The outcomes of intra-aortic balloon pump usage in patients with acute myocardial infarction: a comprehensive meta-analysis of 33 clinical trials and 18,889 patients

Zhong-Guo Fan1,* Xiao-Fei Gao1,2,* Li-Wen Chen1 Xiao-Bo Li1,2 Ming-Xue Shao1,2 Qian Ji1 Hao Zhu1 Yi-Zhi Ren1 Shao-Liang Chen1,2 Nai-Liang Tian1,2

1Department of Cardiology, Nanjing First Hospital, Nanjing Medical University, 2Department of Cardiology, Nanjing Heart Center, Nanjing, People’s Republic of China

*These authors contributed equally to this work

Background: The effects of intra-aortic balloon pump (IABP) usage in patients with acute myocardial infarction remain controversial. This study sought to evaluate the outcomes of IABP usage in these patients.

Methods: Medline, EMBASE, and other internet sources were searched for relevant clinical trials. The primary efficacy endpoints (in-hospital, midterm, and long-term mortality) and secondary endpoints (reinfarction, recurrent ischemia, and new heart failure in the hospital) as well as safety endpoints (severe bleeding requiring blood transfusion and stroke in-hospital) were subsequently analyzed.

Results: Thirty-three clinical trials involving 18,889 patients were identified. The risk of long-term mortality in patients suffering from acute myocardial infarction was significantly decreased following IABP use (odds ratio [OR] 0.66, 95% confidence interval [CI]: 0.48–0.91, P=0.010). Both in-hospital and midterm mortality did not differ significantly between the IABP use group and no IABP use group (in-hospital: OR 0.87, 95% CI: 0.59–1.28, P=0.479; midterm: OR 1.12, 95% CI: 0.53–2.38, P=0.768). IABP insertion was not associated with the risk reduction of reinfarction, recurrent ischemia, or new heart failure. However, IABP use increased the risk of severe bleeding requiring blood transfusion (OR 2.05, 95% CI: 1.29–3.25, P=0.002) and stroke (OR 1.71, 95% CI: 1.04–2.82, P=0.035). In the thrombolytic therapy and cardiogenic shock subgroups, reduced mortality rates following IABP use were observed.

Conclusion: IABP insertion is associated with feasible benefits with respect to long-term survival rates in patients suffering from acute myocardial infarction, particularly those suffering from cardiogenic shock and receiving thrombolytic therapy, but at the cost of higher incidence of severe bleeding and stroke.

Keywords: intra-aortic balloon pump, acute myocardial infarction, cardiogenic shock, thrombolytic therapy, meta-analysis

Introduction

Patients suffering from acute myocardial infarction (AMI) are at an increased risk for high mortality, particularly in the setting of AMI complicated by cardiogenic shock (CS), although both emergency revascularization (ERV) and thrombolysis have been widely used.1 The intra-aortic balloon pump (IABP) has been widely used since it was first used clinically in 1968. It improves diastolic coronary blood flow and reduces both afterload and myocardial oxygen demand,2 changes thought to have positive effects on myocardial recovery following AMI.3,4
According to the American College of Cardiology and American Heart Association (ACC/AHA 2012) guidelines, IABP was recommended for CS and its insertion was suggested at the completion of coronary angiography and revascularization (IIa). The European Society of Cardiology guidelines also recommended IABP as a bridge to reperfusion for patients suffering from CS. In recent years, several large randomized controlled trials (RCTs) and meta-analyses have demonstrated only limited or even no benefits with respect to midterm and long-term all-cause mortality in patients with AMI complicated by CS for whom early revascularization was planned. However, two other meta-analyses have demonstrated that IABP has a positive impact with respect to all-cause mortality in these patients for whom thrombolysis was used as a preferred reperfusion strategy. These conflicting data challenged the recommendations of the current guidelines and these aforementioned meta-analyses did not include all the available relevant clinical trials. Therefore, we sought to conduct an updated, comprehensive meta-analysis involving as many clinical trials as possible to evaluate the evidence pertaining to the performance of IABP performed as an adjunct therapy in patients suffering from an AMI complicated with CS or not.

