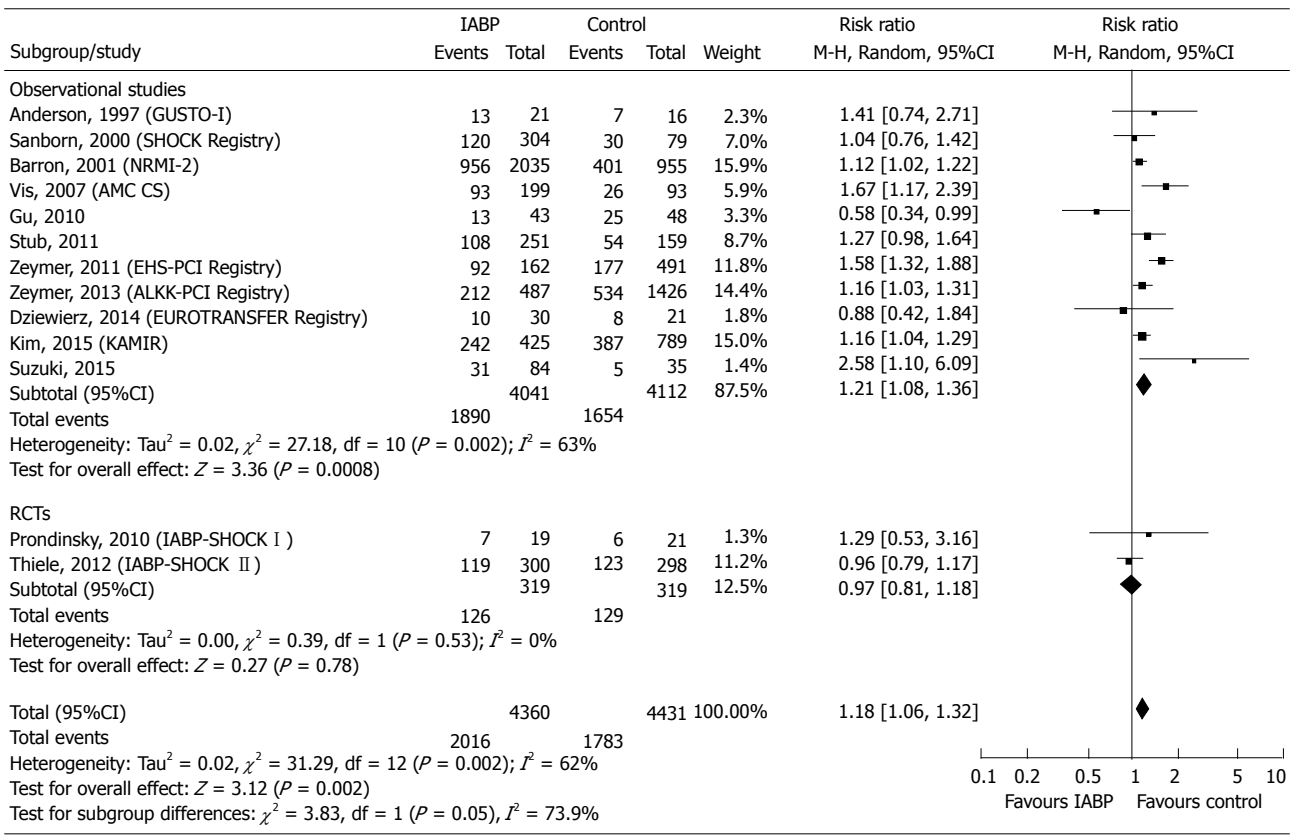


Figure 2 Meta-analysis on risk ratio of inhospital mortality between the patients with intra-aortic balloon pump *vs* medical therapy.

constructed to detect significance, were crossed by the z-curves, demonstrating a detrimental effect of IABP (Table 3, Figure 3).

