The outcome of intra-aortic balloon pump support in acute myocardial infarction complicated by cardiogenic shock according to the type of revascularization: A comprehensive meta-analysis

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Aims Despite the recommendations of the current guidelines, scientific evidence continue to challenge the effectiveness of intra-aortic balloon pump (IABP) in acute myocardial infarction (AMI) complicated by cardiogenic shock. Moreover, 2 recent meta-analyses showed contrasting results. The aim of this study is to test the effect of IABP according to the type of therapeutic treatment of AMI: percutaneous coronary intervention (PCI), thrombolytic therapy (TT), or medical therapy without reperfusion. Articles published from January 1, 1986, to December 31, 2012, were collected and analyzed by meta-analysis.

Methods and results We evaluated the IABP impact on inhospital mortality, on safety end points (stroke, severe bleeding) and long-term survival, using risk ratio (RR) and risk difference (RD) estimates. We found that the risk of death was (i) not significantly different between the IABP and control groups (RR 0.95, $P = .52$; RD –0.04, $P = .28$), (ii) significantly reduced in the TT subgroup (RR 0.77, $P < .0001$; RD –0.16, $P < .0001$), and (iii) significantly increased in the PCI subgroup (RR 1.18, $P = .01$; RD 0.07, $P = .01$). There were no significant differences in secondary end points (P, not significant). In addition, we compared the meta-analyses collected over the same search period.

Conclusion The results show that IABP support is significantly effective in TT reperfusion but is associated with a significant increase of the inhospital mortality with primary PCI. The comparison of the meta-analyses demonstrates the key role of analysing primary clinical treatments to avoid systematic errors. (Am Heart J 2013;165:679-92.)

Acute myocardial infarction (AMI) (ie, ST-elevation myocardial infarction [STEMI] or non-STEMI [NSTEMI]) is the cause of cardiogenic shock (CS) in 7% to 10% of patients, with hospital mortality approaching 50%.[1-7]

As shown in the Shock Trial,[8] early revascularization leads to a significant survival benefit and can be achieved by percutaneous coronary intervention (PCI), surgical revascularization, or thrombolytic therapy (TT). In the 2013 American College of Cardiology Foundation/American Heart Association (AHA) guideline for the management of STEMI emergency revascularization with either PCI or coronary artery bypass grafting (CABG) is recommended in suitable patients with CS caused by pump failure, irrespective of the time delay from AMI onset with the class 1B. In the absence of contraindications, TT should be administered to patients with STEMI and CS who are unsuitable candidates for either PCI or CABG with class 1B.[9,10]

In addition to these treatments, the intra-aortic balloon pump (IABP) is the most widely used device for the treatment AMI complicated by CS. The use of IABP is encouraged by current guidelines for the management with a class IIa according to the AHA/American College of Cardiology guidelines and a class IIc according to the European Society of Cardiology guidelines,[9,10] whereas in previous studies, IABP support was recommended with a class 1B[11,12] and with a class 1C,[13,14] largely influenced by the pathophysiologic considerations and by the benefits observed in patients treated with medical or TT in the pre-PCI era.[15-23] In the observations from the GUSTO-I trial,[18] CS was found in 315 (0.8%) patients. The use of IABP was missing for 5 (1.6%) of them. For the

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remaining 310 patients, the 30-day mortality rate did not significantly differ between the early IABP and no IABP groups after controlling for baseline clinical characteristics. NRMI-2,[19] a prospective observational study (Obs), evaluated patients who had CS at initial examination or in whom CS developed during hospitalisation (n = 23,180). The overall mortality rate for all of the patients who had CS or in whom CS developed was 70%. Intra-aortic balloon pump was used in 7,268 (31%) patients. Intra-aortic balloon pump use was associated with a significant reduction in mortality rates in the patients who received TT (67% vs 49%) but was not associated with any benefit in the patients treated with PCI (45% vs 47%).

In the TACTICS trial,[17] 57 randomized patients with AMI received either TT and IABP or TT alone. The trial ended early because of the difficulty of enrolling and randomizing these critically ill patients. The results, however, showed a positive impact of IABP support associated with TT in patients with CS.

In a recent randomized study, Thiele et al[24] observed no significant effect of IABP support on 30-day mortality in patients with CS complicating AMI for whom an early revascularization strategy was planned. These findings were also confirmed by the results of the Obs by Zeimer et al,[25] (ALKK-PCI Registry) where no benefit of IABP on outcome was observed in patients with CS treated with primary PCI.

In their meta-analysis, Sjauw et al[26] showed that evidence was insufficient to support the guideline recommendations or the use of IABP in STEMI complicated by CS. In contrast, the meta-analysis conducted by Bahekar et al[27] claimed a significant mortality reduction in patients with AMI and CS when using IABP.

In our meta-analysis on Obs and randomized controlled trials (RCTs) of patients with AMI complicated by CS reported in PubMed and The Cochrane Library from January 1, 1986, to December 31, 2012, we aimed to verify the reasons for the discordance in the results by comparing the effect of IABP support vs no IABP support (i) in overall patients and (ii) within subgroups of patients according to the type of revascularization by using both the efficacy (risk ratio, or RR) and the effectiveness (risk difference, or RD) estimates.

Methods

Study definition

We collected articles from a literature search of the PubMed computerized database and The Cochrane Library using the standard Medical Subject Heading terms (MeSHterms) "IABP" or "IABC," "AMI," and "CS." We performed additional manual literature searches through the reference lists of published meta-analyses and reviews. Two investigators independently examined the designs, patient populations, and interventions in the reports, aiming to include only studies that compared IABP vs no support in patients with CS caused by AMI. The search was restricted to English-language journals and excluded studies on non–human subjects as well as articles unrelated to the topic (ie, IABP acronym used with a different meaning).

The study selection process is outlined in Figure 1. The exclusion criteria also regarded the 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. In cases of disagreement, a third reviewer was consulted. Moreover, for a more exhaustive analysis, additional searches were performed from the abstracts presented at the more recent International Congresses and published in journals indexed by PubMed to take into account the most recent available evidence not yet published and referring to studies still in progress.

All patients with AMI complicated by CS were entered into the analysis.

Acute myocardial infarction was defined as evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, in accordance with the criteria listed in the recommendations set forth in the report of the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force for the Redefinition of Myocardial Infarction.[28]

Cardiogenic shock was defined mainly by hemodynamic parameters such as (i) a systolic blood pressure of less than 90 mm Hg lasting for more than 30 minutes (in the absence of hypovolemia) or requiring vasopressors to achieve a systolic blood pressure $\geq$90 mm Hg with (ii) a reduction of cardiac index (1.8 L min^{-1} m^{-2} without support or 2.0-2.2 L min^{-1} m^{-2} with support, depending on the definition used) and (iii) elevated left ventricular (LV) filling pressures.[1,29]

Bleeding was classified severe if it involved intracranial hemorrhage or caused hemodynamic compromise leading to intervention.[18]

Ten meta-analyses published during the same period of the search, aimed at assessing the effect of IABP on inhospital mortality, were extracted from the above-mentioned databases using the following search strategy: "IABP" AND "shock, cardiogenic" AND "meta-analysis." Of these meta-analyses, 6 were excluded for the following reasons: 5 analyzed the use of IABP in patients at high risk for CS undergoing cardiac surgery, 1[30] evaluated a trial written in Spanish and compared IABP with other percutaneous LV assist devices, 1[31] analyzed the use of IABP in patients with AMI without CS, and the last[32] used mechanical support of CS, comparing IABP vs LV assist device. The remaining 2 meta-analyses (Sjauw et al[26] and Bahekar et al[27]) fulfilled our selection criteria and were considered for comparison.

