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Meta-analyses on intra-aortic balloon pump in cardiogenic shock complicating acute myocardial infarction may provide biased results

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Abstract. – OBJECTIVE: Intra-aortic balloon pump (IABP) is the device most commonly investigated in patients with cardiogenic shock (CS) complicating acute myocardial infarction (AMI). Recently meta-analyses on this topic showed opposite results: some complied with the actual guideline recommendations, while others did not, due to the presence of bias. We investigated the reasons for the discrepancy among meta-analyses and strategies employed to avoid the potential source of bias.

MATERIALS AND METHODS: Scientific databases were searched for meta-analyses of IABP support in AMI complicated by CS. The presence of clinical diversity, methodological diversity and statistical heterogeneity were analyzed. When we found clinical or methodological diversity, we reanalyzed the data by comparing the patients selected for homogeneous groups. When the fixed effect model was employed despite the presence of statistical heterogeneity, the meta-analysis was repeated adopting the random effect model, with the same estimator used in the original meta-analysis.

RESULTS: Twelve meta-analysis were selected. Six meta-analyses of randomized controlled trials (RCTs) were inconclusive because underpowered to detect the IABP effect. Five included RCTs and observational studies (Obs) and one only Obs. Some meta-analyses on RCTs and Obs had biased results due to presence of clinical and/or methodological diversity. The reanalysis of data reallocated for homogeneous groups was no more in contrast with guidelines recommendations.

CONCLUSIONS: Meta-analyses performed without controlling for clinical and/or methodological diversity, represent a confounding message against a good clinical practice. The reanalysis of data demonstrates the validity of the current guidelines recommendations in addressing clinical decision making in providing IABP support in AMI complicated by CS.

Key Words:
Cardiogenic shock, Intra-aortic balloon pump, Percutaneous coronary intervention, Myocardial infarction, Meta-analysis.

Introduction

Intra-aortic balloon pump (IABP) is the device most commonly investigated in patients (pts) with cardiogenic shock (CS) complicating acute myocardial infarction (AMI), despite it provides only a modest hemodynamic support to the failing heart[1-3]. In 2009 Sjauw et al[4] showed that there was insufficient evidence endorsing the current guideline recommendation (GR) for the use of IABP therapy in the setting of ST-elevation myocardial infarction (STEMI) complicated by CS. Moreover, they emphasized that the effectiveness of IABP support was related to the primary therapeutic strategy adopted in the treatment of AMI: it was useful when the thrombolysis (TT) was primary clinical treatment (PCT), while it was harmful when percutaneous coronary interventions (PCI) was the first choice for the treatment of AMI. Furthermore, Thiele et al[5,6] failed to demonstrate a benefit from IABP support in CS complicating AMI in pts undergoing PCI. In 2013 and in 2015 ACCF/AHA[7,8] and in 2014 and in 2015 ESC[9,10] released an updated guidelines for pts with CS complicating AMI and recommend IABP support in pts undergoing TT (Class I, level of evidence: A); on the contrary, when

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myocardial revascularization was achieved with PCI, routine use of IABP was not recommended (Class III, level of evidence: C). However, recent meta-analyses[4,11,12], with exception of some[13-21], are compliant with the current GR. We aimed at investigating the reasons for discrepancy among meta-analyses published from 2009 to (June 30) 2017 and the strategies employed to avoid the potential source of bias.

Materials and Methods

Search Strategy and Data Sources

We collected the meta-analyses of IABP support in AMI complicated by CS published from January 2009 until (June 30) 2017 from a literature search of the PubMed computerized database and the Cochrane Library, using the standard Medical Subject Heading terms "IABP" or "IABC," "AMI," and "CS". We conducted and reported this review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[22].

Data Extraction and Inclusion Criteria

Two investigators independently examined the design, patient populations, and the PCT for AMI complicated by CS in the meta-analyses comparing the effect of IABP support *vs.* standard treatment on early mortality (in-hospital or 30-day mortality). The search was restricted to English-language journals. Discrepancy in data extraction was resolved in discussion with a third author, until consensus was achieved.