Methods

Literature search

We searched Medline, EMBASE, and the Cochrane Controlled Trials Registry from their dates of inception until May 2015 for clinical trials comparing outcomes following IABP use with outcomes in the absence of IABP use (defined as the Control group) following AMI. To be certain all relevant studies were included, the electronic databases were searched using combinations of several relevant keywords, including intra-aortic balloon pump, counterpulsation, acute myocardial infarction, and clinical trials. All potentially relevant articles and references from published reviews and meta-analyses were subsequently screened for eligibility.

Inclusion and exclusion criteria

The articles were required to meet the following criteria: 1) adult patients suffering from AMI (age from 18 to 90 years), regardless of CS and 2) clinical trials comparing an IABP group and a control group. The exclusion criteria were as follows: 1) nonhuman or ongoing studies; 2) non-English language studies; 3) reviews or meta-analyses; 4) duplicated studies or different studies using the sample; and 5) patients supported by other cardiac assist devices.

Data extraction, synthesis, and quality assessment

Two investigators (FZG and GXF) independently reviewed all relevant articles to assess their eligibility, using standardized data-abstraction forms. Disagreements were resolved by a third investigator (CLW). We extracted the following data from each included study: the name of the trial or first author, publication year, inclusion and exclusion criteria, baseline demographics, and clinical outcomes at the hospital and/or during follow-up. All included studies were divided into two subgroups based on the design of each study, described as RCTs and observational clinical trials (Obs). To account for the effects of treatment, we also grouped the studies by type of reperfusion, as follows: no reperfusion, ERV alone, including either percutaneous transcoronary angioplasty or coronary artery bypass grafting, thrombolytic therapy alone (TT alone), and ERV plus TT. However, the patients with CS were selected as another subgroup to determine whether they responded to IABP insertion. Moreover, the patients with AMI were divided into two subgroups based on whether they underwent IABP insertion before or after reperfusion to determine the best opportunity for IABP insertion. The quality of all retrieved studies was assessed to ensure minimization of bias, but no formal scoring system was used.

Study endpoints

The primary efficacy endpoint was the rate of all-cause mortality, which was evaluated across three periods based on the follow-up durations of the included trials, including in-hospital mortality, midterm mortality (defined as mortality between 30 days and 2 months), and long-term mortality (defined as mortality after 6 months), and the secondary efficacy endpoints were new heart failure, reinfarction, and recurrent ischemia during hospitalization. The incidences of stroke and severe bleeding requiring blood transfusion in-hospital were evaluated as safety endpoints. The rates of all-cause mortality and new heart failure could be replaced by cardiac death and pulmonary edema, respectively, if the included articles did not have the relevant data. The definitions of the clinical endpoints varied slightly among the included trials, and we evaluated the clinical endpoints using standardized definitions.

Statistical analysis

All endpoints were treated as dichotomous variables, which were analyzed using odds ratio (OR) with 95% confidence interval (CI). Statistical heterogeneity among the included studies was measured using the Cochrane’s Q test and the
Primary efficacy endpoint

In-hospital mortality

As shown in the Figure 2A, the overall risk of in-hospital mortality was not reduced significantly following IABP use (OR 0.87, 95% CI: 0.59–1.28, \( P=0.479 \); \( P<0.001 \), \( I^2=90.6\% \)); similar results were observed for both the RCTs and Obs (RCT: OR 0.89, 95% CI: 0.54–1.49, \( P=0.669 \); \( P=0.298 \), \( F=15.7\% \); Obs: OR 0.84, 95% CI: 0.52–1.35, \( P=0.467 \); \( P<0.001 \), \( I^2=94.4\% \)). The results of the Egger’s test indicted that no publication bias was encountered (\( P=0.406 \), 0.325, 0.175 for Obs, RCT, and overall, respectively).