Outcomes

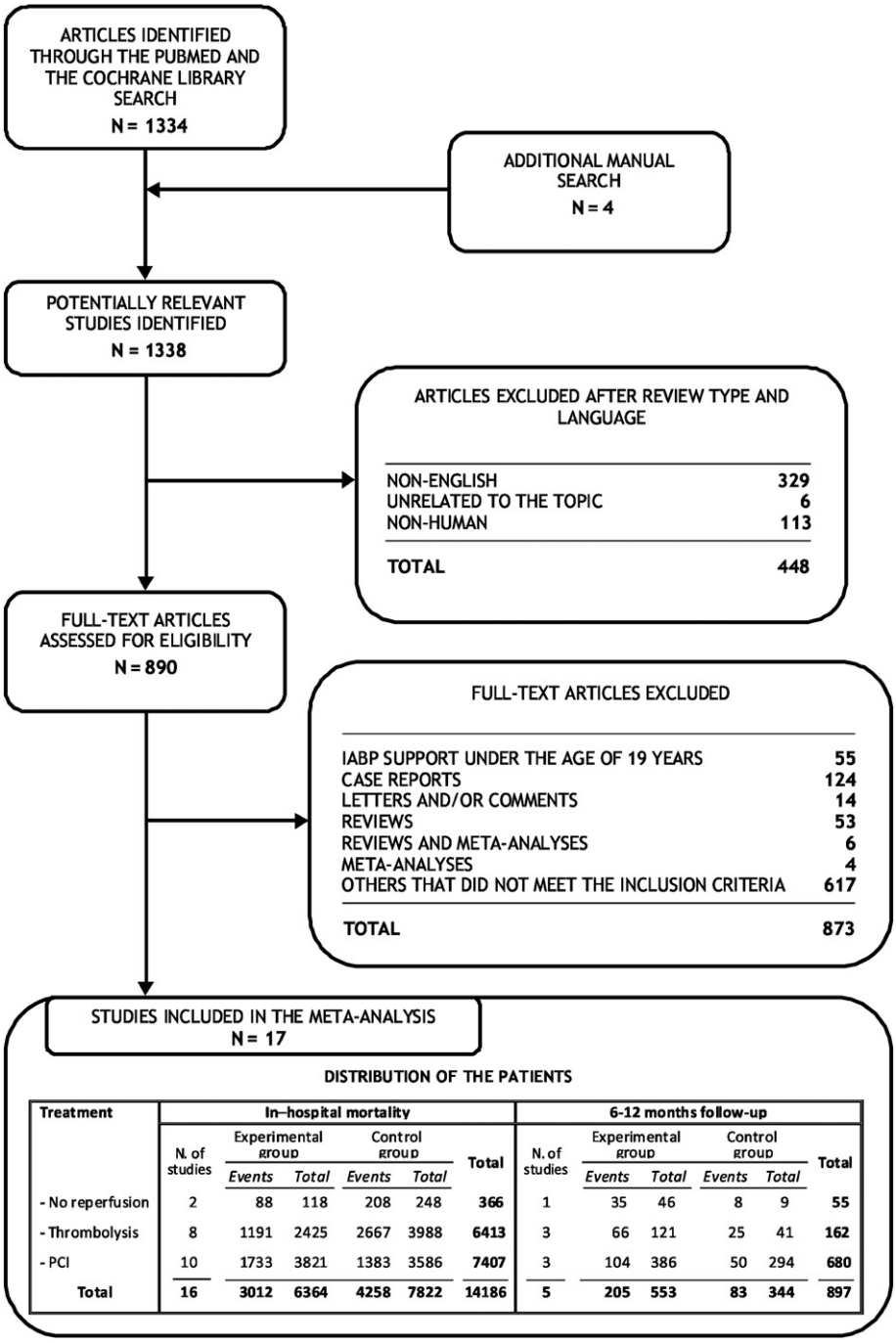
Primary and secondary end points. The primary end point was inhospital mortality. We considered the secondary end point to be the long-term survival at follow-up (from 6 months to 1 year).

Safety end points. Safety end points included (i) stroke and (ii) severe bleeding during the hospital stay.[18]

Statistical analysis

The meta-analysis was performed using Review Manager.[33] The selected studies were previously examined to assess the homogeneity/heterogeneity of the results by (i) visually inspecting the CIs of the risk estimates in the different studies

Figure 1



Treatment	In–hospital mortality						6-12 months follow-up					
	N. of studies	Experimental group		Control group		Total	N. of studies	Experimental group		Control group		Total
		Events	*Total*	*Events*	*Total*			*Events*	*Total*	*Events*	*Total*	
- No reperfusion	2	88	118	208	248	**366**	1	35	46	8	9	**55**
- Thrombolysis	8	1191	2425	2667	3988	**6413**	3	66	121	25	41	**162**
- PCI	10	1733	3821	1383	3586	**7407**	3	104	386	50	294	**680**
Total	**16**	**3012**	**6364**	**4258**	**7822**	**14186**	**5**	**205**	**553**	**83**	**344**	**897**

Flowchart of the study selection process and the distribution of patients according to the type of treatment administered.

and (ii) computing the χ^2 test and (iii) I^2 statistics. A sensitivity analysis was performed when heterogeneity was detected.

We suspected real between-study heterogeneity in cases of (i) poor overlap of CIs, (ii) a significant χ^2 test ($P < .10$ or a χ^2 statistic large with respect to its degrees of freedom), or (iii) a large I^2 statistic.[34] The meta-analysis was performed using RR and RD, and the combined risks were calculated using the Mantel-Haenszel random-effect model to take into account possible heterogeneity among studies. We used RR and RD estimates because their contemporaneous use allows evaluations of both the efficacy and effectiveness of the intervention under study.[34]