Secondary endpoint: The late mortality was assessed in 7041 patients (6262 from 3 observational studies[37,41,44] and 779 from 3 RCTs[4,27,31,55,56]). Mortality rate was higher, but not significantly, in the IABP group respect to control (52.02% *vs* 39.32%). IABP reduced mortality (-8%, P = 0.78) in observational studies and increased mortality (+16%, P = 0.34) in RCTs (Figure 4). In the Funnel plot the studies by Gu *et al*[37] and by Thiele *et al*[56] fell out of the 95%CI, appearing to be the potential source of bias. When we applied the sensitivity analysis by excluding the study by Gu *et al*[37] from observational studies and the study by Thiele *et al*[56]

Table 3 Benefit - harm observed in the experimental group and result of Trial Sequential Analysis

Groups			Mortality rate (%)		RRR	Effect of experimental support				Trial Sequential Analysis	
Experimental		Control	Experimental	Control		NNT	NNH	Harm[1]	Benefit[1]	Required information size	Results
Inhospital mortality											
IABP[2]	*vs*	Medical therapy[2]	45.99	40.62	-13.22		18	5.37		2174	Conclusive
PLVADs	*vs*	IABP	55.93	47.71	-17.23		12	8.22		1161	Inconclusive
ECMO + IABP	*vs*	IABP	36.36	60.53	39.92	5			24.16	150	Conclusive
ECMO + IABP[2]	*vs*	ECMO[2]	61.29	66.67	8.06	19			5.38	Not calculable	Inconclusive
Late mortality											
IABP	*vs*	Medical therapy	52.02	39.32	-32.28		7	12.70		5984	Futility
IABP[2]	*vs*	Medical therapy[2]	52.08	37.68	-38.22		6	14.40		168	Conclusive

[1]Number of patients out of 100; [2]Comparison after sensitivity analysis.

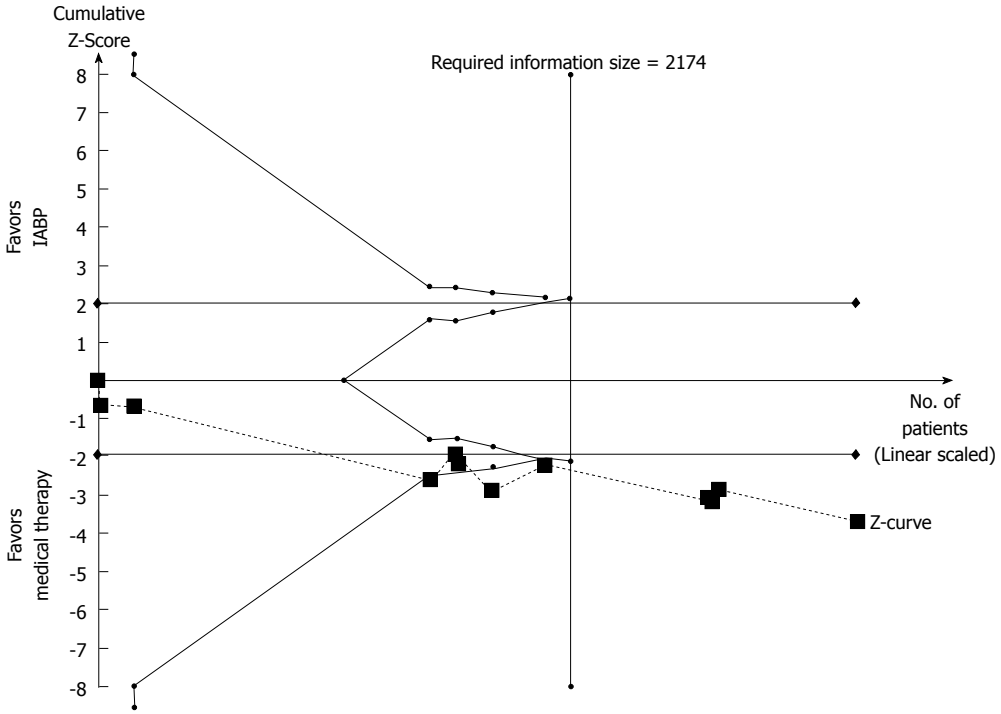


Figure 3 Intra-aortic balloon pump *vs* medical therapy: Trial Sequential Analysis on inhospital mortality. IABP: Intra-aortic balloon pump.