Exclusion Criteria

We established as exclusion criteria meta-analyses in which coronary artery bypass grafting (CABG) was the method of myocardial reperfusion, mechanical support other than IABP and meta-analyses on this issue performed by any author of the present paper.

Risk of Bias Across Studies Included in the Meta-Analyses

We focused our attention on the effect of any kind of heterogeneity among studies included in meta-analyses. Specifically, we checked for: (i) variability in the participants, interventions and outcomes, termed as clinical diversity, (ii) variability in the study design and risk of bias, termed as methodological diversity and (iii) the variability in the effects of intervention among the studies, caused by clinical and/or methodological diversity, termed as statistical heterogeneity[23,24].

Clinical and methodological diversity were investigated by revising the original studies and checking both the design and the intervention, besides to the demographic and clinical characteristics of pts enrolled.

Statistical heterogeneity was investigated by the visual inspection of the reported Forest plot and/or by the reported results of the Cochrane Q and the I^2 statistics. We checked if the adopted estimator (risk ratio (RR), risk difference (RD) and Odd's ratio (OR)) and the model (Fixed or Random effect), were the most appropriate to deal with the heterogeneity among studies, if any.

Data Analysis

When we found clinical and/or methodological diversity, we reanalyzed the data by grouping pts into homogeneous groups.

In case of statistical heterogeneity, when all the dispersion in the observed effects could not be attributed to sampling error, but to the real difference in effect size across studies[23,24] and the original analysis was performed using the fixed effect model, we reanalyzed the data adopting the random effect model, with the same estimator of the original meta-analysis.

The revision process was performed with the Review Manager [Computer program] Version 5.3. (Copenhagen, Denmark)[25]. Forest plots were examined to detect homogeneity/heterogeneity among studies. Homogeneity/heterogeneity were quantified with the Cochrane Q-test and I^2 statistics. When subgroups were introduced, the test of subgroup difference was also performed to investigate the inconsistency among subgroups. Bidirectional, α error <0.05 was considered for statistical significance. Our results were then compared with those reported in the original meta-analyses.

Results

Twelve meta-analyses met the search criteria[4,11-21]. The selection strategy is reported in the Figure 1. Six of 12 selected articles analyzed the effect of IABP on AMI complicated or not by CS[15,16,18-21]. In the evaluation of CS complicating AMI, 6 meta-analyses included only randomized controlled trials (RCTs)[13,14,17,18,20,21], 5 included RCTs and observational studies (Obs)[11,12,15,16,19] and 1 only Obs[4]. Following, we report the design and the potential source of bias of the selected me-

ta-analyses grouping them into: meta-analyses of RCTs alone, Obs alone and Obs plus RCTs. Details of the studies and pts enclosed, the estimator, the model employed and the agreement with the current GR are reported in Table I. With respect to the meta-analyses by Romeo et al[11,12], we report in Table I only the design without any comment, due to contribution provided by authors of the present article.

Meta-Analyses of RCTs

Even if globally only 4 RCTs (1 not in English) were on pts with AMI complicated by CS (3 on pts treated with PCI, 1 on pts treated with TT alone)[5,26-28], the 6 selected meta-analyses include a different number of studies according to their design as follows:

1-2. Unverzagt et al[13] in their meta-analysis included only pts with AMI complicated by CS and compare the IABP effect both *vs.* control (3 RCTs) and *vs.* pLVADs (3 RCTs). Potential source of bias: we found clinical diversity in the analysis of 30-day mortality because pts were grouped regardless PCT for AMI[26-28]. Clinical diversity persisted in up-to-date meta-analysis[14].

