Original Investigation

Intra-aortic Balloon Pump Therapy for Acute Myocardial Infarction
A Meta-analysis

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IMPORTANCE Intra-aortic balloon pump (IABP) therapy is a widely used intervention for acute myocardial infarction with cardiogenic shock. Guidelines, which previously strongly recommended it, have recently undergone substantial change.

OBJECTIVE To assess IABP efficacy in acute myocardial infarction.

DATA SOURCES Human studies found in Pubmed, Embase, and Cochrane libraries through December 2014 and in reference lists of selected articles. Search strings were "myocardial infarction" or "acute coronary syndrome" and "intra-aortic balloon pump" or "counterpulsation."

STUDY SELECTION Randomized clinical trials (RCTs) and observational studies comparing use of IABP with no IABP in patients with acute myocardial infarction.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted the data, and risk of bias in RCTs was assessed using the Cochrane risk of bias tool. We conducted separate meta-analyses of the RCTs and observational studies. Data were quantitatively synthesized using random-effects meta-analysis.

MAIN OUTCOMES AND MEASURES Thirty-day mortality.

RESULTS There were 12 eligible RCTs randomizing 2123 patients. In the RCTs, IABP use had no statistically significant effect on mortality (odds ratio [OR], 0.96 [95% CI, 0.74-1.24]), with no significant heterogeneity among trials (I^2 = 0%; P = .52). This result was consistent when studies were stratified by the presence (OR, 0.94 [95% CI, 0.69-1.28]; P = .69, I^2 = 0%) or absence (OR, 0.98 [95% CI, 0.57-1.69]; P = .95, I^2 = 17%) of cardiogenic shock. There were 15 eligible observational studies totaling 15 530 patients. Their results were mutually conflicting (heterogeneity I^2 = 97%; P < .001), causing wide uncertainty in the summary estimate for the association with mortality (OR, 0.96 [95% CI, 0.54-1.70]). A simple index of baseline risk marker imbalance in the observational studies appeared to explain much of the heterogeneity in the observational data (R^2_{meta} = 46.2%; P < .001).

CONCLUSIONS AND RELEVANCE Use of IABP was not found to improve mortality among patients with acute myocardial infarction in the RCTs, regardless of whether patients had cardiogenic shock. The observational studies showed a variety of mutually contradictory associations between IABP therapy and mortality, much of which was explained by the differences between studies in the balance of risk factors between IABP and non-IABP groups.

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Acute myocardial infarction complicated by cardiogenic shock has a mortality of more than 50%.[1,2] In this challenging clinical scenario, one therapeutic option is insertion of an intra-aortic balloon pump (IABP). The IABP, inserted via the femoral artery and positioned in the descending aorta, assists circulation. In systole, its deflation reduces ventricular workload and helps the ventricle push blood into the aorta. In diastole, its inflation enhances coronary artery perfusion and promotes flow to systemic organs.[3,4] Half of all patients with acute myocardial infarction and cardiogenic shock undergoing cardiac catheterization receive an IABP.[5]

Some observational studies had reported much better outcomes in patients receiving IABP therapy than in those not receiving it. The 2008 European[6] and 2009 American guidelines[7] issued class I recommendations for the use of IABP in acute myocardial infarction with cardiogenic shock. Within the past 5 years, however, new randomized clinical trial (RCT) data from the IABP-SHOCK II trial[2,8] prompted these guideline systems to soften their recommendations. The 2013 US guidelines reduced it to class IIa.[9] The 2014 European guidelines went farther, designating it as class III, which is reserved for therapies that are neutral or harmful.[10]

We conducted an updated meta-analysis examining all available observational and RCT evidence for the use of IABP in acute myocardial infarction, including the recent landmark RCT.[2] We address studies of patients with cardiogenic shock and those without, and patients treated either by no reperfusion, fibrinolysis (sometimes called thrombolysis), or primary percutaneous coronary intervention (PCI). Because of the potential for heterogeneity, it was important to consider a random-effects analysis approach. Because of the wide variation in event rate in the control groups, we used odds ratios (ORs) as the expression of the results of each study.

Studies have been reported to display a range of associations between IABP therapy and mortality. To make this easy to visualize, we devised a simple index of baseline risk marker imbalance in observational studies. This could be displayed as a metaregression plot, allowing the reader to infer from a group of observational studies the likely result of an observational study that had balanced risk markers in the treatment and control groups.

Methods

We carried out a meta-analysis of studies that evaluated IABP in acute myocardial infarction. We conducted the meta-analysis in accordance with published guidance.[11]

Search Strategy

We searched the MEDLINE, Cochrane, and Embase databases (1950 to December 2014) for all trials of IABPs. Our search strings were "myocardial infarction" or "acute coronary syndrome" and "intra-aortic balloon pump" or "counterpulsation." We excluded nonhuman studies.