from RCTs, the overall I^2 decreased from 85% to 0% (Table 2). Moreover, the test for subgroup differences showed that the heterogeneity between observational and RCTs was lower (I^2 = 0%) and an overall significant detrimental effect of IABP was found (Table 2). Trial Sequential Analysis was performed: (1) by including all studies; and (2) by excluding the study by Gu *et al*[37] and that by Thiele *et al*[56] according to the sensitivity analysis (Table 3). With inclusion of all studies, there was a 32.28% mortality increase in the IABP group with about 13 more deaths every 100 treated patients. When studies by Gu *et al*[37] and Thiele *et al*[56] were excluded, IABP support resulted in a 38.22% risk increase, and Trial Sequential Analysis showed that data were sufficient to highlight the harmful effect of IABP support on the late mortality (Table 3).

PLVADs vs IABP

We compared the effect of PLVADs *vs* IABP in 271 patients; 171 from 3 observational studies[45-47] and 100 from 3 RCTs[28-30].

Primary endpoint: The overall inhospital mortality increased although not significantly, in PLVADs group compared to IABP group, both in the observational studies (+16%, P = 0.20) and the RCTs (+6%, P = 0.80) (Figure 5). The test for subgroup differences did not show significant differences between observational studies and RCTs (χ^2 = 0.13, P = 0.72, I^2 = 0%). Indeed, in the Forest plot the confidence intervals overlapped, P values of the χ^2 tests were all greater than 0.10 and the I^2 statistics were all equal to zero, showing the homogeneity among the studies within both