3. Altayyar et al[17] in a meta-analysis of 4 RCTs assessed the effect of IABP on short-term mortality (in-hospital mortality and 30-day mortality) according to PCT for AMI.
   Potential source of bias: we found clinical diversity when they did not excluded pts affected by AMI not complicated by CS[26].
4. Su et al[18] in their meta-analysis of 17 RCTs, in 14 RCTs evaluated the effect of IABP support on short-term mortality in AMI complicated or not by CS.
   Potential source of bias: we found clinical diversity in the subgroup of pts with AMI complicated by CS with regard to PCT for AMI

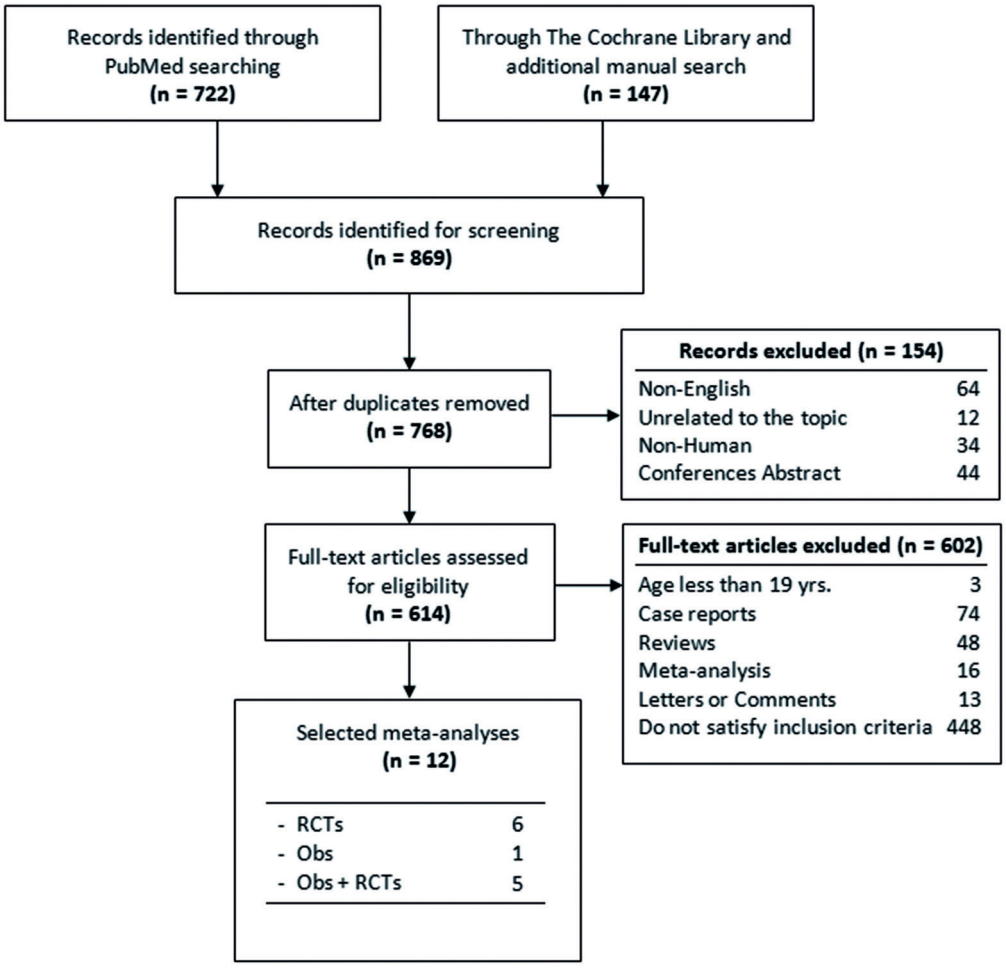

Figure 1. Flowchart of the study selection process. CS: cardiogenic shock; Obs: Observational studies; RCTs: Randomized controlled trials.

Table I. IABP effect vs control on early mortality in the meta-analyses of AMI complicated by CS.