Inclusion and Exclusion Criteria

Studies were eligible if they compared IABP recipients with a control group in the setting of acute myocardial infarction. Both observational studies and RCTs were separately identified. Studies of IABP therapy in elective PCI were not eligible.

Data Abstraction

Abstracts were reviewed by 2 authors (Y.A. and J.O.) to determine suitability for inclusion and full-text articles retrieved. Any disagreements were resolved by a third author (D.P.F.). Reference lists of retrieved articles, reviews, and meta-analyses were hand searched to identify additional studies.

Assessment of Risk of Bias

The RCTs were assessed using the Cochrane risk of bias tool,[12] which considers the quality of randomization, allocation concealment, blinding, incomplete outcome data, and the completeness of reporting of outcomes. The meta-analysis of observational studies was performed in accordance with published guidance.[13] In addition, we assessed baseline differences and considered methodological issues. Publication bias was investigated by means of a funnel plot.

Data Analysis

We conducted separate random-effects meta-analyses for the RCTs and the observational studies. The primary end point was 30-day mortality. We used Review Manager, version 5.2.1.[14] Heterogeneity[15] was assessed using the I^2 and τ^2 statistics.

Baseline Inequality Index

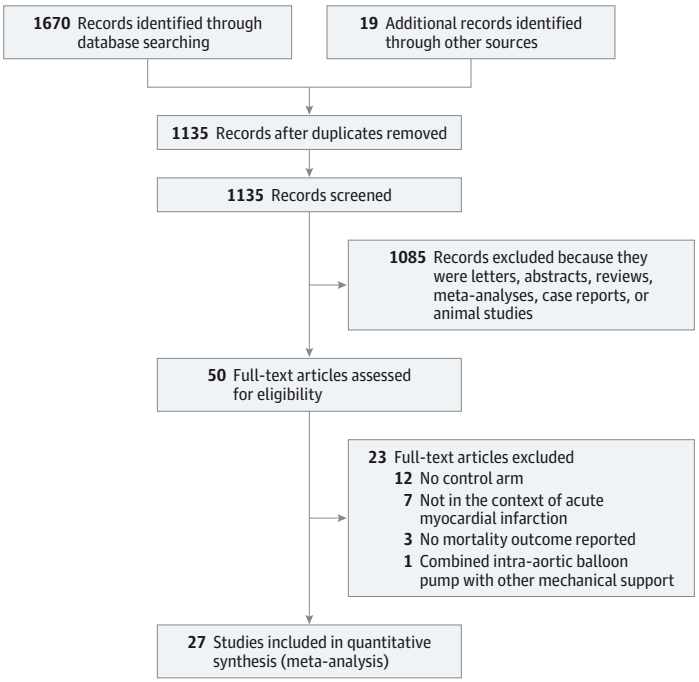
To assess the baseline inequality between treatment and control groups in observational studies, and its relationship with apparent benefit, we devised a simple baseline inequality index. It needed to be a method that could be applied across all studies even when data presentation was parsimonious, lacking standard deviation information.

To do this, we prepared a list of baseline characteristics that are recognized markers of risk, as follows: age, prior myocardial infarction, history of diabetes mellitus, heart failure, peripheral arterial disease, hypertension, presence of pulmonary edema, systolic blood pressure, and treatment with angioplasty (in which the lack of treatment would confer increased risk).

Within each study, and for each marker, we assessed whether the published central estimate (mean or median, whichever was reported) was higher in the IABP group than the control group (which we scored as +1) or lower (which we scored −1). If the values of a marker were equal or not given, we scored 0. For each study, we totaled this score.

For the observational studies, we devised a simple index of baseline inequality in risk factors between treatment and control groups. We then performed a random-effects metaregression using the baseline inequality index as a moderator using the statistical programming environment R[16] and its "metafor" package.[17] We generated a scatter plot showing the relationship between the log OR of death and the baseline inequality index, overlaid with the metaregression.

Figure 1. Search Strategy and Source of Included Studies



Results

Search Results

There were 12 eligible RCTs (3 in patients with[2,18,19] and 9 in patients without cardiogenic shock[20-28]) randomizing 2123 patients. There were 15 eligible observational studies[29-43] totaling 15 530 patients. The search strategy is outlined in **Figure 1**.

Characteristics of Studies and Risk of Bias

The study characteristics are shown in eTable 1 and eTable 2 in the Supplement. Two RCTs included patients who did not receive reperfusion therapy[20,23]; 2 included patients reperfused by fibrinolysis[18,22]; and the remaining 8 included patients receiving PCI.[2,19,21,24-28] In total, there were 1050 patients in the IABP groups and 1073 in the control groups in the RCTs. One observational study included patients who did not receive reperfusion therapy[34]; 8 included patients reperfused by fibrinolysis[29,31,33,35,37,38,42,43]; 1 included patients reperfused by either fibrinolysis or PCI[30]; and the remaining 5 included patients receiving PCI.[32,36,39-41] Eight of the 15 observational studies were single center,[30-32,36-38,41,42] whereas the remaining 7 were multicenter studies.[29,30,33,35,39,40,43]

Although none used a sham device and therefore all were unblinded, we believe that the use of mortality as the primary outcome would prevent the lack of blinding from contributing substantial bias. The summary table for risk of bias is shown in eTable 3 in the Supplement. Publication bias was assessed using a funnel plot, which did not show significant asymmetry (eFigure in the Supplement).