Table I. Main characteristics of the 17 selected studies

Study	Conduction of the study	Study design	Period	Method of allocation	Exclusion criteria	Diagnosis	Patients enrolled (n)	No. of patients included in the meta-analysis
Moloupoulos et al[15]	Europe (Greece)	Obs; single-center	Not specified, before 1985	Group allocation biased by knowledge of contraindication for IABP in the control group	Pts improved with conventional therapy	AMI with intractable CS (not responding under intensive treatment for 2-48 h)	49	49
Bengtson et al[20]	USA (North Carolina)	Obs; single-center	1987-1988	Among 1611 pts with AMI, 200 met the diagnostic criteria for CS	Pts without CS	AMI complicated by CS	200	200
Waksman et al[23]	Asia (Israel)	Obs; single-center	Two periods: 1989 1980-1984	1989: consecutive pts with AMI and CS admitted to 2 intensive coronary units: - Unit A (IABP available) - Unit B (IABP not available), according to their area of residence 1980-1984: pts receiving IABP without TT	Not specified	AMI complicated by CS	80 AMI treated with TT: - Group A (IABP), n = 20 (16 pts underwent PCI or CABG) - Group B (no IABP), n = 21 No-reperfusion group (no TT treatment): - Group C (IABP), n = 35 - Group D (No IABP), n = 0	25, only pts undergoing TT
Stomel et al[22]	USA (Michigan)	Obs; single-center	1985-1991	Consecutive observed pts	Pts without CS	AMI complicated by CS	64 - Group 1 (TT), n = 13 - Group 2 (IABP), n = 29 - Group 3 (TT + IABP), n = 22	35, pts undergoing TT or TT + IABP
Anderson et al[18] (GUSTO-I)	USA (North Carolina, Minnesota, Michigan, Ohio), Europe (Belgium)	Obs; multicenter	1990-1993	Subgroup analysis from the GUSTO-I study	Pts with previous stroke, active bleeding, previous treatment with streptokinase or anistreplase, recent trauma or major operation, previous trial participation or noncompressible punctures	STEMI with CS, within 6 h of chest pain	310; 5 pts were excluded because IABP status was missing.	285; pts undergoing TT or PCI
Kovack et al[21]	USA (Michigan, North Carolina)	Obs; 2-center	1985-1995	335 hospital records with discharge diagnosis code for MI and CS from 2 community hospitals were reviewed checking for pts with AMI complicated by CS	CS caused by septicemia or hypovolemia (n = 80) Pts not meeting the criteria for AMI (n = 64) Pts not undergoing TT (n = 126) or undergoing TT beyond 12 h from AMI (n = 19)	AMI complicated by CS	46	46
Sanborn et al[16] (SHOCK Registry)	USA (Massachusetts, Michigan, New Jersey, New York), Canada, Europe (Belgium), New Zealand (Auckland)	Obs; multicenter registry	1993-1997	1190 pts with suspected CS complicating AMI were enrolled at 36 participating centers	CS caused by other causes (n = 306) IABP placed before CS (n = 26) Pts with incomplete data (n = 2)	AMI complicated by CS caused by predominant LV failure	856	856
Barron et al[19] (NRMI-2)	USA (Los Angeles, San Francisco, Seattle, Worcester)	Obs; multicenter registry	1994-<2000	A large registry including pts with AMI. Data collected on pts admitted to registry hospitals were forwarded to an independent data collection center.	Pts without CS	AMI complicated by CS at initial examination or during hospitalization	23,180	8671; pts undergoing TT and/or PCI

Table I (*continued*)

Study	Conduction of the study	Study design	Period	Method of allocation	Exclusion criteria	Diagnosis	Patients enrolled (n)	No. of patients included in the meta-analysis
French et al[41]	USA (Massachusetts, Illinois, New Jersey, New York), Canada, Europe (Belgium), New Zealand (Auckland)	RCT; multicenter	1993-1998	Random (within 12 h of AMI)	Other causes of shock Pts with NSTEMI	Pts with electrocardiographic evidence consistent with coronary occlusion developing CS within 36 h from AMI	302; 12-mo survival data available	301; data of 1 pt missing
Ohman et al[17] (TACTICS)	USA (Kentucky, Michigan, New York, New Jersey, North Carolina), Europe (Greece, Norway), Australia	RCT; parallel multicenter	1996-1999	Random (based on random number table with block randomization)	Absolute contraindication to fibrinolytic, heparin or aspirin therapy; known internal bleeding <1 mo before enrollment; valvular disease, vascular disease, low hematocrit or platelets	AMI or reinfarction complicated by sustained hypotension, possible CS or heart failure	57 - IABP group, n = 30 (12 with CS) - No IABP group, n = 27 (10 with CS)	22; pts with CS
Vis et al[38,39] (AMC CS)	Europe (the Netherlands)	Obs; single-center	1997-2005	Consecutive observed pts	Mechanical complications of STEMI, sepsis, aortic regurgitation, severe cerebral damage, resuscitation >30 min, severe peripheral vascular disease, pts with CABG and other diseases with reduced life expectancy	Pts with STEMI treated with PCI	3038; only 292 pts had CS at admission	292; pts with CS at admission
Gu et al[36]	Asia (China)	Obs; single-center	2003-2008	Consecutive observed pts	Mechanical complications of STEMI, sepsis, aortic regurgitation, severe cerebral damage, resuscitation >30 min, severe peripheral vascular disease, pts with CABG and other diseases with reduced life expectancy	STEMI complicated by CS	91	91
Prondzinsky et al[40] (IABP-SHOCK)	Europe (Germany)	RCT; single-center	2003-2004	Random (based on random number table with block randomization)	Lower limb pulses precluding IABP use or any mechanical complication of AMI	CS secondary to AMI	45	40 5 pts excluded from analysis: - Not fulfilled shock criteria (n = 3) - No postrandomization data (n = 1) - distance to MI >48 h (n = 1) - 1 crossover to IABP
Zeymer et al[35] (Euro Heart Survey PCI)	Europe (33 countries in Europe and the Mediterranean basin)	Obs; multicenter registry	2005-2008	47,407 consecutive pts undergoing PCI coming from 176 centers in 33 countries of Europe and Mediterranean basin were enrolled into the registry. Of them, 7141 had STEMI and 5315 had NSTEMI, and CS was observed in 578 (8.1%) and 75 (1.4%) pts, respectively	NA	Pts with STEMI or NSTEMI and CS undergoing PCI	653	653

(*continued on next page*)

Table I (*continued*)

Study	Conduction of the study	Study design	Period	Method of allocation	Exclusion criteria	Diagnosis	Patients enrolled (n)	No. of patients included in the meta-analysis
Stub et al[37]	Europe (England)	Obs; multicenter registry	2004-2010	Data from Melbourne Interventional Group: multicenter PCI registry in Melbourne	NA	Pts with ACS and CS undergoing PCI	410	410
Thiele et al[24] (IABP-SCHOCK II)	Europe (Germany)	RCT; multicenter	2009-2012	Random (randomization performed centrally with the use of an Internet-based program, with stratification according to center)	Age > 90 y, resuscitation >30 min, no intrinsic heart action, cerebral deficit with fixed dilated pupils, mechanical infarction complication, onset of shock >12 h, shock of other causes, massive pulmonary embolism, severe peripheral artery disease, aortic regurgitation greater than grade II, comorbidity with life expectancy <6 mo, participation in another trial	Pts with STEMI or NSTEMI and CS undergoing early revascularization (by means of PCI or CABG)	600	598; 598 pts were included in the analysis of the primary end point (30-d all-cause mortality)
Zeymer et al[25] (ALKK-PCI)	Europe (Germany)	Obs; multicenter registry	2006-2011	55,008 consecutive pts with acute coronary syndromes undergoing PCI in 41 hospitals were enrolled in the prospective ALKK-PCI registry	NA	Pts with STEMI or NSTEMI and CS undergoing PCI	1913	1913

Pts, Patients; *MI*, myocardial infarction; *NA*, not available; *ACS*, acute coronary syndrome; *ALKK*, Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte.