Midterm mortality

The comparison between IABP use and no IABP use demonstrated no significant differences with respect to the risk of midterm mortality (OR 1.12, 95% CI: 0.53–2.38, \( P=0.768 \); \( P<0.001 \), \( I^2=93.4\% \); Figure 2B), as well as no significant reductions in risk in the RCTs and Obs (RCT: OR 0.84, 95% CI: 0.43–1.64, \( P=0.609 \); \( P=0.122 \), \( F=45.0\% \); Obs: OR 1.18, 95% CI: 0.40–3.47, \( P=0.760 \); \( P<0.001 \), \( I^2=95.5\% \)). No publication bias was observed based on the results of
Table 1 The characteristics of randomized controlled trials pertaining to the use of an intra-aortic balloon pump in the setting of AMI

| Study                          | Publication year | Type of reperfusion | Inclusion criteria                                    | Excluded CS | Follow-up duration (d) |
|-------------------------------|------------------|---------------------|-------------------------------------------------------|-------------|------------------------|
| Waksman et al<sup>19</sup>    | 1993             | Thrombolysis        | AMI with CS                                           | No          | 360                    |
| TACTICS<sup>17</sup>          | 2005             | Thrombolysis, RV    | AMI with hypotension or severe HF                     | No          | 30, 180                |
| Li et al<sup>27</sup>         | 2007             | RV                  | AMI with CS                                           | No          | 360                    |
| SHOCK Trial<sup>28</sup>      | 2010             | ERV                 | AMI with CS                                           | No          | In-hospital            |
| IABP-SHOCK II<sup>18</sup>    | 2013             | ERV                 | AMI with CS                                           | No          | 30, 360                |
| O’Rourke et al<sup>22</sup>   | 1981             | No reperfusion      | AMI with acute HF                                     | NA          | 450                    |
| Flaherty et al<sup>15</sup>   | 1985             | No reperfusion      | AMI without CS                                        | Yes         | 14, 60                 |
| Ohman et al<sup>11</sup>      | 1994             | ERV                 | AMI without CS                                        | Yes         | In-hospital            |
| Kono et al<sup>21</sup>       | 1996             | Failed thrombosis   | AMI without CS                                        | Yes         | 30                     |
| PAMI-II<sup>44</sup>          | 1997             | ERV                 | AMI without CS                                        | Yes         | In-hospital            |
| Vijayalakshmi et al<sup>24</sup> | 2007         | ERV                 | AMI without CS                                        | Yes         | 30                     |
| Gu et al<sup>27</sup>         | 2011             | ERV                 | AMI without CS                                        | Yes         | 30, 180                |
| CRISP AMI<sup>30</sup>        | 2011             | ERV                 | AMI without CS                                        | Yes         | 30, 180                |
| BCIS-I<sup>10</sup>           | 2013             | ERV                 | AMI without CS                                        | Yes         | 1,530                  |
| Van’t Hof et al<sup>23</sup>  | 1999             | ERV                 | AMI with ST↑/↓>20 mm                                   | NA          | 180                    |

Abbreviations: AMI, acute myocardial infarction; CS, cardiogenic shock; d, days; ERV, emergency revascularization; HF, heart failure; NA, not available; RV, revascularization, including percutaneous transcoronary angioplasty and coronary artery bypass grafting; ST, ST-segments.

the Egger’s test (P=0.135, 0.843, 0.813 for Obs, RCT, and overall, respectively).

Long-term mortality
A significantly lower incidence of long-term mortality rate was observed in the IABP group compared with the control group (OR 0.66, 95% CI: 0.48–0.91, P=0.010; P=0.025, P=47.4%; Figure 2C), without publication bias (Egger’s test: P=0.132). A similar result was observed in the RCTs (OR 0.71, 95% CI: 0.50–0.99; P=0.046; P=0.177, P=30.2%; Egger’s test: P=0.191), and no significant difference was observed in Obs (OR 0.60, 95% CI: 0.31–1.19, P=0.145; P=0.012, P=68.9%; Egger’s test: P=0.359). A sensitivity analysis confirmed the beneficial effects of IABP with respect to the long-term mortality.