Author	Period of interest	Number of studies included in the analysis of primary endpoint										Clinical characteristics								Meta-analysis				
		With CS			Without CS			With/Without CS			Overall	Type of Studies	Concurrent analysis of inhospital and 30 day mortality	Number of pts	PCT for AMI	Pts without CS incuded in the analysis	Control for confounders			Estimator	Model	Useful in decision making	Results against actual guidelines recommendation	Results against guidelines after reanalysis
		Obs	RCTs	**Total**	Obs	RCTs	**Total**	Obs	RCTs	**Total**							Subgroup analysis (with CS; without CS)	Subgroup analysis according to PCT	Simultaneous control for both confounders: CS and PCT					
Unverzagt et al[13]	1968 to January 2010	-	3[a]	**3**	-	-	**-**	-	-	-	**3**	RCTs	No	102	- TT - PCI	No	*Only CS*	No	===	**OR**	Random effect	No	Insufficient data[g]	----
Unverzagt et al[14]	1968 to October 2013	-	4[a]	**4**	-	-	**-**	-	-	**-**	**4**	RCTs	No	700	- TT - PCI	No	*Only CS*	No	===	**OR**	Random effect	No	Insufficient data[g]	----
Altayyar et al[17]	From inception to November 2014	-	3	**3**	-	-	**-**	-	1[b]	**1**	**4**	RCTs	Yes	735	- TT - PCI	Yes	No	Yes	No	**RR**	Fixed effect	No	Insufficient data[g]	----
Su et al[18]	1966 - 2014	-	3[c]	**3**	-	9	**9**	-	2[b]	**2**	**14**	RCTs	Yes	863 .	- TT - PCI	Yes	Yes	No	No	**RR**	Not reported	No	Insufficient data[g]	----
Wan et al[21]	From inception to May 2015	-	2	**2**	-	3	**3**	-	-	**-**	**5**	RCTs	Yes	638	- PCI *(- CABG)*[f]	Yes	Yes, in the analysis restricted to PCI studies. No, when considering also CABG studies	*Only PCI*	===	**RR**	Random effect	No	Insufficient data[g]	----
Zheng et al[20]	Until December 2015	-	2	**2**	-	4[e]	**4**	-	-	-	**6**	RCTs	Yes	640	- PCI	Yes	Yes	*Only PCI*	===	**OR**	Random effect	No	Insufficient data[g]	----
Sjauw et al[4]	1966 to December 2007	9[d]	-	**9**	-	-	-	-	-	**-**	**9**	Obs	Yes	10,529	- No reperfusion - TT - PCI	Yes	Yes	Yes	Yes	**RD**	Fixed effect	Yes	No	No
Bahekar et al[15]	1966 - 2009	6[c]	-	**6**	2	7	**9**	**-**	**-**	**-**	**15**	RCTs plus Obs	Yes	Not reported	- No reperfusion - TT - PCI	Yes	No	No	None	**RR**	Random effect	No	Yes	No
Romeo et al[11]	1986 - 2012	13[d]	3[a]	**16**	-	-	**-**	**-**	**-**	**-**	**16**	RCTs plus Obs	Yes	14,186	- No reperfusion - TT - PCI	No	*Only CS*	Yes	===	**RR, RD**	Random effect	Yes	No	----
Ahmad et al[16]	1950 -2014	12[c]	2	**14**	2	9	**11**	1	1[b]	**2**	**27**	RCTs plus Obs	Yes	13,880	- No reperfusion - TT - PCI	Yes	Yes *(irrespective for PCT)*	Yes *(irrespective for CS)*	No	**OR**	Random effect	No	Yes	No
Romeo et al[12]	1997 - 2015	11	2	**13**	-	-	**-**	-	-	-	13	RCTs plus Obs	Yes	8791	- PCI	No	*Only CS*	*Only PCI*	===	**RR**	Random effect	Yes	No	----
Fan et al[19]	From inception to May 2015	11[c]	3	**14**	3	6	**9**	-	-	-	**23**	RCTs plus Obs	Yes	Not reported	- No reperfusion - TT - PCI	Yes	Yes	No	None	**OR**	Random effect	No	Yes	No

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CS, cardiogenic shock; IABP, intra-aortic balloon pump; Obs, observational studies; PCI, percutaneous coronary intervention; PCT, primary clinical treatment; pts, patients; RCTs, randomized controlled trials; OR, odds ratio; RD, risk difference; RR, risk ratio; TT, thrombolysis. apts by TACTICS Trial without CS were excluded. bpts by TACTICS Trial without CS were not excluded. cThe study by Waksman et al was incorrectly classified as RCT. dThe study by Waksman et al was correctly classified as Obs. eInclude 2 studies on high risk PCI without CS. fStudies on CABG were excluded. gLow sample size related to the observed Relative Risk Reduction.

and the inclusion of pts with heart failure (Killip class ≥2). Furthermore, Obs by Waksman et al[29] was incorrectly classified as RCT.