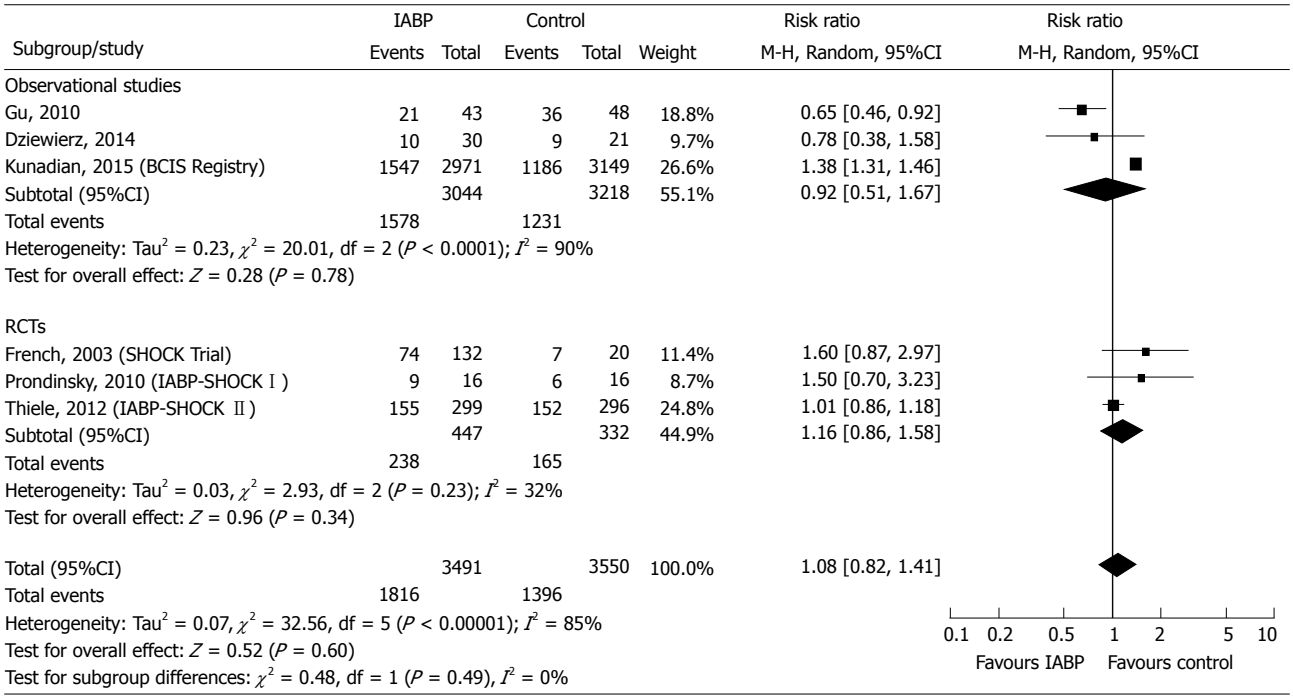


Figure 4 Meta-analysis on risk ratio of late mortality between the patients with intra-aortic balloon pump *vs* medical therapy.

observational and RCTs (Figure 5). In the Funnel plot, all studies were enclosed into 95%CI and the larger studies were plotted at the central top of the graph, demonstrating a convergence in risk estimation while increasing the sample size. RRR equaled -17.23%; when translated into clinical terms, use of PLVADs resulted 8 more deaths every 100 patients treated. For appropriate Trial Sequential Analysis, more patients would have to be included (Table 3).

ECMO plus IABP vs IABP

Primary endpoint: We compared the effect of ECMO plus IABP *vs* IABP in 164 patients from 3 observational studies[18,21,48]. We did not find any RCTs on the topic. In the Forest plot the χ^2 test and the I^2 statistics detected the absence of significant heterogeneity (I^2 = 7%). In the Funnel plot analysis, all studies within 95%CI were included. The inhospital mortality was higher when IABP was used alone rather than in combination with ECMO (60.53% *vs* 36.36%, respectively). ECMO plus IABP group showed a 44% reduction in mortality (Figure 6). The observed RRR was 39.92%, which means that there were 24 fewer deaths for every 100 treated patients. Trial Sequential Analysis showed that the cumulative Z-curve crossed the alpha-spending boundaries, demonstrating that a significant RRR was obtained when ECMO support was used in association with IABP (Figure 7). The required numbers of patients was reached and the meta-analysis could be considered conclusive (Table 3, Figure 7).

ECMO plus IABP vs ECMO

Primary endpoint: We compared the effect of ECMO plus IABP *vs* IABP in 301 patients from 6 observational studies[49-54]. We did not find any RCTs that analyzed this topic. We found a significantly lower inhospital mortality (RR = -22%, P = 0.008) in the group of patients treated with ECMO plus IABP compared to ECMO alone (Figure 6). In the Funnels plot analysis, only the study by Yamauchi *et al*[49] could be a potential source of bias. After the sensitivity analysis I^2 decreased to 0% while the significant effect of ECMO plus IABP *vs* ECMO remained substantially unchanged (RR = -20%, P = 0.006) (Table 2). Despite these results, Trial Sequential Analysis could not be performed because of the small number of patients included (Table 3).

DISCUSSION

All recent reviews on the use of support devices in AMI patient with CS undergoing PCI thus far show lack of a meta-analytic estimates[11-15], probably because the results were based mainly on registry data.

Meta-analyses of data from observational studies represent an area of innovation in statistical science. This analysis can be performed when the question of interest cannot be answered by a review of randomized controlled trials. Even though observational studies are prone to bias (including confounding variables), strategies to adjust for unmeasured confounding variables can be adopted[23]. In the present review, we identified only a small number of randomized trials, which by themselves were underpowered to assess the efficacy of the support devices on inhospital mortality. To increase the power of the analysis we included observational data, which enabled us to add 14909 additional patients to the 890 from the RCTs selected. Further, to avoid bias we used the Funnel plot analysis,