Secondary efficacy endpoints
Reinfarction
The impact of IABP insertion did not significantly differ from no IABP use with respect to the reduction of risk

Table 2 The characteristics of observational trials pertaining to the use of an intra-aortic balloon pump in the setting of AMI

| Study                          | Publication year | Type of reperfusion | Inclusion criteria                                    | Excluded CS | Follow-up duration (d) |
|-------------------------------|------------------|---------------------|-------------------------------------------------------|-------------|------------------------|
| Moulopoulos et al<sup>31</sup> | 1986             | No reperfusion      | AMI with CS                                           | No          | In-hospital            |
| Bengtson et al<sup>32</sup>   | 1992             | NA                  | AMI with CS                                           | No          | In-hospital            |
| Stomel et al<sup>33</sup>     | 1994             | Thrombolysis, ERV   | AMI with CS                                           | No          | In-hospital            |
| Kovack et al<sup>13</sup>     | 1997             | Thrombolysis        | AMI with CS                                           | No          | 30, 360                |
| GUSTO-I<sup>44</sup>          | 1997             | Thrombolysis, RV    | AMI with CS                                           | No          | 30, 360                |
| SHOCK Trial Registry<sup>18</sup> | 2000         | Thrombolysis, ERV   | AMI with suspected CS                                 | No          | In-hospital            |
| NMRM-I<sup>29</sup>           | 2001             | Thrombolysis, ERV   | AMI with CS                                           | No          | In-hospital            |
| French et al<sup>40</sup>     | 2003             | Thrombolysis, ERV   | AMI with CS                                           | No          | 360                    |
| Gu et al<sup>41</sup>         | 2010             | ERV                 | AMI with CS                                           | No          | 30, 180                |
| Sten et al<sup>33</sup>       | 2011             | RV                  | ACS with CS                                           | No          | 30                     |
| EHS PCI Registry<sup>42</sup> | 2011             | ERV                 | AMI with CS                                           | No          | In-hospital            |
| AMC CS<sup>34</sup>           | 2012             | ERV                 | AMI with CS                                           | No          | 30                     |
| ALKK-PCI Registry<sup>44</sup> | 2013         | ERV                 | AMI with CS                                           | No          | In-hospital            |
| Zdziewicz et al<sup>46</sup>  | 2014             | ERV                 | AMI with CS                                           | No          | 30, 360                |
| Ohman et al<sup>46</sup>      | 1991             | Thrombolysis        | AMI without CS                                        | Yes         | In-hospital            |
| Mahmoud et al<sup>44</sup>    | 2012             | ERV                 | AMI without CS                                        | Yes         | In-hospital            |
| Brodie et al<sup>18</sup>     | 1999             | ERV                 | AMI without prior TT                                  | NA          | 30                     |
| Kumbasar et al<sup>27</sup>   | 1999             | Thrombolysis        | AMI ≤6 h                                              | NA          | In-hospital            |

Abbreviations: AMI, acute myocardial infarction; CS, cardiogenic shock; d, days; ERV, emergency revascularization; h, hours; NA, not available; RV, revascularization, including percutaneous transcoronary angioplasty and coronary artery bypass grafting; ST, ST-segments.
Table 3 The baseline characteristics of randomized controlled trials pertaining to the use of an IABP in the setting of AMI