5. Wan et al[21] in a meta-analysis of 12 RCTs evaluated the effects of IABP on short-term mortality in pts undergoing high-risk coronary revascularization with either CABG or PCI. Of the 5 RCTs on PCI, only 2 included pts with CS[5,28]. Potential source of bias: we found clinical diversity when pts with AMI undergoing PCI were grouped regardless the presence or the absence of CS.
6. Zheng et al[20] in a meta-analysis of 7 RCTs evaluated the effect of IABP support in pts undergoing PCI. In 6 RCTs was assessed the effect of IABP on 30-day mortality in the subgroups: (*1*) high risk-PCI without CS[30,31], (*2*) AMI complicated by CS[5,28] and (*3*) AMI uncomplicated[32,33]. Potential source of bias: we found clinical diversity in the sensitivity analysis performed in all 6 RCTs, using the leave-one-out approach, regardless to the clinical features of the subgroups.

Meta-Analysis of Obs

Sjauw et al[4] in meta-analysis of IABP in STEMI assessed the effect of IABP support in STEMI complicated by CS in 9 Obs. Pts were subgrouped according to PCTs for AMI in: no-reperfusion, TT and PCI. The analysis was performed using RD and fixed effect model.

Moreover, as previously described[11], pts by Sanborn et al[34] and Anderson et al[35] were all allocated in the TT subgroup, despite PCT of some of them was no-reperfusion or PCI.

Potential source of bias: the fixed effect model seems not appropriate because of the high heterogeneity observed into PCI subgroup (Chi^2=5.02, df=1 (p=0.03), I^2=80%).

Meta-Analyses of RCTs plus Obs

As listed below, the 5 meta-analyses[11,12,15,16,19] included a different number of studies according to their design:

1. Bahekar et al[15] in a meta-analysis of 6 RCTs and 9 Obs assessed the effect of IABP on in-hospital mortality in AMI complicated or not by CS. Potential source of bias: we found clinical diversity because the overall analysis was irrespective of the presence/absence of CS. However, PCT for AMI was never take into account and the numbers of pts/events analyzed were not reported. Furthermore, the Obs by Waksman et al[29] was incorrectly classified as RCT.
2. Ahmad et al[16] in a meta-analysis of 12 RCTs and 15 Obs assessed the effect of IABP support in AMI complicated or not by CS. Potential source of bias: the analysis of RCTs was irrespective of PCT for AMI. In the analysis of Obs, pts were grouped (*1*) according to the presence/absence of CS but neglecting the PCT for AMI, (*2*) according to the PCT for AMI but ignoring the presence/absence of CS. In the analysis of Obs, we found clinical diversity and statistical heterogeneity because pts by Sanborn et al[34] and Anderson et al[35] were all allocated in the TT subgroup, despite PCT of some of them was no-reperfusion or PCI. Pts by Brodie et al[36] were all allocated in AMI without CS despite 119 pts had CS; moreover, data of the in-hospital mortality were not available for subgroups of pts with and without CS.
3. Fan et al[19] evaluated the effect of IABP in AMI with or without CS in a meta-analysis of 15 RCTs and 18 Obs. Potential source of bias: in the analysis of data they did not take into account the presence/absence of CS nor the PCT for AMI, therefore causing clinical diversity. Moreover, the number of pts/events was not reported. Subsequently, when the analysis was restricted to the subgroup of pts with AMI complicated by CS, we found clinical diversity because it was irrespective of the PCT for AMI. In the analysis on midterm mortality, pts were grouped according to PCT for AMI, regardless the presence/absence of CS.

Reanalysis

We reanalyzed only the meta-analyses of Obs alone, or Obs plus RCTs. We did not reanalyze the meta-analyses of RCTs alone, because of the small number of studies and pts enrolled.

Meta-Analysis of Obs

Data by Sjaux et al[4] were reanalyzed using the random effect model. The results are reported in Table IIa. In TT subgroup the results were unchanged, due to the low heterogeneity. On the contrary, the harmful effect of IABP in PCI subgroup was no more significant.