A Forest plot was used for a graphical presentation of the results, reporting the effect estimates for the individual studies together with the meta-analysis of the overall measure of effect. A 2-sided α error of <.05was defined as statistically significant.

To investigate the effect of IABP, we compared the group of patients with IABP support (the experimental group) with the group of patients without IABP support (the control group), in the overall set of patients and in the following subgroups related to primary clinical treatment: (i) medical stabilization therapy without reperfusion (no-reperfusion), (ii) TT, and (iii) PCI.

Furthermore, we analyzed the impact of IABP support among the 3 subgroups of patients with a test for subgroup differences, using the I^2 statistic to describe the percentage of variability in effect estimates that was attributable to genuine subgroup differences rather than to chance. When the test showed that IABP worked differently in independent subgroups, we compared the subgroups with each other to explain the source of the gap.

The presence of confounding factors may distort the results of the meta-analysis when neglecting to assess the key role of primary clinical treatment. To verify the above, we analyzed separately the data in those articles in which both TT and PCI were investigated.[16,18,19] We therefore performed (i) stratified analysis by subgroups to detect the actual effect of IABP and (ii) the analysis of all studies regardless the specific therapeutic approach.

Finally, to determine whether the different treatment strategies taken individually had a significant impact on the differences in the inhospital mortality rate, we only analyzed the control group excluding the IABP support. For the analysis, we used the χ^2 test (i) within each subgroup, (ii) among the 3 subgroups, and (iii) between subgroup-paired comparisons.

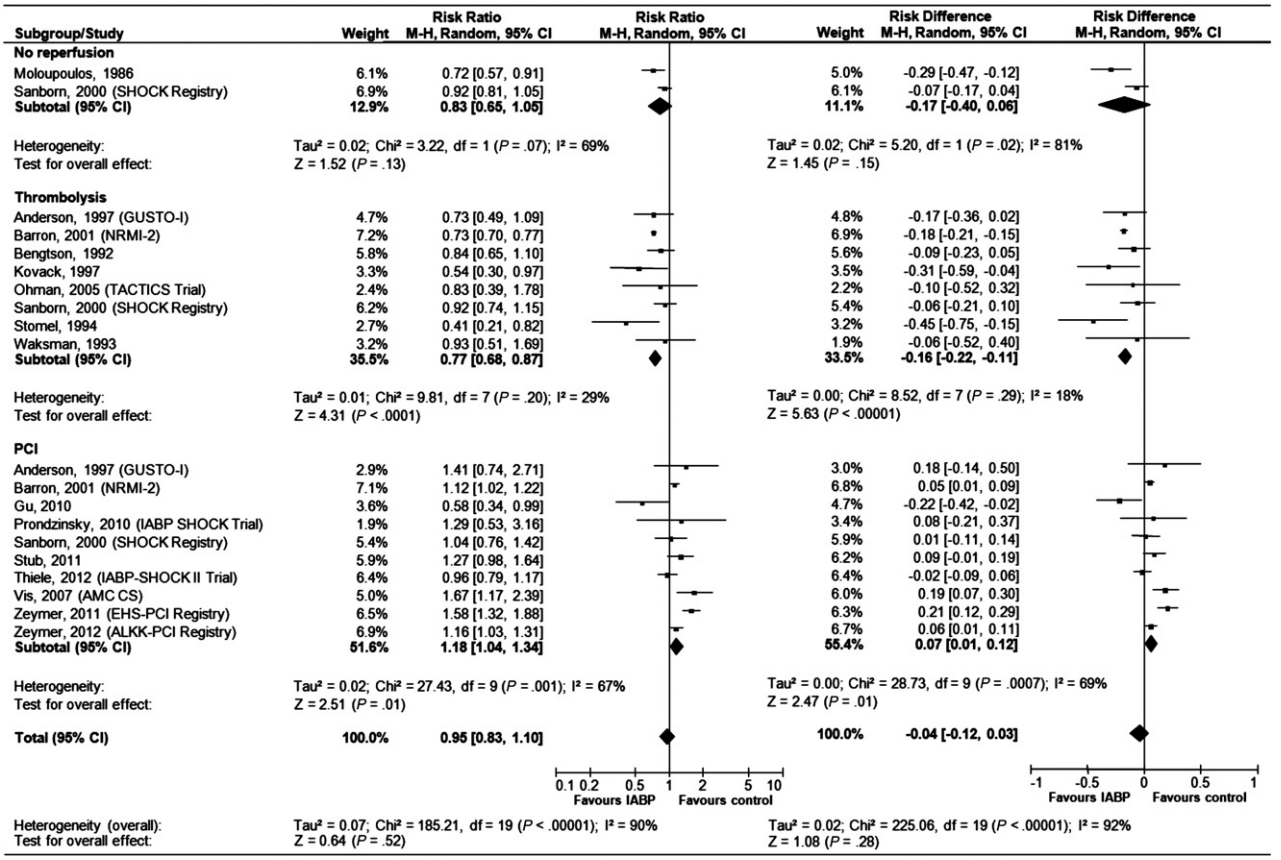
Results

Of 890 of the 1,338 studies that met the initial screening criteria, after detailed review, only 17 were selected: 13 Obs[15,16,18-23,25,35-39] and 4 RCTs[17,24,40,41] that included 14,186 patients. The main characteristics of the selected studies are reported in Table I. We analyzed the impact of IABP support on inhospital mortality in 6,413 patients of the TT subgroup, 7407 patients of the PCI subgroup and 366 patients of the no-reperfusion subgroup (Figures 1 and 2). The analysis of the impact of IABP on long-term survival was based on a smaller number of patients (Figure 3).

Inhospital mortality

The risk of inhospital mortality was analyzed in 16 studies (13 Obs[15,16,18-23,25,35-39] and 3 RCTs, contributing with 22,[17] 40,[40] and 598[24] patients, respectively).

Figure 2



Meta-analysis on RR and RD of inhospital mortality between the patients with IABP support vs the control group according to the primary clinical treatment. The effect measure for each subgroup is represented as a diamond whose lateral points indicate the 95% CI. Overall adjusted risks were computed as weighted averages of the stratum-specific risks, with the weights depending on the trial size and on the standard deviation of the study risk estimate. The vertical line represents no effect.