| Study                   | Patients, N (IABP/control) | Mean age, years (IABP/control) | Male, n (IABP/control) | Hypertension, n (IABP/control) | Diabetes, n (IABP/control) | Prior MI, n (IABP/control) |
|-------------------------|-----------------------------|--------------------------------|------------------------|--------------------------------|---------------------------|---------------------------|
| Wakman et al²⁰          | 24/21                       | 66.8/67.8                      | 14/15                  | 14/10                          | NA/NA                     | 15/11                     |
| TACTICS³⁰               | 30/27                       | 68+/67*                        | 23/20                  | NA/NA                          | NA/NA                     | 9/3                       |
| Li et al¹⁷              | 20/19                       | 67.4/64.9                      | 12/12                  | NA/NA                          | NA/NA                     | 9/8                       |
| SHOCK Trial³⁶           | 19/21                       | 62.1/66.1                      | 14/17                  | 8/10                           | 10/10                     | 4/5                       |
| IABP-SHOCK II³⁶         | 299/296                     | 70+/69*                        | 202/211                | 213/199                        | 105/90                    | 71/61                     |
| O’Rourke et al²²        | 14/16                       | 60/54                          | 12/12                  | NA/NA                          | NA/NA                     | 2/5                       |
| Flaherty et al³⁵        | 10/10                       | 52/53                          | 9/8                    | NA/NA                          | NA/NA                     | 4/4                       |
| Ohman et al³¹           | 96/86                       | 56/55                          | 71/65                  | 47/37                          | 16/15                     | 19/20                     |
| Kono et al³⁷            | 23/22                       | 54/60                          | 20/16                  | 10/13                          | 6/6                       | NA/NA                     |
| PAMI-II³³              | 211/226                     | 64.7/63.7                      | 158/170                | 116/126                        | 45/33                     | 45/49                     |
| Vijayalakshmi et al³⁴   | 17/16                       | 57.5/59                        | 14/14                  | 6/6                            | 3/4                       | 2/4                       |
| Gu et al³⁷              | 51/55                       | 67.4/66.6                      | 29/36                  | 35/33                          | 18/19                     | 2/3                       |
| CRISp AMI³⁰            | 156/173                     | 56.1+/57.7*                    | 132/144                | 39/60                          | 27/36                     | 0/0                       |
| BCIS-1³⁰               | 151/150                     | 71/71                          | 122/117                | 95/91                          | 56/50                     | 113/108                   |
| Van’t Hof et al³⁵       | 118/120                     | 59/56                          | 99/101                 | NA/NA                          | 12/9                      | 17/16                     |

Note: *Median.
Abbreviations: AMI, acute myocardial infarction; IABP, intra-aortic balloon pump; MI, myocardial infarction; NA, not available.

of reinfarction during hospitalization (OR 1.10, 95% CI: 0.68–1.78, *P*=0.706; *P*=0.094, *F*=34.3%; Figure 3A), and the results from the RCTs and Obs were similar (Obs: OR: 1.25, 95% CI: 0.48–3.25, *P*=0.644; *P*=0.027, *F*=55.6%; RCT: OR 0.91, 95% CI: 0.60–1.40, *P*=0.680; *P*=0.580, *F*=0.0%). No publication bias was observed for reinfarction (Egger’s test: *P*=0.548, 0.667, 0.837 for Obs, RCT, and overall, respectively).

Table 4 The baseline characteristics of observational clinical trials pertaining to the use of an IABP in the setting of AMI