Randomized Clinical Trials

In the 12 RCTs (2123 patients) (**Figure 2**), there was no significant effect on mortality overall (OR, 0.96 [95% CI, 0.74-1.24]; $P = .74$). There was no significant evidence of heterogeneity ($\tau^2 = 0.00$, $I^2 = 0\%$; $P = .52$). There were 177 deaths in the 1050 patients randomized to IABP and 184 in the 1073 randomized to control.

In the patients with cardiogenic shock, the odds ratio was 0.94 (95% CI, 0.69-1.28; $P = .69$), whereas in those without shock it was 0.98 (95% CI, 0.57-1.69; $P = .95$). Three-quarters of deaths were in patients with cardiogenic shock: 134 of 177 (75.7%) in the IABP groups and 138 of 184 (75.0%) in the control groups.

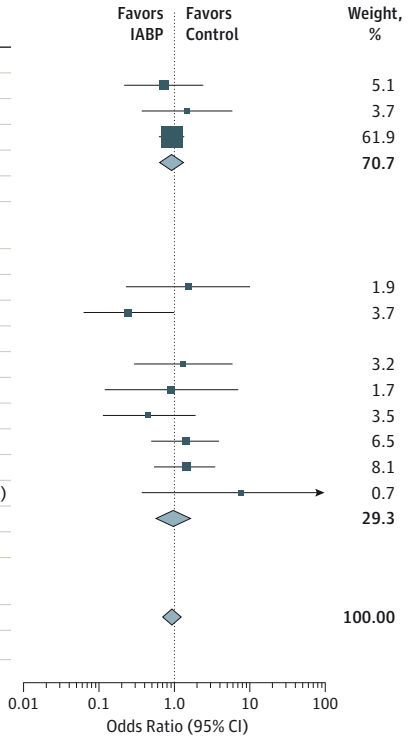
Observational Studies

In contrast, there was significant heterogeneity among the 15 nonrandomized studies ($\tau^2 = 1.04$, $I^2 = 97\%$; $P < .001$ [15 530 patients]). Assembled as a single group (**Figure 3**), they showed a neutral outcome (OR, 0.96 [95% CI, 0.54-1.70]; $P = .89$). There were 2904 deaths in the 6161 IABP recipients and 4147 in the 9369 patients who did not receive IABP.

The observational data can be considered in categories of patient status: with or without cardiogenic shock; or in categories of reperfusion strategy: no reperfusion, fibrinolysis, or primary PCI. The observational data in patients with cardiogenic shock showed statistically nonsignificant lower mortality in the IABP group (OR, 0.70 [95% CI, 0.47-1.05]; $P = .09$) albeit with significant heterogeneity ($I^2 = 92\%$, $\tau^2 = 0.36$; $P < .001$). In contrast, the studies addressing patients without cardiogenic shock showed a significant opposite association (OR, 7.73 [95% CI, 2.64-22.63]; $P < .001$), again with sig-

Figure 2. Randomized Controlled Trials Comparing Intra-Aortic Balloon Pump (IABP) Therapy With Control for the Outcome of Mortality in Patients With Acute Myocardial Infarction, Stratified by the Presence or Absence of Cardiogenic Shock

Study or Subgroup	IABP Events	IABP Total	Control Events	Control Total	Odds Ratio (95% CI)	Weight, %
Cardiogenic shock						
Ohman et al,[18] 2005	8	30	9	27	0.73 (0.23-2.27)	5.1
Prondzinsky et al,[19] 2010	7	19	6	21	1.46 (0.39-5.51)	3.7
Thiele et al,[2] 2012	119	300	123	298	0.94 (0.67-1.30)	61.9
Subtotal (95% CI)		**349**		**346**	**0.94 (0.69-1.28)**	**70.7**
Total events	**134**		**138**			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.62$, df = 2 ($P = .73$); $I^2 = 0\%$						
Test for overall effect: $z = 0.39$ ($P = .69$)						
No cardiogenic shock						
Flaherty et al,[20] 1985	4	10	3	10	1.56 (0.24-9.91)	1.9
Gu et al,[32] 2011	3	51	11	55	0.25 (0.07-0.96)	3.7
Kono et al,[22] 1996	0	23	0	22	Not estimable	
O'Rourke et al,[23] 1981	7	14	7	16	1.29 (0.30-5.43)	3.2
Ohman et al,[24] 1994	2	96	2	86	0.89 (0.12-6.48)	1.7
Patel et al,[28] 2011	3	161	7	176	0.46 (0.12-1.80)	3.5
Stone et al,[25] 1997	9	211	7	226	1.39 (0.51-3.81)	6.5
van 't Hof et al,[26] 1999	12	118	9	120	1.40 (0.57-3.45)	8.1
Vijayalakshmi et al,[27] 2007	3	17	0	16	7.97 (0.38-167.53)	0.7
Subtotal (95% CI)		**701**		**727**	**0.98 (0.57-1.69)**	**29.3**
Total events	**43**		**46**			
Heterogeneity: $\tau^2 = 0.10$; $\chi^2 = 8.43$, df = 7 ($P = .30$); $I^2 = 17\%$						
Test for overall effect: $z = 0.06$ ($P = .95$)						
Total (95% CI)		**1050**		**1073**	**0.96 (0.74-1.24)**	**100.00**
Total events	**177**		**184**			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 9.09$, df = 10 ($P = .52$); $I^2 = 0\%$						
Test for overall effect: $z = 0.33$ ($P = .74$)						
Test for subgroup differences: $\chi^2 = 0.02$, df = 1 ($P = .89$); $I^2 = 0\%$						