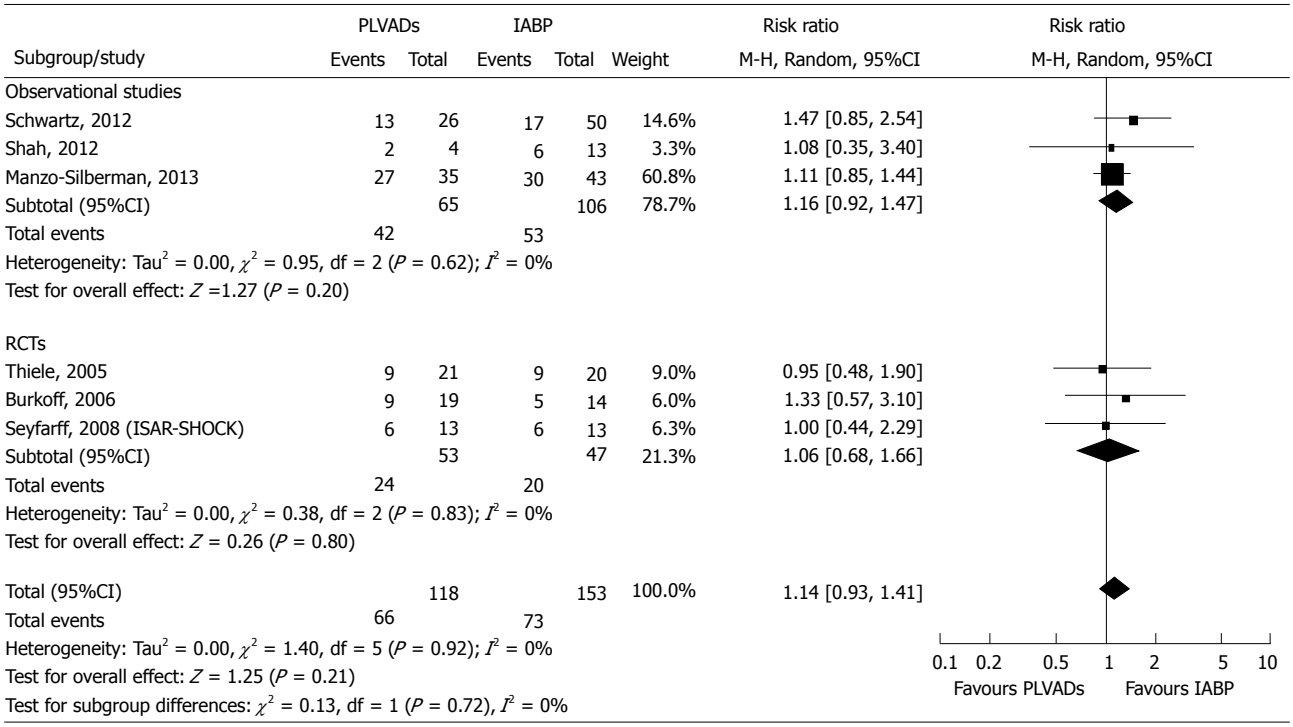


Figure 5 Meta-analysis on risk ratio of inhospital mortality between the patients with percutaneous left ventricular assist devices *vs* intra-aortic balloon pump. IABP: Intra-aortic balloon pump; PLVADs: Percutaneous left ventricular assist devices.