| Study                   | Patients, N (IABP/control) | Mean age, years (IABP/control) | Male, n (IABP/control) | Hypertension, n (IABP/control) | Diabetes, n (IABP/control) | Prior MI, n (IABP/control) |
|-------------------------|-----------------------------|--------------------------------|------------------------|--------------------------------|---------------------------|---------------------------|
| Moulopoulos et al³¹     | 35/14                       | 60.3/61.1                      | 29/13                  | NA/NA                          | NA/NA                     | 6/16                      |
| Bengston et al³²        | 99/101                      | 64/67                          | NA/NA                  | NA/NA                          | NA/NA                     | 9/3                       |
| Stemel et al³³          | 51/13                       | 66/66                          | 23/8                   | 31/6                           | 11/3                      | 16/2                      |
| Kovack et al³⁴          | 27/19                       | 62/64                          | 16/12                  | 10/11                          | 7/5                       | 6/1                       |
| GUSTO-I³⁵              | 62/248                      | 64+/68*                        | 42/154                 | 23/99                          | 14/57                     | 19/67                     |
| Shock Registry³⁶        | 439/417                     | 65.2/73.4                      | 294/250                | 203/233                        | 137/141                   | 154/188                   |
| NRMI-II³⁷              | 4,215/4,456                 | –67/74.1                      | –60.5%/50.5%           | –47%/49%                       | –29%/32%                  | –26%/30%                  |
| French et al³⁸         | 260/41                      | 65.3/67.4                      | 175/30                 | 124/17                         | 83/10                     | 84/14                     |
| Gu et al³⁹             | 43/48                       | 70/64.9                        | 27/31                  | 33/32                          | 17/17                     | NA/NA                     |
| Sth et al³⁵             | 251/159                     | 65.7/67.7                      | 189/110                | 142/99                         | 71/39                     | 54/38                     |
| EHS PCI Registry³⁶      | 162/491                     | 65.3/65.4                      | 110/335                | 95/316                         | 44/138                    | 58/136                    |
| AMC CS³⁸               | 199/93                      | 64.7/61.5                      | 136/61                 | 69/29                          | 36/16                     | 60/22                     |
| ALKK-PCI Registry³⁵     | 487/1,426                   | 67.7/69.9                      | 372/970                | 359/1,084                      | 159/462                   | 171/549                   |
| Dzewiecki et al³⁶      | 30/21                       | 64.5+/72*                      | 25/8                   | NA/NA                          | 8/1                       | 8/4                       |
| Ohman et al³⁶          | 85/725                      | 58/56                          | 69/580                 | 40/297                         | 17/102                    | 21/87                     |
| Mahmoudi et al³⁷       | 70/70                       | –59/60.6                       | –71.4%/69.2%           | –73.9%/80%                     | –21.9%/27%                | –12.4%/9.6%               |
| Brodie et al³⁸         | 213/1,277                   | NA/NA                          | 126/916                | NA/NA                          | 23/85                     | 56/229                    |
| Kumbasar et al³⁷       | 25/20                       | 53.4/53.5                      | 22/17                  | 9/10                           | 10/5                      | NA/NA                     |

Note: *Median.
Abbreviations: AMI, acute myocardial infarction; IABP, intra-aortic balloon pump; MI, myocardial infarction; NA, not available.

Recurrent ischemia
As depicted in Figure 3B, there was no significant difference between IABP use and no IABP use with respect to the risk of in-hospital ischemia recurrence (OR 0.87, 95% CI: 0.36–2.12, *P*=0.754; *P*=0.001, *F*=75.7%), in either the RCTs or Obs (RCT: OR 0.49, 95% CI: 0.18–1.31, *P*=0.155; *P*=0.060, *F*=59.4%; Obs: OR 2.31, 95% CI: 1.20–4.46, *P*=0.013; *P*=0.744, *F*=0.0%). No publication
Figure 2 (Continued)
bias was observed ($P=0.855, 0.836$ for RCTs and overall, respectively).

**New heart failure**

The overall incidence of new heart failure was similar between the two subgroups (OR 1.40, 95% CI: 0.72–2.72, $P=0.320$; $P<0.001, F=82.3\%$; Figure 3C), as well as in the RCTs (OR 0.89, 95% CI: 0.63–1.28, $P=0.541$; $P=0.404, F=2.0\%$), whereas the risk of new heart failure increased significantly in the Obs (OR 3.29, 95% CI: 1.29–8.38, $P=0.013$; $P=0.005, F=87.5\%$). The results from the Egger’s test suggested no publication bias regarding the incidence of new heart failure ($P=0.875, 0.866$ for RCTs and overall, respectively).