Odds ratios are calculated by random-effects Mantel-Haenszel analysis.

nificant heterogeneity (I^2 = 82%, τ^2 = 0.60; P = .003). Almost all deaths occurred in patients with cardiogenic shock: 2803 of the 2904 deaths (96.5%) in IABP recipients and 4068 of 4147 deaths (98.1%) in those who did not receive IABP.

The observational data in patients treated with primary PCI (**Figure 4**) showed higher mortality in the IABP recipients (OR, 1.96 [95% CI, 1.01-3.83]; P = .05) with significant heterogeneity (I^2 = 96%, τ^2 = 0.64; P < .001). In contrast, the studies addressing patients treated with fibrinolysis showed statistically nonsignificant lower mortality in the IABP recipients (OR, 0.64 [95% CI, 0.34-1.21]; P = .17), again with significant heterogeneity (I^2 = 93%, τ^2 = 0.72; P < .001). In the 1 study with neither fibrinolysis nor primary PCI, there was a finding of statistically nonsignificant lower mortality with IABP (OR, 0.08 [95% CI, 0.00-1.38]; P = .08). In patients receiving IABP therapy, mortality was equal in the fibrinolysis and primary PCI groups: 1440 of 2904 (49.6%). In patients not receiving IABP therapy, the majority of deaths were in the fibrinolysis group: 2922 of 4147 deaths (70.5%) occurred in the fibrinolysis group and 1210 of 4147 deaths (29.2%) in the PCI group.

Relationship Between Between-Group Difference in Mortality and Baseline Inequality in Risk Factors

A univariate metaregression analysis found a significant association between the baseline inequality score and the between-group difference in mortality (P = .002) (**Figure 5**). Whereas in the RCTs, the OR for mortality was uniform across trials (I^2 = 0%), in the observational studies it was extremely heterogeneous between the studies (I^2 = 97%). On metaregression analysis, much of this heterogeneity was explained by baseline imbalance in risk markers (R^2_{meta} = 46.2%; P < .001).

The metaregression analysis allows estimation from the observational studies of what the OR would be when the baseline inequality index is zero (ie, baseline risk markers balanced between study groups). This is the intercept of the regression line at the point where the baseline inequality index is zero. At this point, lnOR was 0.02 (95% CI, −0.53 to 0.56), which in terms of OR is 1.02 (95% CI, 0.59 to 1.76; P = .96).

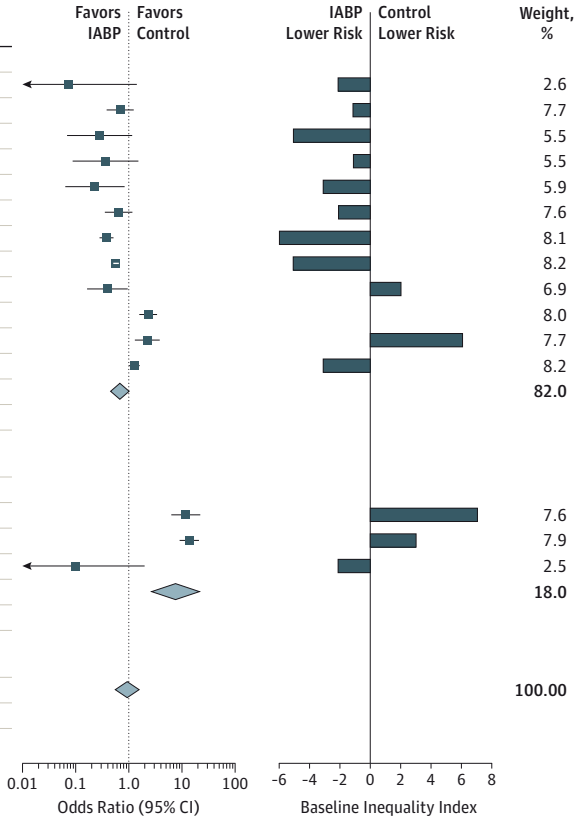
Discussion

Despite 3 decades of research, there is no prospectively specifiable group of patients with acute myocardial infarction whose mortality is reduced by the insertion of an IABP. The evidence covers more than 17 000 patients and spans the eras during which the concomitant therapy has been no reperfusion, fibrinolysis, and primary PCI. This neutral finding is consistent in patients with and without cardiogenic shock.