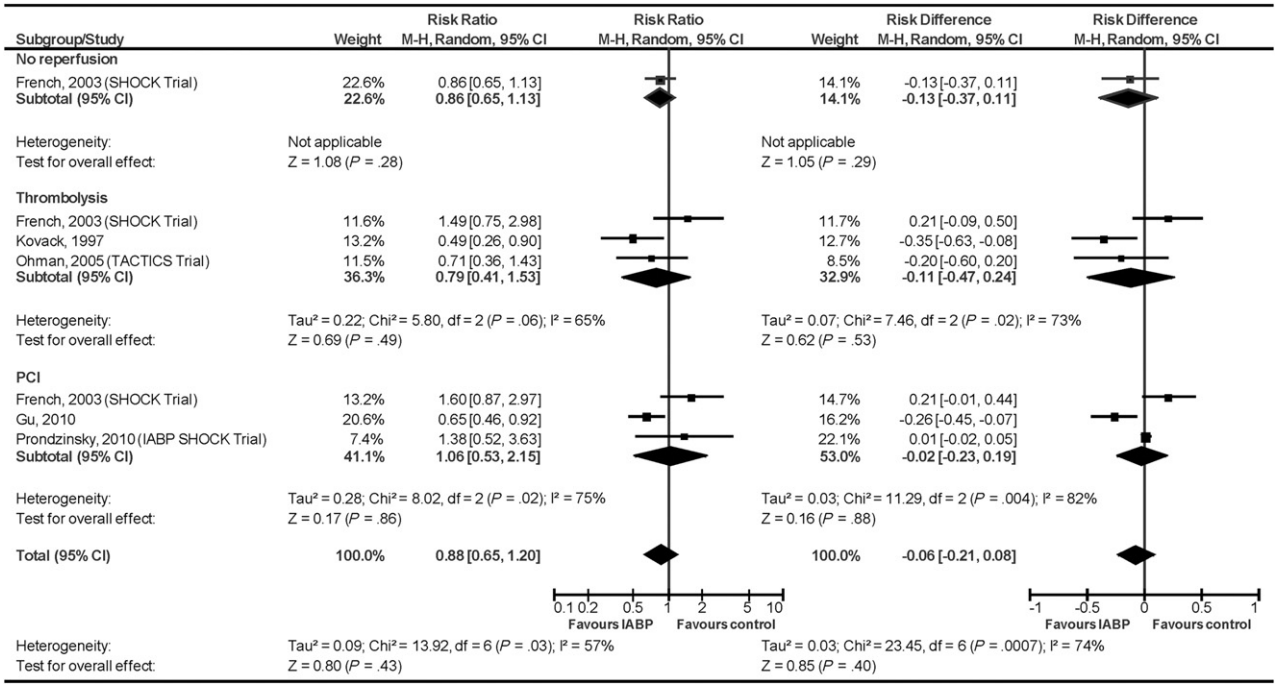
In the comparison between the experimental and control groups, the overall RR and RD from the Obs and the RCTs showed no significant reduction of the risk in patients with IABP support (RR 0.95, $P = .52$; RD −0.04, $P = .28$) (Figure 2). Moreover, we observed (i) no significant risk reduction in the no-reperfusion subgroup (RR 0.83, $P = .13$; RD −0.17, $P = .15$), (ii) a significant risk reduction in the TT subgroup (RR 0.77, $P < .0001$; RD −0.16, $P < .0001$), and (iii) a significant risk increase in the PCI subgroup (RR 1.18, $P = .01$; RD 0.07, $P = .01$) (Figure 2). It should be noted that in the PCI subgroup, the study of Sanborn et al[16] showed no distinction between the patients undergoing revascularization with PCI and those who underwent coronary artery bypass graft surgery. When we excluded Sanborn et al, the results remained substantially unchanged and confirmed the significantly higher risk of mortality in patients with IABP support compared with the controls (RR 1.19, $P = .01$; RD 0.07, $P = .01$).

The test for subgroup differences showed that the impact of IABP support on the risk varied significantly among the subgroups. The paired comparisons showed that the significant differences were caused by comparisons between (i) the PCI subgroup vs no-reperfusion subgroup and (ii) the PCI subgroup vs TT subgroup (Table II).

Furthermore, we found high heterogeneity in the PCI subgroup ($I^2 = 67\%$ for RR and 69% for RD). From the Forest plot, we could note the opposite effect of IABP observed in the study by Gu et al[36] with respect to all other studies. When we applied the sensitivity analysis by excluding Gu et al, I^2 decreased to 61% for RR and 62% for RD. At same time, the risk in the experimental group further increased (the RR point estimate increased from 1.18 to 1.22, $P = .001$; the RD point estimate increased from 0.07 to 0.08, $P < .001$).

The inhospital mortality rate observed in the control group was not significantly different within each

Figure 3



Meta-analysis on RR and RD of long-term survival between the patients with IABP support vs the control group according to the primary clinical treatment.

Table II. Test for subgroup differences

			RR				RD			
Comparisons			χ^2	*df*	*P*	I^2 (%)	χ^2	*df*	*P*	I^2 (%)
No-reperfusion	vs	TT	0.34	1	.56	0	0.00	1	.96	0
No-reperfusion	vs	PCI	6.42	1	.01	84.4	3.89	1	.05	74.3
TT	vs	PCI	22.80	1	<.0001	95.6	33.56	1	<.0001	97.0
Overall			23.66	2	<.0001	91.5	34.73	2	<.0001	94.2

subgroup. However, its incidence was significantly different among the 3 subgroups ($P < .001$). The paired comparisons showed that it was significantly higher (i) in no-reperfusion subgroup compared with the TT ($P < .001$) and the PCI ($P < .001$) subgroups and (ii) in the TT subgroup compared with the PCI subgroup ($P < .001$) (Figure 4).