**Safety endpoints**

**Severe bleeding requiring blood transfusion**

The incidence of severe bleeding requiring blood transfusion was higher in the IABP group than in control group (OR 2.05, 95% CI: 1.29–3.25, $P=0.002$; $P=0.001, F=78.5\%$; Figure 4A); a similar result was observed in the Obs (OR 3.48, 95% CI: 2.09–5.79, $P<0.001$; $P=0.003, F=65.1\%$), whereas no significant difference was observed in RCTs (OR 1.14, 95% CI: 0.87–1.49, $P=0.338$; $P=0.804, F=0.0\%$). The sensitivity analysis demonstrated that the inferior effects of IABP insertion in the setting of AMI on severe bleeding requiring blood transfusion were always observed by omitting a single study at a time.

**Stroke**

IABP usage was associated with a higher in-hospital incidence of stroke (OR 1.71, 95% CI: 1.04–2.82, $P=0.035$, Figure 4B) without any heterogeneity ($P=0.636, F=0.0\%$), which contrasted with the results of RCTs and Obs (OR 1.70, 95% CI: 0.73–3.97, $P=0.220$; $P=0.302, F=17.3\%$ for RCTs; Obs: OR 1.72, 95% CI: 0.93–3.19, $P=0.085$;
**A**

| Study ID               | Reinfarction | OR (95% CI) | % weight |
|------------------------|--------------|-------------|----------|
| RCT                    |              |             |          |
| IABP-SHOCK II²⁻³       |              | 2.27 (0.69, 7.46) | 9.55     |
| TACTICS²⁻³             |              | 0.90 (0.05, 15.07) | 2.59     |
| Ohman et al²¹          |              | 0.36 (0.09, 1.45)  | 7.91     |
| PAMI-II²⁴              |              | 0.76 (0.36, 1.59)  | 14.84    |
| Vijayalakshmi et al²⁵  |              | 3.00 (0.11, 79.13) | 1.98     |
| Gu et al²⁹             |              | 1.08 (0.07, 17.73) | 2.63     |
| BCIS-I⁻¹⁻²⁰            |              | 0.94 (0.48, 1.83)  | 15.78    |
| Li et al²⁷             |              | (Excluded)      | 0.00     |
| Flaherty et al¹⁵       |              | (Excluded)      | 0.00     |
| Subtotal (I²=0.0%, P=0.580) |          | 0.91 (0.60, 1.40) | 55.28    |

**B**

| Study ID               | Recurrent ischemia | OR (95% CI) | % weight |
|------------------------|--------------------|-------------|----------|
| RCT                    |                    |             |          |
| Flaherty et al¹⁵       |                    | 2.25 (0.38, 13.47) | 12.44    |
| Ohman et al²¹          |                    | 0.16 (0.05, 0.51)  | 17.83    |
| Kono et al²³           |                    | 0.29 (0.03, 3.00)  | 9.15     |
| PAMI-II²⁴              |                    | 0.63 (0.38, 1.06)  | 23.02    |
| BCIS-II²⁰              |                    | (Excluded)      | 0.00     |
| Subtotal (I²=69.4%, P=0.060) |          | 0.49 (0.18, 1.31) | 62.45    |

| Study ID               | Recurrent ischemia | OR (95% CI) | % weight |
|------------------------|--------------------|-------------|----------|
| Kovack et al¹⁵         |                    | 1.92 (0.54, 6.91) | 16.50    |
| GUSTO-I³¹              |                    | 2.47 (1.14, 5.31)  | 21.06    |
| Subtotal (I²=0.0%, P=0.744) |          | 2.31 (1.20, 4.46) | 37.55    |

Overall (I²=75.7%, P=0.001)  
0.87 (0.36, 2.12)  100

*Figure 3 (Continued)*
In the analysis pertaining to the opportunity for IABP insertion, a reduced risk of long-term mortality was observed among the patients suffering AMI for whom IABP was inserted before reperfusion compared with no IABP use (OR 0.49, 95% CI: 0.34–0.73, P<0.001, Figure 5D), although no significant difference was observed between no IABP use and IABP insertion after reperfusion (OR 0.90, 95% CI: 0.35–2.31, P=0.825).