The results of the RCTs are extraordinarily uniform, with no statistically detectable heterogeneity. In contrast, in the larger and more representative populations addressed by the observational studies, there is very high heterogeneity. In these

Figure 3. Observational Studies Reporting on Intra-Aortic Balloon Pump (IABP) Therapy and the Outcome of Mortality in Patients With Acute Myocardial Infarction

Study or Subgroup	IABP Events	IABP Total	Control Events	Control Total	Odds Ratio (95% CI)
Cardiogenic shock					
Moulopoulos et al,[34] 1986	24	34	15	15	0.08 (0.00-1.38)
Bengtson et al,[31] 1992	48	99	58	101	0.70 (0.40-1.22)
Waksman et al,[38] 1993	11	20	17	21	0.29 (0.07-1.17)
Stomel et al,[37] 1994	28	51	10	13	0.37 (0.09-1.49)
Kovack et al,[33] 1997	9	27	13	19	0.23 (0.07-0.81)
Anderson et al,[29] 1997	30	62	146	248	0.65 (0.37-1.15)
Sanborn et al,[35] 2000	219	439	301	417	0.38 (0.29-0.51)
Barron et al,[30] 2001	2024	4215	2747	4455	0.57 (0.53-0.63)
Gu et al,[21] 2010	13	43	25	48	0.40 (0.17-0.94)
Zeymer et al,[39] 2011	92	162	177	491	2.33 (1.62-3.35)
Sjauw et al,[36] 2012	93	199	26	93	2.26 (1.33-3.85)
Zeymer et al,[40] 2013	212	487	533	1426	1.29 (1.05-1.59)
Subtotal (95% CI)		**5838**		**7347**	**0.70 (0.47-1.05)**
Total events	**2803**		**4068**		
Heterogeneity: $\tau^2 = 0.36$; $\chi^2 = 139.50$, df = 11 ($P < .001$); $I^2 = 92\%$					
Test for overall effect: $z = 1.71$ ($P = .09$)					
No cardiogenic shock					
Ohman et al,[43] 1991	27	85	28	725	11.59 (6.41-20.96)
Brodie et al,[41] 1999	74	213	48	1277	13.63 (9.11-20.40)
Kumbasar et al,[42] 1999	0	25	3	20	0.10 (0.00-2.02)
Subtotal (95% CI)		**323**		**2022**	**7.73 (2.64-22.63)**
Total events	**101**		**79**		
Heterogeneity: $\tau^2 = 0.60$; $\chi^2 = 11.38$, df = 2 ($P = .003$); $I^2 = 82\%$					
Test for overall effect: $z = 3.73$ ($P < .001$)					
Total (95% CI)		**6161**		**9369**	0.96 (0.54-1.70)
Total events	**2904**		**4147**		
Heterogeneity: $\tau^2 = 1.04$; $\chi^2 = 432.45$, df = 14 ($P < .001$); $I^2 = 97\%$					
Test for overall effect: $z = 0.14$ ($P = .89$)					
Test for subgroup differences: $\chi^2 = 16.80$, df = 1 ($P < .001$); $I^2 = 94.0\%$					



Odds ratios are calculated by random-effects Mantel-Haenszel analysis.

observational studies, there at first appear to be differences in outcome between patients with and without cardiogenic shock, with a trend toward lower mortality for patients with cardiogenic shock if they receive an IABP. However, these findings may result from the clear inequality of baseline risk factors, with the IABP recipients having a better baseline risk profile (Figure 3).

Such study-specific inequalities in baseline risk factors between therapy groups also appear to be responsible for the differing outcome associations between observational studies with no reperfusion, those with fibrinolysis, and those with primary PCI (Figure 3). In the majority of these studies, there was a clear tendency for the IABP recipients to have lower risk characteristics during the no-reperfusion and fibrinolysis eras (8 of 9 studies). The metaregression analysis (Figure 5) indicates baseline inequality to be a powerful driver of outcome differences between patient groups in observational studies. More importantly, this method of analyzing the observational studies highlights that an observational study with no baseline inequality would be expected to have equal mortality in the 2 study groups, a finding consistent with the RCT data where it can be observed more simply.