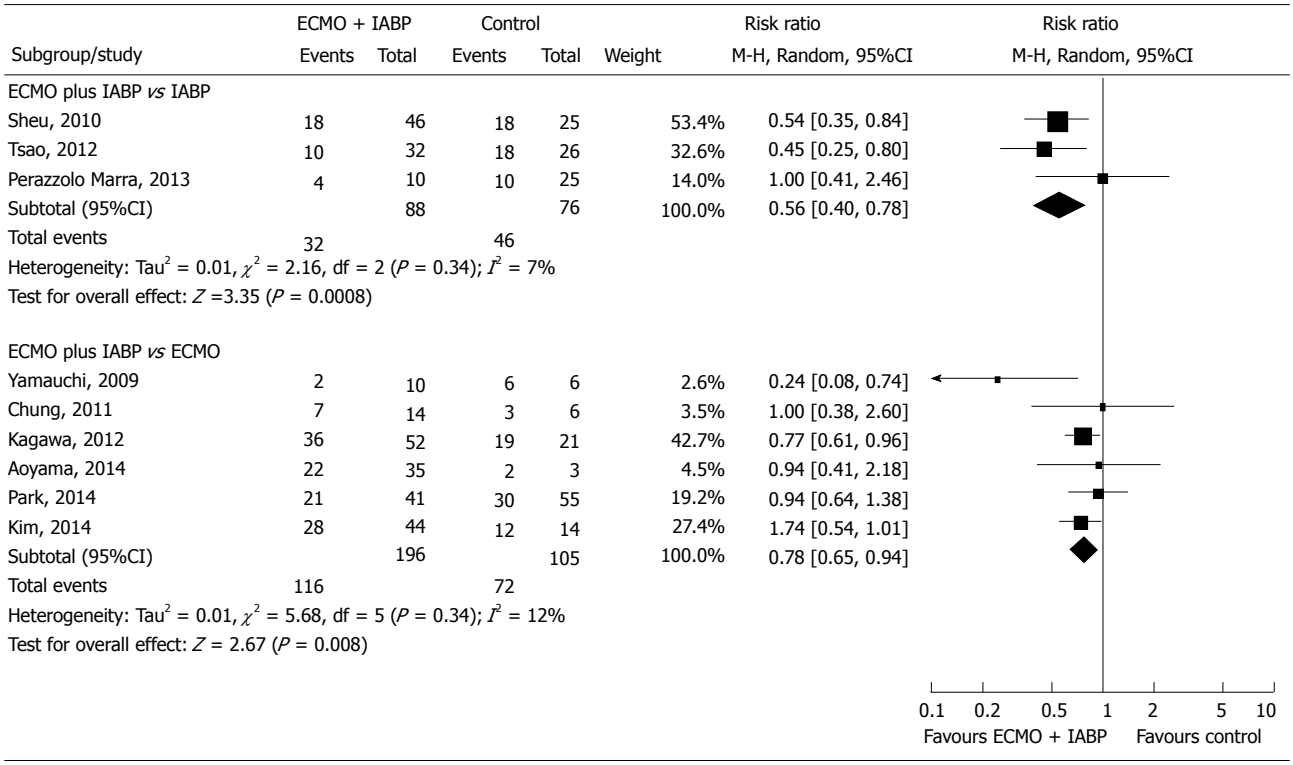


Figure 6 Meta-analysis on risk ratio of inhospital mortality between the patients with extracorporeal membrane oxygenation plus Intra-aortic balloon pump *vs* intra-aortic balloon pump or extracorporeal membrane oxygenation alone. IABP: Intra-aortic balloon pump; ECMO: Extracorporeal membrane oxygenation.

the Cochran's *Q* test and I^2 statistics to test differences between groups and subgroups. The sensitivity analysis allowed us to make comparisons not affected by excessive heterogeneity.

From the meta-analysis we can make the following conclusions

First, in the comparison between IABP *vs* Medical therapy, the analysis confirmed that IABP support