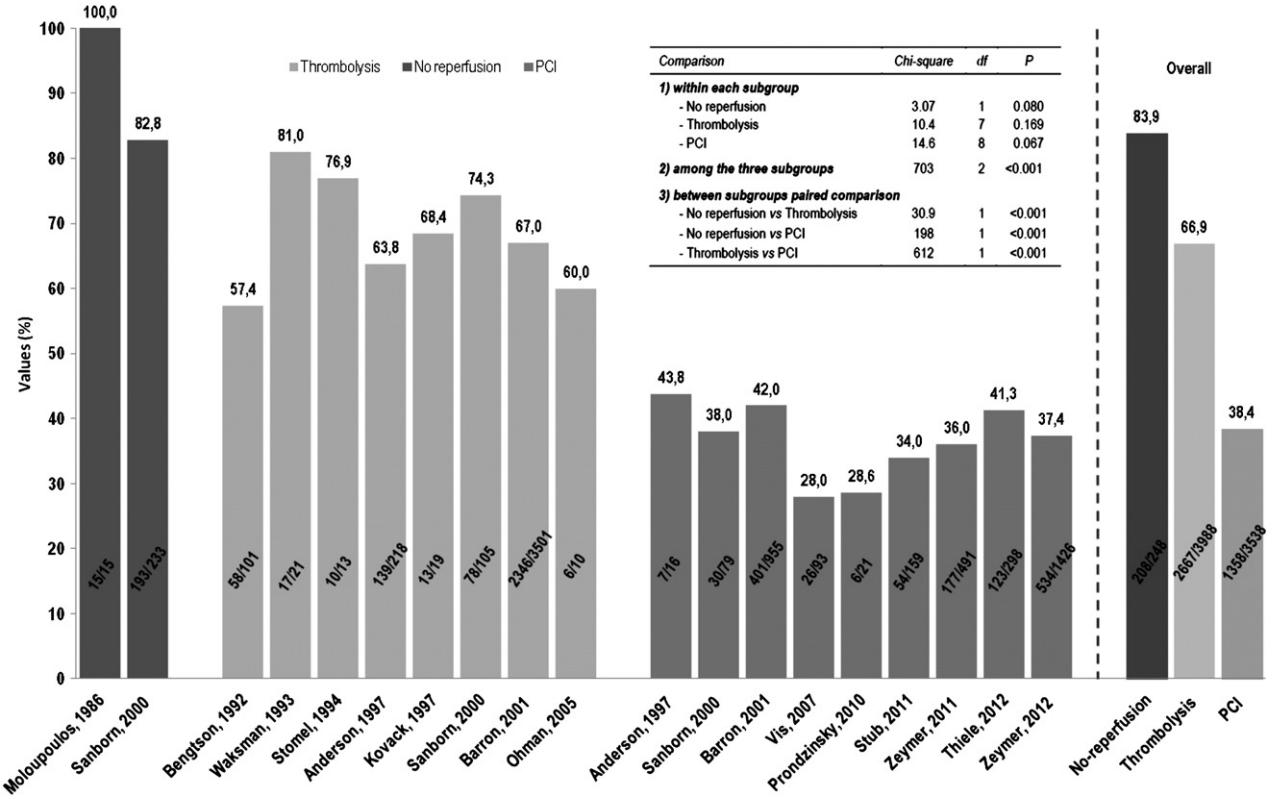
Long-term survival

Survival was assessed from 6 to 12 months in 2 Obs[21,36] and 3 RCTs.[17,40,41] The impact of IABP support on long-term survival showed no significant effect on overall RR (equal to 0.88, $P = .43$) or RD (equal to −0.06, $P = .40$) or in the analysis according to each subgroup of treatment (Figure 3).

The main features of the selected meta-analyses

Bahekar et al[27] analyzed 6 studies, whereas Sjauw et al[26] included 9 studies in their meta-analysis. Details on the studies included in each meta-analysis are reported in Table III. In their assessment of IABP effect, Bahekar et al[27] analyzed all studies and all patients regardless of the specific therapeutic approach. In contrast, Sjauw et al[26] took into account possible sources of clinical heterogeneity, such as the specific primary clinical treatment performed on patients (ie, no-reperfusion, TT, and PCI). Similarly to Sjauw et al, we performed stratified analyses to detect the actual effect of IABP apart from the primary clinical treatment. The numbers of patients, risk estimates, and events analyzed in the 3 meta-analyses under comparison are reported in Table III.

Figure 4



The inhospital mortality rate observed in each study of the control group. The studies within the primary clinical treatment are reported in chronological order. χ^2 Test was performed (i) within each subgroup, (ii) among the 3 subgroups, and (iii) between subgroup-paired comparisons.

Safety assessments

The analysis on the safety end points of the IABP vs no IABP support showed that there were no significant differences between the 2 groups in overall patients and within the subgroups of treatment (TT, PCI) with respect to stroke and major bleeding incidence (Figure 5).

Discussion

The rationale for this work after 2 earlier published pooling projects is justified by the fact that these meta-analyses showed contrasting results; 2 additional studies published in the fourth quarter of 2012, one RTC[24] and the other Obs,[25] do not support the clinical evidences on IABP benefits in AMI complicated by CS; and, finally, the number of studies analyzed has been considerably enlarged, as it can be seen in Table III.

Thiele et al[24] pointed out that the inhospital mortality in AMI complicated by CS may result from hemodynamic deterioration, occurrence of multiorgan dysfunction, and the development of the systemic inflammatory response syndrome.[24,40,42] However, they considered the primary efficacy end point 30-day all-cause mortality. Safety assessments included major bleeding, peripheral ischemic complications, sepsis, and stroke.

Prondzinsky et al,[40] in a randomized trial addressing addition of IABP in patients with CS undergoing PCI, showed that mechanical support was associated only with modest effects on reduction of Acute Physiology and Chronic Health Evaluation II score as a marker of severity of disease, improvement of cardiac index, reduction of inflammatory state, or reduction of plasma brain natriuretic peptide biomarker status compared with medical therapy alone. However, the limitations of the trial precluded any definitive conclusion, but requested for a larger prospective, randomized, multicenter trial with mortality as primary end point.

The scientific evidence of IABP support is based mainly on registry data. This limitation can explain the scarcity of articles that evaluated all factors related to inhospital mortality in older studies and their increasing frequency of assessment in recent RCTs. Therefore, we assessed the impact of IABP on (i) inhospital mortality, (ii) long-term

Table III. Comparison of the overall studies enclosed in the 3 meta-analyses with the absolute number and their impact on the effect estimate

		Romeo et al. IABP in AMI complicated by CS. Method: RR and RD estimators, random effect within subgroup, and overall analysis (studies enclosed: n = 16)					Sjauw et al.[26] IABP in STEMI complicated by CS. Method: RD estimator, fixed effect within subgroup, and overall analysis (studies enclosed: n = 9)					Bahekar et al.[27] IABP in AMI complicated by CS. Method: RR estimator, random effect, and overall analysis (studies enclosed: n = 6)				
Subgroup/Author	**Type of study**	**Weight (RD)**	**IABP, events/total**		**Control, events/total**		**Weight (RD)**	**IABP, events/total**		**Control, events/total**		**Weight (RR)**	**IABP, events/total**		**Control, events/total**	
No-reperfusion														NI	NI	
Moloupoulos et al[15]	Obs	5.0%	24	34	15	15	0.4%	24	34	15	15			NI	NI	
Sanborn et al[16] (SHOCK Registry)	Obs	6.1%	64	84	193	233	*	–	–	–	–					
Subtotal		11.1%	88	118	208	248	0.4%	24	34	15	15					
TT																
Anderson et al[18] (GUSTO-I)	Obs	4.8%	14	30	139	218	2.1%	30	62	146	248	19.57%		†	‡	†
Barron et al[19] (NRMI-2)	Obs	6.9%	1068	2180	2346	3501	55.7%	1068	2180	2346	3501	36.50%		†	‡	†
Bengtson et al[20]	Obs	5.6%	48	99	58	101	2.1%	48	99	58	101				NI	
Kovack et al[21]	Obs	3.5%	10	27	13	19	0.5%	10	27	13	19	1.60%		†		†
Ohman et al[17] (TACTICS)	RCT	2.2%	6	12	6	10			NI						NI	
Sanborn et al[16] (SHOCK Registry)	Obs	5.4%	35	51	78	105	8.9%	220	439	300	417	24.47%		†	‡	†
Stomel et al[22]	Obs	3.2%	7	22§	10	13	0.4%	28	51	10	13	5.80%		†		†
Waksman et al[23]	Obs	1.9%	3	4‖	17	21	0.4%	11	20	17	21	12.05%		†		†
Subtotal		33.5%	1191	2425	2667	3988	70.0%	1415	2878	2890	4320					
PCI																
Anderson et al[18] (GUSTO-I)	Obs	3.0%	13	21	7	16	*	–	–	–	–			†	‡	†
Barron et al[19] (NRMI-2)	Obs	6.8%	956	2035	401	955	26.9%	956	2035	401	955			†	‡	†
Gu et al[36]	Obs	4.7%	13	43	25	48			NI						NI	
Prondzinsky et al[40]	RCT	3.4%	7	19	6	21			NI						NI	
Sanborn et al[16] (SHOCK Registry)	Obs	5.9%	120	304	30	79	*	–	–	–	–			†	‡	†
Stub et al[37]	Obs	6.2%	108	251	54	159			NI						NI	
Thiele et al[24] (IABP-SHOCK II)	RCT	6.4%	119	300	123	298			NI						NI	
Vis et al[38,39] (AMC CS)	Obs	6.0%	93	199	26	93	2.6%	93	199	26	93				NI	
Zeymer et al[35] (EHS-PCI Registry)	Obs	6.3%	92	162	177	491			NI	NI					NI	
Zeymer et al[25] (ALKK-PCI Registry)	Obs	6.7%	212	487	534	1426			NI	NI					NI	
Subtotal		55.4%	1733	3821	1383	3586	29.6%	1049	2234	427	1048					
Total		100.0%	3012	6364	4258	7822	100.0%	2488	5146	3332	5383	100.00%	2135	†	3137	†
Overall population				14,186					10,529					†		
Overall events				7270					5820					5272		