Meta-analysis of Obs plus RCTs

1. We extracted and reanalyzed data from the 6 Obs included by Bahekar et al[15] in the analysis of AMI complicated by CS. Even if the overall effect is in favor of IABP, the heterogeneity is extremely high, so the result is misleading (Table IIb). Indeed, when taking into account the PCT for AMI,

Table II. Results of reanalysis.

	Original meta-analysis				After correction			
Meta-analyses	**Studies**	**I^2 (%)**	**Estimator [95% CI], model**	***p***	**Studies**	**I^2 (%)**	**Estimator [95% CI], model**	***p***
A) Sjauw et al[4]			RD, Mantel-Haenszel fixed				RD, Mantel-Haenszel random	
- No-reperfusion	1	NA*	-0.29 [-0.47, -0.12]	0.0009	2	81	-0.17 [-0.40, -0.06]	0.15
- TT	7	0	-0.18 [-0.20, -0.16]	<0.00001	7	29	-0.16 [-0.23, -0.10]	<0.00001
- PCI	2	80	0.06 [0.03, 0.10]	0.0008	4	51	0.08 [0.00, 0.16]	0.04
Overall	**9**	**94**	**-0.11 [-0.13, -0.09]**	**<0.0001**	**9**	**91**	**-0.08 [-0.18, 0.01]**	**0.08**
Test for subgroup differences:	Chi^2=127.92, df=2 (p< 0.00001), I^2=98.4%				Chi^2= 23.10, df = 2 (p < 0.00001), I^2 = 91.3%			
B) Bahekar et al[15]			RR, Mantel-Haenszel random				RR, Mantel-Haenzel random	
- No-reperfusion	-		Not Performed		1	NA*	0.92 [0.81, 1.05]	0.22
- TT	-		Not Performed		6	43	0.75 [0.64, 0.88]	0 .0005
- PCI	-		Not Performed		2	0	1.12 [1.03, 1.21]	0.009
Overall	**6**	**58.9**	**0.72 [-0.60,0.86]**	**0.0004**	**6**	**89**	**0.86 [0.72, 1.04]**	0.12
Test for subgroup differences:			No subgroups		Chi^2 = 20.55, df = 2 (p < 0.0001), I^2 = 90.3%			
C) Ahmad et al[16]			OR, Mantel-Haenszel random				OR, Mantel-Haenszel random	
-No-reperfusion	1	NA*	0.08 [0.00, 1.38]	0.08	2	55	0.35 [0.05, 2.60]	0.31
-TT	9	93	0.64 [0.34, 1.21]	0.17	7	0	0.48 [0.43, 0.54]	<0.00001
-PCI	6	96	1.96 [1.01, 3.83]	0.05	7	74	1.38 [1.04, 1.83]	0.02
Overall	**15**	**97**	**0.98 [0.59, 1.64]**	**0.95**	**12**	**92**	**0.84 [0.58, 1.21]**	**0.35**
Test for subgroup differences:	Chi^2 = 8.83, df = 2 (p = 0.01), I^2 = 77.3%				Chi^2 = 47.56, df = 2 (p = 0.004), I^2 = 95.8%			
D) Fan et al[19]			OR, Mantel-Haenszel random				OR, Mantel-Haenszel random	
-No-reperfusion	-		Not Performed		2	55	0.35 [0.05, 2.60]	0.31
-Thrombolysis	-		Not Performed		8	0	0.48 [0.43, 0.53]	<0.00001
-PCI	-		Not Performed		8	64	1.33 [1.05, 1.68]	0.02
Overall	**14**	**90.9**	**0.68 [0.49, 0.99]**	**0.045**	**14**	**91**	**0.81 [0.57, 1.15]**	**0.35**
Test for subgroup differences:			No subgroups		Chi^2 = 58.50, df = 2 (p < 0.00001), I^2 = 96.6%			

CI, confidence interval; CS, cardiogenic shock; OR, Odds ratio; PCI, percutaneous coronary intervention; RD, risk difference; RR, risk ratio; TT, thrombolysis. *Not applicable.

in TT subgroup the results were in favor of IABP, while an harmful IABP effect was observed into PCI subgroup.