Our analysis extends the 2009 meta-analysis in several ways.[44] First, it incorporates important recent data sets including the large IABP SHOCK II RCT[2] and several large observational studies.[39,40] Second, it applies random-effects meta-analysis (rather than fixed effect) because there is severe heterogeneity among the observational studies (I^2 = 97%). Third, it includes 3 separate analyses of the observational studies: meta-analysis stratified by the presence or absence of cardiogenic shock, meta-analysis stratified by modality of reperfusion, and a metaregression analysis adjusting for baseline inequality index. Fourth, our analysis used OR as the summary statistic instead of risk difference. We chose OR because it allows fairer comparison of studies with different background risk levels. This may be important here because control group mortality varied among studies from 3.8%[41] to 80.9%.[38]

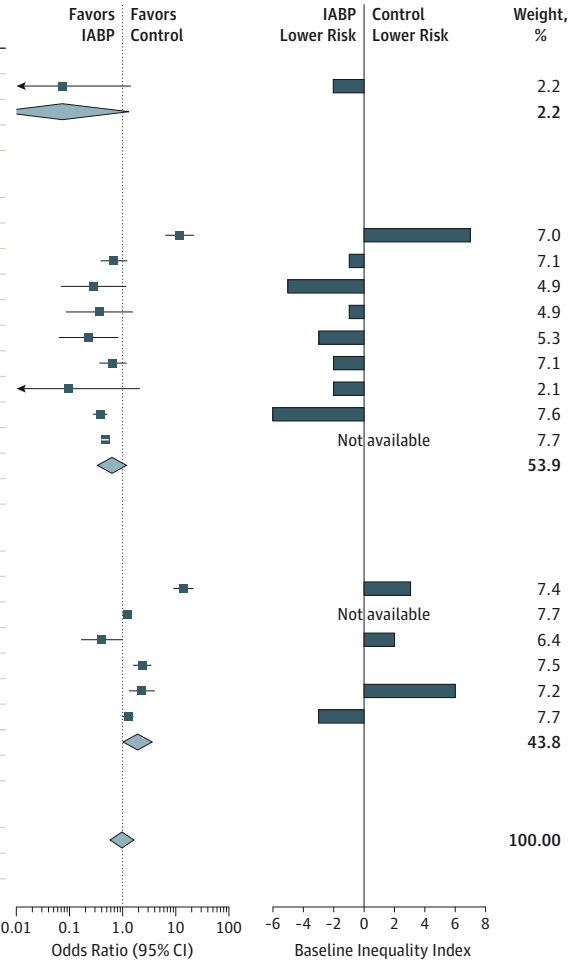
The Era of Appropriate Use

It can be difficult to change established clinical practice. In patients with cardiogenic shock, the prognosis is bleak, with few therapeutic options. A very large registry[30] showing better outcomes in patients with cardiogenic shock who receive IABP is frequently discussed, yet the extent of baseline patient inequality is rarely mentioned, perhaps because its importance is not universally realized. Charts such as Figure 4 and Figure 5 may assist clinicians in recognizing this.

In the challenging clinical situation of acute myocardial infarction complicated by cardiogenic shock, there is an understandable desire to do something rather than appear to do noth-

Figure 4. Observational Studies Reporting on Intra-Aortic Balloon Pump (IABP) Therapy and the Outcome of Mortality in Patients With Acute Myocardial Infarction, Stratified by Mode of Reperfusion (Primary Percutaneous Coronary Intervention, Fibrinolysis, or No Reperfusion)