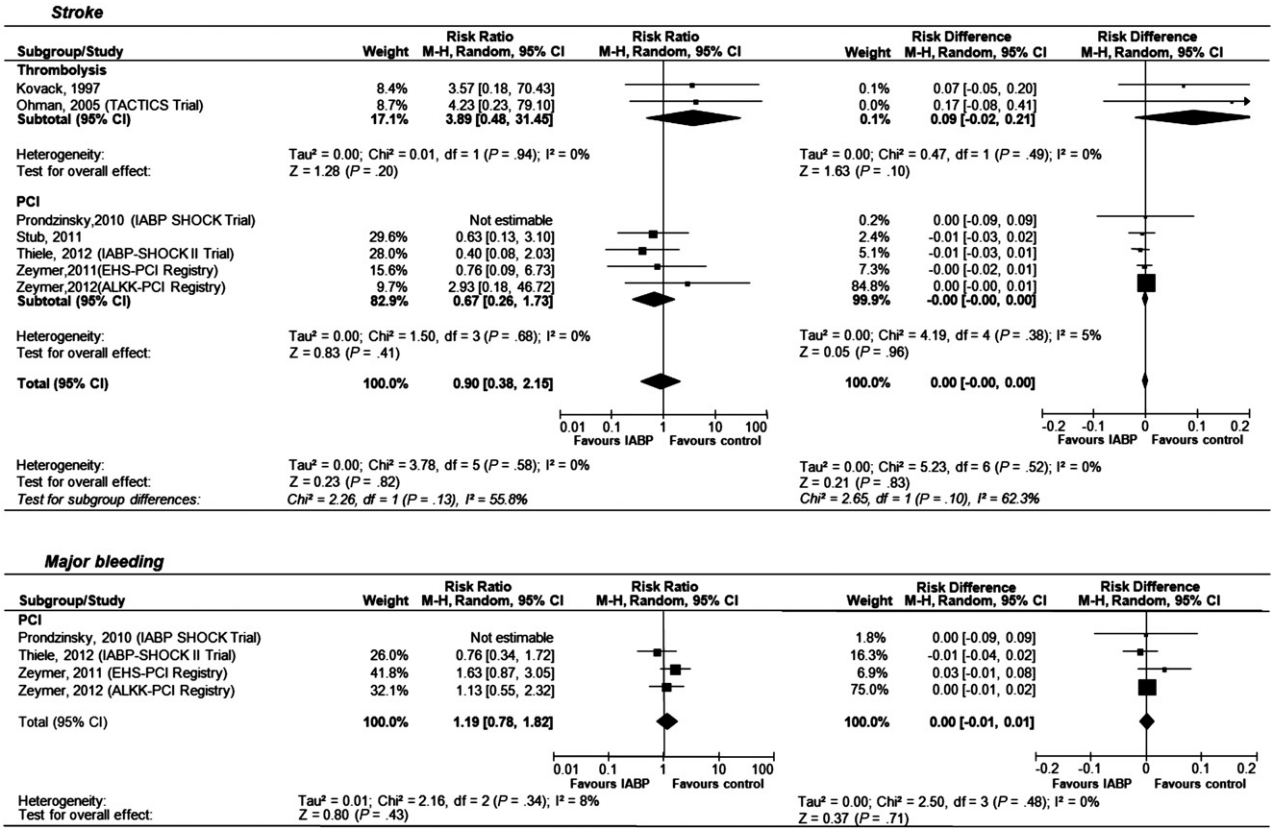
	No.	**M-H, random (95% CI)**	***P***	**No.**	**M-H, fixed (95% CI)**	***P***	**No.**	**M-H, random, (95% CI)**	***P***
Subgroup/RD results									
- No-reperfusion	2	–0.17 (–0.40 to 0.06)	.15	1	–0.29 (–0.47 to –0.12)	.0009			
- TT	8	–0.16 (–0.22 to –0.11)	<.0001	7	–0.18 (–0.20 to –0.16)	<.0001		Not performed	
- PCI	10	0.07 (0.01 to 0.12)	.01	2	0.06 (0.03 to 0.10)	.0008			
Overall	20	–0.04 (–0.12 to 0.03)	<.0001	10	–0.11 (–0.13 to –0.09)	<.0001			
Subgroup/RR results									
- No-reperfusion	2	0.83 (0.65 to 1.05)	.13						
- TT	8	0.77 (0.68 to 0.87)	<.0001		Not performed			Effect of therapeutic strategy not investigated	
- PCI	10	1.18 (1.04 to 1.34)	.01						
Overall	20	0.95 (0.83 to 1.10)	<.0001				6	0.72 (0.60 to 0.86)	0.0004

M-H, Mantel-Haenszel; *NI*, not included.
* All patients were included in the TT subgroup, independently of clinical treatment for AMI actually received.
† Number not reported.
‡ The data were analyzed as single group, regardless primary clinical treatment.
‖ Waksman: 16 patients with IABP support who underwent revascularization were excluded.
§ Stomel reported 3 groups: thrombolysis without IABP (n = 13), IABP without thrombolysis (n = 29), thrombolysis plus IABP (n = 22). Patients with IABP support without TT treatment were excluded.

survival, and (iii) safety end points (stroke and major bleeding) having selected the relevant data from the articles for an adequate analysis.

In our meta-analysis, the overall estimates of RR and RD showed no significant impact on inhospital mortality or long-term survival of IABP support in AMI complicated by CS. These results were likely caused by the inclusion of a large number of studies performed on patients undergoing PCI (published after 2009), which counterbalanced the effects of IABP support in no-reperfusion and TT patients. When separately examining the 3 subgroups of patients, no significant effect in favor of IABP support was observed in the no-reperfusion subgroup. In the TT subgroup, IABP support showed a significant decrease in the risk of inhospital mortality, whereas this procedure negatively affected survival in the PCI subgroup of patients. The 2 risk estimates were different, with the RR apparently inflating the detrimental effect of IABP. The discordant IABP effects among the 3 subgroups of patients were also confirmed by the test for subgroup

Figure 5



Meta-analysis on RR and RD of the safety end points. There are no significant differences between groups.

differences. No significant impact of IABP support was found on long-term survival.