2. In the reanalysis of data by Ahmad et al[16], we excluded pts with AMI without CS. The results showed a drastic reduction of heterogeneity within the TT subgroup (I^2 fall from 93% to 0%) and a significant protective effect of the IABP, which is not evident in the original analysis (Table IIc). On the contrary, IABP was significantly harmful in PCI subgroup, in which the heterogeneity, although reduced, was still high (I^2 fall from 96% to 74%) (Table IIc). To explain the source of the wide variation in mortality in control group observed by Ahmad et al[16], we plotted the event rate (with 95% confidence intervals) of in-hospital mortality in relation to the number of pts: (1) actually included in the meta-analysis, and (2) appropriately re-allocated, by excluding those without CS. As expected, the incidence of in-hospital mortality rate among pts with AMI complicated by CS was higher than in those without CS (Figure 2).
3. In the meta-analysis by Fan et al[19] we performed the reanalysis by grouping pts according to the PCT for AMI, excluding pts without CS (Table IId). The test for differences among the three subgroups indicated the presence of high heterogeneity. The results showed that the effect of IABP on in-hospital mortality was not significant in the no-reperfusion subgroup, while was significantly in favor of IABP in TT subgroup and significantly in disfavor in PCI subgroup.

Discussion

Some meta-analyses had been performed in the effort to clarify the utility of IABP in CS complicating AMI. However, the results were not always in agreement. In medical research it is undoubtedly that the best evidence comes from RCTs, while Obs are often considered studies of poorer quality. However, in the specific field of research on AMI complicated by CS, the randomization of pts undergoing IABP support is hard to achieve. Moreover, the occurrence of mortality at the baseline can be lower than expected when planning the RCTs, as highlighted by Perera et al[37] in a recent published editorial, in which they hypothesized "that the enrolled population was a lower risk cohort than predicted, or may reflect the advances that have been made in the management of cardiogenic shock". This lower basal risk results in a lower benefit that can be produced by the treatment under study[37,38]. In contrast, the fact that more pts have been studied with Obs shows the benefit of the latter to reflect a real clinical setting. As clearly stated by Anglemyer et al[39], factors other than study design *per se*, can account for disagreement between Obs and RCTs. Furthermore, apart from the comprehensiveness of the literature search, the clinical homogeneity/heterogeneity of the comparisons must be taken into account.

We could not reanalyze meta-analyses including only RCTs due to the low number of pts available. Meta-analyses of Obs either associated or not to RCT, in disagreement with the current GR, had many flaw in the design of the study and/or in the method chosen to analyze the data. Mainly, the effect of the IABP support was investigated without taking into account the PCT for AMI (i.e. no-reperfusion, TT or PCI) and/or the presence/absence of CS (Table I). When we reallocated the data according to PCT and CS status, the results were coherent with current GR. In particular the biased results from the meta-analysis by Bahekar et al[15] after the reanalysis were in favor of IABP only in subgroup treated with TT, while a detrimental IABP effect was evident when PCI was PCT for AMI (Table IIb), that was in accordance with the current GR. Furthermore, the meta-analysis by Ahmad et al[16] did not show any difference in mortality rate between IABP and control group because was affected by clinical diversity. Ahmad et al[16] did not take into account the presence/absence of CS or the PCT for AMI. The heterogeneity in the reanalysis decreased and was found a significant protective effect of IABP when TT was PCT for AMI (Table IIc). On the contrary, IABP was significantly harmful in PCI subgroup. These findings were in agreement with those by Sjauw et al[4] and Ro-