Study or Subgroup	IABP Events	IABP Total	Control Events	Control Total	Odds Ratio (95% CI)	Weight, %
No reperfusion						
Moulopoulos et al,[34] 1986	24	34	15	15	0.08 (0.00-1.38)	2.2
Subtotal (95% CI)		**34**		**15**	**0.08 (0.00-1.38)**	**2.2**
Total events	**24**		**15**			
Heterogeneity: Not applicable Test for overall effect: $z = 1.74$ ($P = .08$)						
Fibrinolysis						
Ohman et al,[43] 1991	27	85	28	725	11.59 (6.41-20.96)	7.0
Bengtson et al,[31] 1992	48	99	58	101	0.70 (0.40-1.22)	7.1
Waksman et al,[38] 1993	11	20	17	21	0.29 (0.07-1.17)	4.9
Stomel et al,[37] 1994	28	51	10	13	0.37 (0.09-1.49)	4.9
Kovack et al,[33] 1997	9	27	13	19	0.23 (0.07-0.81)	5.3
Anderson et al,[29] 1997	30	62	146	248	0.65 (0.37-1.15)	7.1
Kumbasar et al,[42] 1999	0	25	3	20	0.10 (0.00-2.02)	2.1
Sanborn et al,[35] 2000	219	439	301	417	0.38 (0.29-0.51)	7.6
Barron et al,[30] 2001	1068	2180	2346	3500	0.47 (0.42-0.53)	7.7
Subtotal (95% CI)		**2988**		**5064**	**0.64 (0.34-1.21)**	**53.9**
Total events	**1440**		**2922**			
Heterogeneity: $\tau^2 = 0.72$; $\chi^2 = 117.96$, df = 8 ($P < .001$); $I^2 = 93\%$ Test for overall effect: $z = 1.37$ ($P = .17$)						
Primary percutaneous coronary intervention						
Brodie et al,[41] 1999	74	213	48	1277	13.63 (9.11-20.40)	7.4
Barron et al,[30] 2001	956	2035	401	955	1.22 (1.05-1.43)	7.7
Gu et al,[21] 2010	13	43	25	48	0.40 (0.17-0.94)	6.4
Zeymer et al,[39] 2011	92	162	177	491	2.33 (1.62-3.35)	7.5
Sjauw et al,[36] 2012	93	199	26	93	2.26 (1.33-3.85)	7.2
Zeymer et al,[40] 2013	212	487	533	1426	1.29 (1.05-1.59)	7.7
Subtotal (95% CI)		**3139**		**4290**	**1.96 (1.01-3.83)**	**43.8**
Total events	**1440**		**1210**			
Heterogeneity: $\tau^2 = 0.64$; $\chi^2 = 139.81$, df = 5 ($P < .001$); $I^2 = 96\%$ Test for overall effect: $z = 1.98$ ($P = .05$)						
Total (95% CI)		**6161**		**9369**	0.98 (0.59-1.64)	**100.00**
Total events	**2904**		**4147**			
Heterogeneity: $\tau^2 = 0.89$; $\chi^2 = 493.04$, df = 15 ($P < .001$); $I^2 = 97\%$ Test for overall effect: $z = 0.07$ ($P = .95$) Test for subgroup differences: $\chi^2 = 8.83$, df = 2 ($P = .01$); $I^2 = 77.3\%$						



Odds ratios are calculated by random-effects Mantel-Haenszel analysis.

ing. This natural human tendency is established in the behavioral literature as "action bias."[45] With the greater data set now available, and the increasing focus on judicious use of limited resources, it is our duty to be continually reassessing the net utility of interventions.

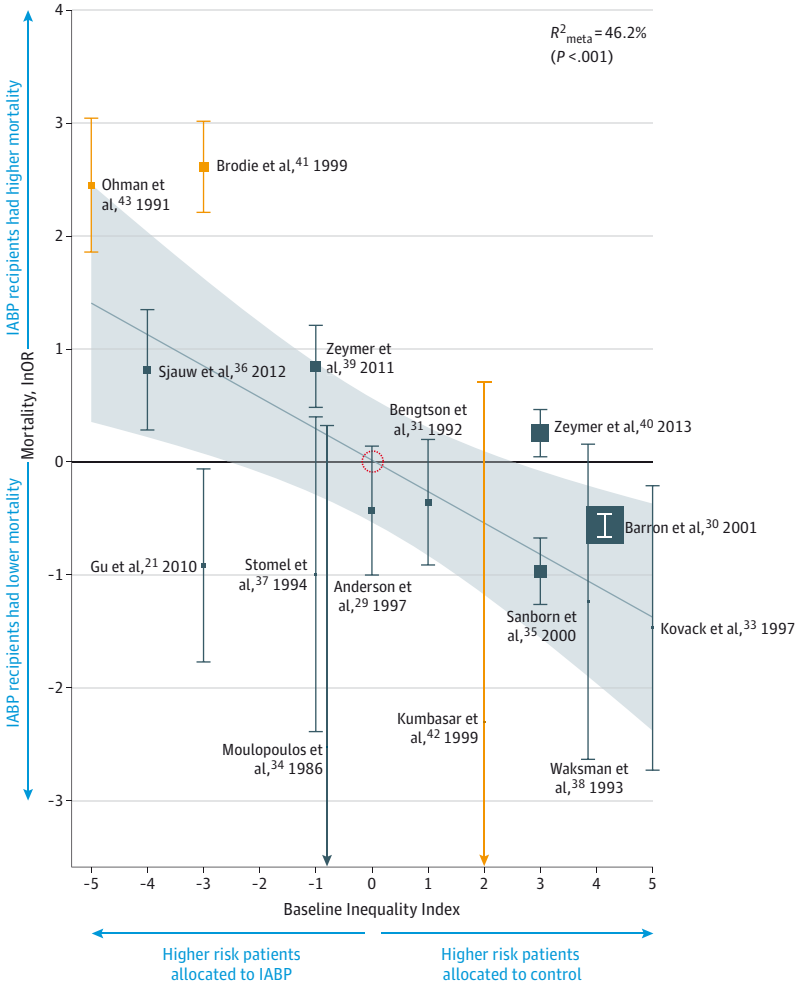
Limitations

We only examined results of published studies and cannot exclude the possibility that there are studies with other results that have not been published. Furthermore, the lack of statistically significant evidence of publication bias on the funnel plot does not give complete reassurance.