Sjauw et al[26] showed a significant absolute reduction of inhospital mortality consequent upon the use of IABP. This observation was the result of 2 opposite effects: (i) the significant reduction of RD in both the no-reperfusion subgroup and the TT subgroup, and (ii), at the same time, the significant RD increase upon IABP use in patients undergoing PCI, reported in only 2 studies. The greater weight of the TT subgroup could have affected the overall RD effect estimates.

In contrast with our results and those of Sjauw et al,[26] Bahekar et al[27] reported a significant reduction in the RR of the inhospital mortality in patients with high-risk AMI with CS. However, they (i) performed the meta-analysis mainly on patients undergoing TT compared with them underwent PCI or surgical revascularization and (ii) did not take into account the primary medical treatment.

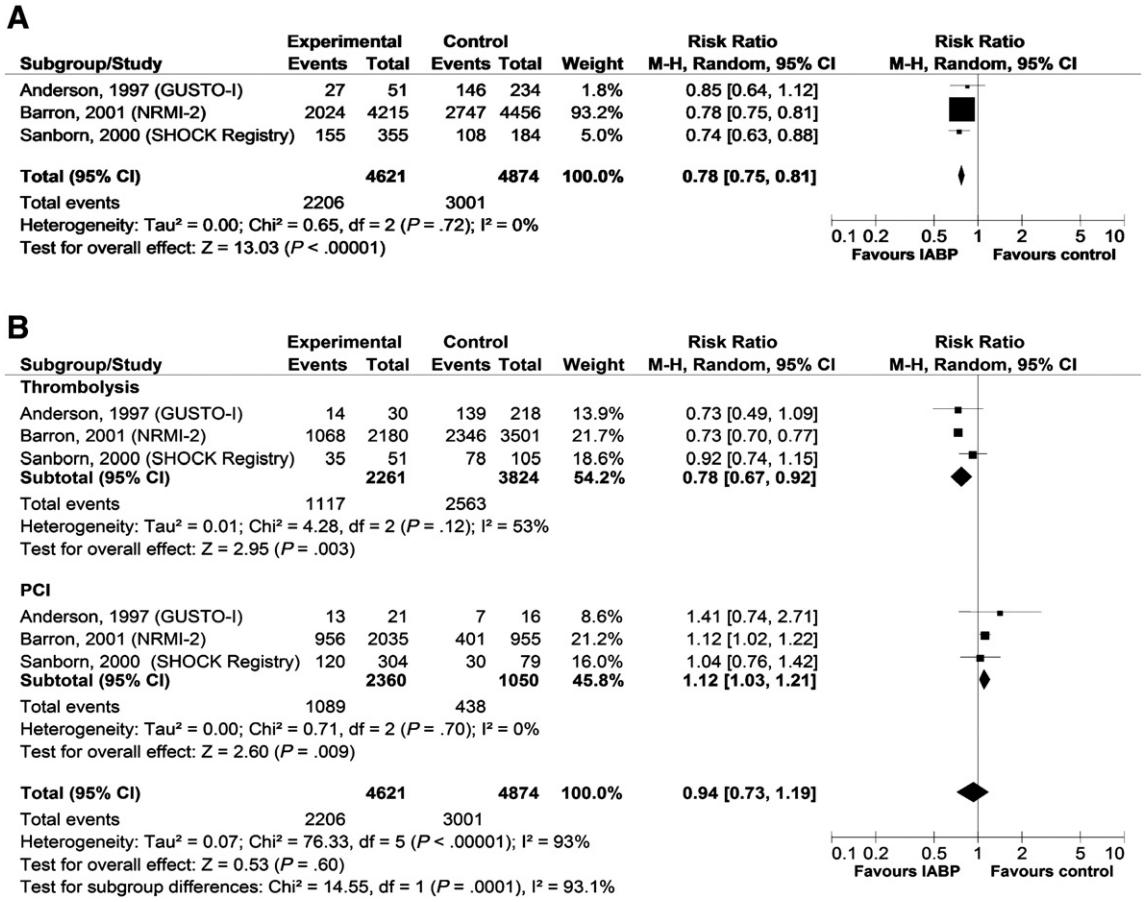
The confirmation of the importance of the evaluation of the primary clinical treatment is demonstrated by the reanalysis of the data from the studies by Anderson et al,[18] Barron et al,[19] and Sanborn et al,[16] who reported both subgroups TT and PCI. In the comparison between the experimental and control groups, regardless of the primary clinical treatment, we found a significant reduction of inhospital mortality in favor of the IABP support group. In contrast, in the subgroup comparisons according to the primary medical treatment, IABP support showed a significant protective effect in TT subgroup, significant nonprotective effect in PCI subgroup, and no significant effect on inhospital mortality of overall weighted RR estimate (Figure 6). The above shows that the overall estimate obtained from the comparison between the groups could be biased. In fact, the overall protective effect was likely caused by the larger size of the TT subgroup.

Similarly, we can suppose that the discordance between our results and those of Bahekar et al and Sjauw et al could come from the underestimation of the primary clinical treatment. The tests for subgroup differences (Table II) further supported the above conclusion.

Potential limitations

Meta-analyses of Obs represent an area of innovation in statistical science, and in contrast to RCTs, which are the

Figure 6



Meta-analysis on RR to examine the role of primary clinical treatment. The studies were analyzed regardless primary clinical treatment (**A**) and were subgrouped for the primary clinical treatment administered to the patients (**B**).

criterion standard for proving causation, Obs are prone to biases (including confounding). However, to adjust for unmeasured confounding, we combined random-effects models with probabilistic sensitivity analysis techniques. In addition, Concato et al[43] showed that the results of well-designed Obs (with either cohort or case-control design) do not systematically overestimate the magnitude of treatment effects compared with RCTs. The review on observational research by Bluhm[44] serves as a further reference on this topic.

Another potential limitation of the analysis is that the effect in favor of IABP in the no-reperfusion subgroup could be not significant because of the low power of the studies. The analysis of inhospital mortality observed in no-reperfusion, TT, and PCI subgroups shows that the mortality in patients without IABP support was highest when no reperfusion was performed (83.9%), decreased when TT was administered (66.9%), and was dramatically reduced when PCI was adopted (38.4%). These results suggest that IABP support may be useful when patients have no definitive reperfusion options, which is increasingly rare in the current clinical practice.

Conclusions

The present study objectively evaluated the efficacy of several interventions, combined the existing evidence to resolve issues with high uncertainty, and explored and explained differences among results from distinct studies. The lasting impact may include fostering the design and execution of new studies. Our results appear to confirm recent scientific evidence that recommends IABP under the logistic and environmental conditions in which TT is the preferred method of reperfusion, but the results do not show any benefit, and perhaps even a worsening, when AMI is acutely treated with PCI. However, before abandoning the use of IABP, we suggest testing its potential benefits through large RCTs aimed at assessing the effect of IABP in AMI complicated by CS in a thrombolytic-treated population and in the patients undergoing primary PCI.

Disclosures

No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Conflict of interest: None declared.

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