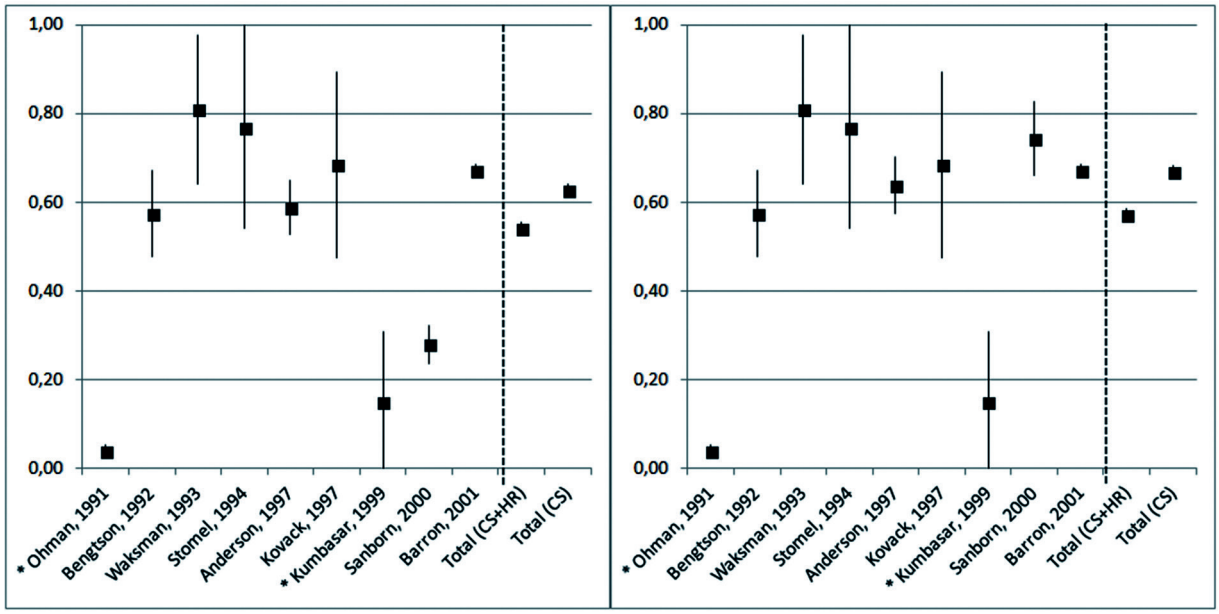

Figure 2. Mortality rate (with 95% confidence interval) in thrombolysis control subgroup by Ahmad et al[16] meta-analysis. ***A***, original analysis; ***B***, after the reanalysis of appropriate data by Sanborn et al[34] and Anderson et al[35]. Mortality rates of patients with CS (*without asterisk*) were higher than those of patients without CS (*with asterisk*), affecting the overall effect.

meo et al[11,12] and no longer in contrast with the GR (Table I and Table IIc). In addition, "because of the wide variation in event rate in the control groups", Ahmad et al[16] adopted OR as expression of study results. The wide variation in event rate in control group can be explained on the basis of the heterogeneity of pts included in the meta-analysis. The results of the reanalysis demonstrate that the basal risk of in-hospital mortality was significantly lower in AMI without CS with respect to AMI with CS, thus affecting the overall effect (Figure 2). Finally, Fan et al[19] chose to evaluate midterm mortality (from 30 day up to two months) arbitrarily, since the window for the definition of in-hospital mortality can exceed 30 days in case of complicated disease course. In addition, the separation between in-hospital and 30-day mortality yielded the reduction of the number of pts included in each analysis and the consequent loss of power in the evaluation of IABP effect. The high heterogeneity we found was caused by a biased analysis. When pts without CS were excluded and pts with AMI complicated by CS were grouped according to PCT for AMI, the results were compliant with the recommendations of the current guidelines (Table I, IId).

Conclusions

Controlling for statistical heterogeneity by the adoption of the correct estimator and model in performing a meta-analysis is not *di per se* sufficient to avoid erroneous results. When planning the meta-analysis, it is crucial to analyze any source of clinical heterogeneity in order to obtain results that help to identify which pts will benefit most, which is least likely to benefit, and who is at greatest risk of experiencing adverse outcomes by a treatment. The importance of accounting for clinical diversity was first demonstrated by Sjauw et al[4] since 2009; thereafter, the guidelines specifically linked the IABP recommendation to the therapeutic context. Therefore, the recent meta-analyses performed without controlling for clinical diversity represent a confounding message against a good clinical practice. The reanalysis performed in the present review, testing the potential bias, may demonstrate the validity of the current guidelines recommendations in addressing clinical decision of provide IABP support in pts with AMI complicate by CS.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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