The RCTs have provided a very consistent result in terms of low heterogeneity between trials; the observational studies, in contrast, have shown intense heterogeneity. However, it should be remembered that RCTs can only cover the subset of patients who agree to be randomized. With few exceptions,[2] RCT entrance criteria are restrictive, which may limit their representativeness. The requirement for prior written informed consent limits the patients who could even be considered for an RCT, a limitation that is only now being addressed by new trial designs,[46] which are controversial.[47] Randomized clinical trials also often require a complex series of follow-up assessments, which can affect who will agree to be enrolled. Moreover, the intensely supervised environment of RCTs can deliver different concomitant care than that experienced by the general patient population to whom the results will eventually be applied.

The outcome assessed in this study was 30-day mortality, chosen because the ultimate motivation for IABP use is to improve the high mortality in these patients. Moreover, it can be assessed without bias, which is important because all the studies were unblinded. There may be other benefits of IABP, but there are challenges to using them for guiding recommendations for therapy. For example, hemodynamic aspects such as cardiac output and blood pressure are consistently increased by IABP therapy, but this has not translated into a beneficial effect on mortality. Other clinical end points are available, but measuring the effect of IABP without bias in an unblinded study is challenging, even with randomization. Length of stay, for ex-

Figure 5. Metaregression Analysis of the Relationship Between the Baseline Inequality Index and Odds Ratio (OR) of Mortality Between Intra-Aortic Balloon Pump (IABP) and Control in Observational Studies



The baseline inequality index explains almost half of the variance between included studies. The index was also significantly associated with mortality (*P* = .002). Notably, when the difference in the baseline inequality index was zero (y-intercept, red circle) there was no difference in mortality between the IABP and control groups (OR, 0.02 [95% CI, −0.53 to 0.56]; *P* = .96). Meta-regression analysis was performed using restricted maximum likelihood estimation. Symbols indicate ORs, and error bars, 95% CIs. Gray shading indicates the 95% CIs around the regression line. Blue and orange symbols indicate patients with and without cardiogenic shock, respectively. Size of data markers indicates study weight.

ample, is decided by physicians. Better ventricular function or quality of life are desirable, but relying on them as end points requires elaborate steps to deliver blinding. Without blinding, there can be inadvertent assessment bias, and the magnitude of this can be surprisingly large.[48,49]

In contrast to RCTs, observational studies can cover more comprehensive cohorts of patients and provide larger data sets. They can provide important data on the magnitude of health care problems and identify cohorts with particularly bad outcomes. The challenge in interpreting the outcome associations of therapy in an individual observational study is that there may be baseline imbalance between study groups.[50] This can cause the results to not point in the same direction as RCTs, a lesson painfully learned with estrogen therapy for prevention of ischemic heart disease.[51] It is important that well-conducted observational studies provide baseline information because this allows analyses such as those in Figures 3, 4, and 5, which may help reconcile results of observational studies with those of RCTs.

The baseline inequality index is a nonparametric score. In attempting to quantify unequal baseline allocation of high-risk patients, we used an approach that readers can understand and reproduce easily. Although more advanced scores might be more desirable in principle, many studies do not report information that would be necessary, for example presenting the mean without the standard deviation.

Conclusions

Intra-aortic balloon pump therapy has now been studied for 30 years, in the context of no reperfusion, fibrinolysis, and primary PCI. Intra-aortic balloon pump therapy does not improve mortality in acute myocardial infarction in the populations studied in RCTs, regardless of the presence or absence of cardiogenic shock. Overall, the observational studies also did not show better outcomes for patients treated with IABP. There was, however, substantial heterogeneity among the observational studies with IABP. These differences may be explained by the different baseline inequalities in the different observational studies.

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Editor's Note

High-Risk Medical Devices
Why Do We Not Better Understand Effectiveness and Safety?

Joseph S. Ross, MD, MHS

The intra-aortic balloon pump (IABP), a mechanical device designed to increase both myocardial perfusion and cardiac output, was pioneered in the 1960s to treat patients in cardiogenic shock. An innovation at the time, the device was made available for use prior to passage of the 1976 Medical Device Amendments, which gave the US Food and Drug Administration (FDA) authority to require evidence of effectiveness and safety for high-risk medical devices before granting market clearance. It is likely that no clinical data were submitted for FDA review prior to market clearance of the IABP. More than 70 000 IABPs are inserted annually in the United States for a broad array of indications including acute coronary syndromes, cardiac surgery, complications of heart failure, and cardiogenic shock. Some estimate that half of all patients hospitalized for acute myocardial infarction (AMI) complicated by cardiogenic shock receive IABP therapy.

Related articles pages 931 and 941

The evidence to support IABP therapy has never been as strong as the enthusiasm for its use. In this issue of *JAMA Internal Medicine*, Ahmad and colleagues[1] systematically reviewed and meta-analyzed the published evidence examin-