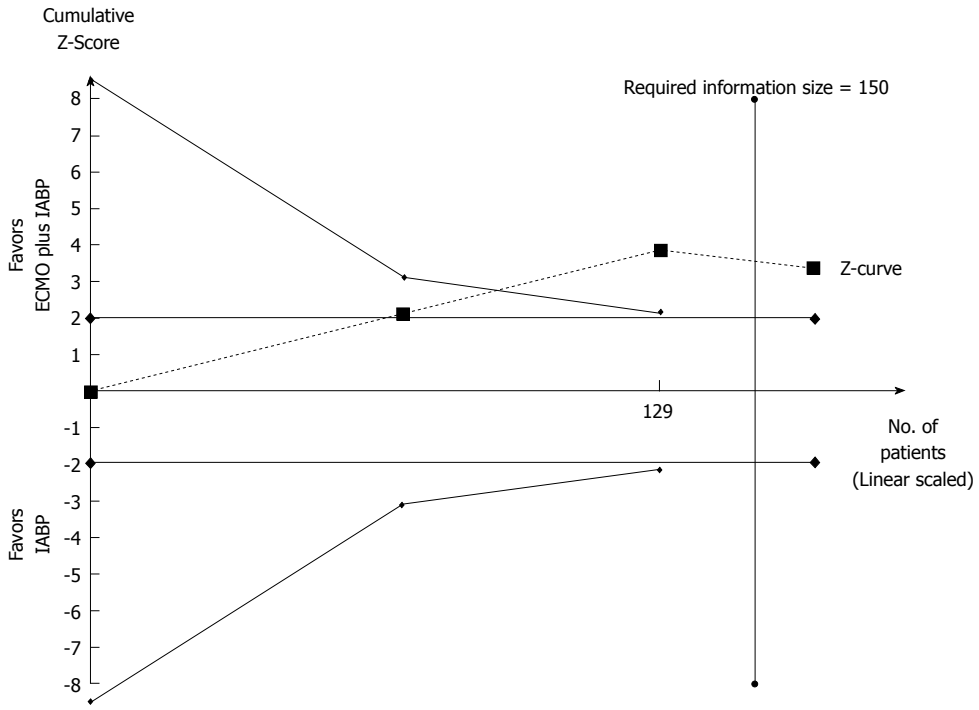


Figure 7 Extracorporeal membrane oxygenation plus Intra-aortic balloon pump support *vs* Intra-aortic balloon pump alone: Trial Sequential Analysis on inhospital mortality. IABP: Intra-aortic balloon pump; ECMO: Extracorporeal membrane oxygenation.

was associated with a significant increase inhospital mortality (Figure 2). The results of RCTs were marginal probably because of the small sample size and the results could be considered a chance occurrence (Figures 2 and 4). When we included the data from observational studies and applied the sensitivity analysis the results were affected only low heterogeneity (I^2 = 19%). Trial Sequential Analysis showed that the *Z*-curves surpassed not only the conventional boundaries but also the alpha-spending boundaries, constructed to control for type 1 error as the source of bias. Thus, the meta-analysis can be considered conclusive in terms of showing a detrimental effect of IABP (Figure 3). With regard to late mortality, we did not identify any difference in both observational studies or in RCTs. However, after sensitivity analysis a significantly higher late mortality was observed in IABP-treated patients and was confirmed by Trial Sequential Analysis, that was conclusive (Table 3).

Second, relative the comparison between IABP *vs* PLVADs, recently reported studies have failed to show a hemodynamic or survival benefit of mechanical support in AMI patients with CS and undergoing PCI. The meta-analysis by Cheng *et al*[57] dates back to 2009, performed on 3 RCTs and included 100 patients, showed that although PLVADs provided superior haemodynamic support in patients with CS compared to IABP, the use of these more powerful devices did not significantly improve early survival. Afterwards only observational studied were performed on this topic. O'Neill *et al*[58] suggested that early initiation of hemodynamic support prior to PCI with Impella 2.5 was associated with more complete revascularization and improved survival in the setting of refractory CS complicating AMI.

In our analysis, the PLVADs increased, although non significantly, the mortality as compared with IABP. The Trial Sequential Analysis showed that 1161 patients will need be analyzed in order to demonstrate its detrimental effect. Our meta-analysis was as such inconclusive and additional perspective investigations would be needed to definitive conclusion.

Third, relative to comparisons of ECMO plus IABP *vs* IABP or ECMO plus IABP *vs* ECMO, the meta-analysis showed a significant protective effect of ECMO plus IABP on inhospital mortality compared to IABP or ECMO used alone (Figure 6). Moreover, Trial Sequential Analysis showed that in the comparison ECMO plus IABP *vs* IABP the required numbers of patients was reached and the meta-analysis could be considered conclusive (Figure 7).

Potential limitation

The main limitation of this meta-analysis is the inclusion of the observational studies, since they are viewed as having less validity than RCTs, due to the absence of randomization. Indeed, we cannot exclude that CS was more severe in the IABP group compared to Medical therapy in some observational studies included in our meta-analysis. However, we repeated the analysis, including only the observational studies, between IABP *vs* control group, selected according to the same severity of shock. The results were substantially unchanged (RR = 1.11, 95%CI = 1.02 to 1.21), significantly in favour of Medical therapy. The heterogeneity was absent (I^2 = 0%). If RCTs were

added to the analysis, the heterogeneity appeared equally low (I^2 = 38%). Moreover, RCTs conducted to assess the role of haemodynamic support in patients with CS complicating AMI reported in the scientific literature are few, perhaps due to ethical issues and feasibility, involving randomization of very severely sick patients. Thus, the inclusion of well-performed observational studies may be acceptable to allow for risk estimation in such situations. Concato *et al*[59] analyzed published meta-analyses based on randomized clinical trials and observational studies that examined identical clinical topics and found that the average results of well-designed observational studies (with either a cohort or a case-control design) were markedly similar to those of the RCTs. Therefore, an integrated approach should be adopted using both experimental and observational studies, as long as well-designed and conducted. Finally, "discarding observational evidence when randomised trials are available is missing an opportunity. Conversely, abandoning plans for randomised trials in favour of quick and dirty observational designs is poor science[60]".

Another limitation was the lack of the analysis of the baseline characteristics (such as age, gender, race, *etc*.) that are recognized markers of risk. Unfortunately, these data available at baseline were not reported in the outcome.

Conclusion

The results of our meta-analysis showed that in AMI patients with CS and undergoing PCI: (1) the inhospital mortality was significantly higher with IABP support *vs* Medical therapy; (2) PLVADs increased, although non significantly, the mortality as compared with IABP; and (3) ECMO plus IABP had significant protective effect compared to IABP or ECMO alone. Trial Sequential Analysis of data on inhospital mortality in IABP *vs* control and ECMO plus IABP *vs* IABP showed that the analyses were sufficient to highlight the harmful effect of IABP and further studies would no longer be needed. Based on the results we can conclude that in CS complicating AMI: (1) routinely use of IABP and PLVADs is not recommended; and (2) the beneficial effect of the reduction inhospital mortality provided by ECMO plus IABP could be attributed to the synergistic action of the two devices in supporting the failing heart. IABP decreasing afterload and myocardial oxygen consumption, can avoid the negative effects on myocardial protection that can occur when using ECMO alone.

COMMENTS

Background

Despite major technical advances the inhospital mortality of patients with cardiogenic shock (CS) complicating AMI continues to remain high. To support the failing heart [intra-aortic balloon pump (IABP)], percutaneous left ventricular assist devices (PLVADs) and extracorporeal membrane oxygenation (ECMO) are used. Unfortunaletely randomized controlled trials (RCTs) on this issue are performed in small numbers, perhaps due to ethical issues and feasibility, involving randomization of patients with CS.

Research frontiers

The question of impact of cardiac support percutaneous devices cannot be answered by a review of RCTs alone. Meta-analyses of observational studies increase the power of the analysis by adding more data to the RCTs to have more comprehensive results.

Innovations and breakthroughs

In the present study, the authors investigated the impact of IABP, PLVADs and ECMO on inhospital mortality and late survival in patients with CS complicating acute myocardial infarction (AMI) undergoing percutaneous coronary intervention (PCI). Meta-analysis of observational studies in addition to the RCTs enabled them to increase the power of the analysis.

Applications

The results of the meta-analysis allow us to understand the impact of percutaneous cardiac support with IABP, PLVAD and ECMO in patients with CS complicating AMI undergoing PCI.

Terminology

This is a systematic review and meta-analysis of observational studies and RCTs.

Peer-review

In this study, the authors collected the data from 30 published research papers (total 15799 patients) and used meta-analysis to analyze in hospital and late mortality of percutaneous mechanical support. This is an interesting study. The findings in this study have the potential to help the clinical doctor work out the guideline for reducing mortality in acute myocardial infarction complicated by cardiogenic shock.

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