**Discussion**

The major finding of this comprehensive meta-analysis was that IABP insertion was associated with reduced long-term mortality in patients suffering from AMI compared with no IABP use at the cost of potential high risk of stroke and severe bleeding requiring blood transfusion. The subgroup analyses demonstrated that IABP insertion before reperfusion may be an optimal treatment for patients suffering from AMI complicated by CS or patients receiving TT.

Since IABP was first reported for clinical application in 1968, it has been widely used in patients suffering from AMI, particularly patients following AMI complicated by CS. Both the ACC/AHA (2012) and the European
A

Study ID  | Bleeding requiring blood transfusion  | OR (95% CI)  | % weight |
---|---|---|---|
Observational trials  |  |  |  |
French et al 19  |  | 3.39 (1.38, 8.36)  | 7.68 |
Stomel et al 23  |  | 0.80 (0.03, 20.82)  | 1.69 |
Kovack et al 26  |  | 2.21 (0.09, 57.14)  | 1.69 |
GUSTO-I 24  |  | 6.39 (3.41, 11.97)  | 9.05 |
AMC CS  |  | 1.40 (0.76, 2.56)  | 9.16 |
Dzwierz et al 44  |  | 0.69 (0.04, 11.68)  | 2.13 |
Ohman et al 16  |  | 6.99 (4.35, 11.23)  | 9.76 |
Brodie et al 38  |  | 3.27 (2.24, 4.76)  | 10.15 |
Kumbasar et al 17  |  | 8.58 (0.43, 169.58)  | 1.95 |
Subtotal (I²=65.1%, P=0.003)  |  | 3.48 (2.09, 5.79)  | 53.25 |
RCT  |  |  |  |
IABP-SHOCK II 7,8  |  | 1.07 (0.69, 1.63)  | 9.95 |
O’Rourke et al 22  |  | 10.04 (0.47, 213.63)  | 1.87 |
TACTICS 19  |  | 0.87 (0.26, 2.91)  | 6.22 |
Ohman et al 21  |  | 1.36 (0.70, 2.65)  | 8.86 |
Kono et al 23  |  | 0.45 (0.04, 5.40)  | 2.62 |
PAMI-II 24  |  | 1.16 (0.71, 1.87)  | 9.73 |
Van’t Hof et al 25  |  | 1.14 (0.45, 2.92)  | 7.49 |
SHOCK Trial 24  | (Excluded)  |  | 0.00 |
Subtotal (I²=0.0%, P=0.804)  |  | 1.14 (0.87, 1.49)  | 46.75 |
Overall (I²=78.5%, P=0.000)  |  | 2.05 (1.29, 3.25)  | 100 |

B

Study ID  | Stroke  | OR (95% CI)  | % weight |
---|---|---|---|
RCT  |  |  |  |
IABP-SHOCK II 7,8  |  | 0.39 (0.08, 2.04)  | 21.63 |
TACTICS 19  |  | 4.82 (0.22, 105.10)  | 2.10 |
Ohman et al 21  |  | 0.89 (0.06, 14.53)  | 4.53 |
PAMI-II 24  |  | 12.07 (0.66, 219.54)  | 2.04 |
BCIS-1 10  |  | 5.03 (0.24, 105.73)  | 2.14 |
Van’t Hof et al 25  |  | 1.02 (0.06, 16.45)  | 4.27 |
Kono et al 23  | (Excluded)  |  | 0.00 |
Subtotal (I²=17.3%, P=0.302)  |  | 1.70 (0.73, 3.97)  | 36.71 |
Observational trials  |  |  |  |
Kovack et al 26  |  | 3.82 (0.17, 84.29)  | 2.31 |
GUSTO-I 24  |  | 0.80 (0.09, 8.95)  | 8.54 |
EHS PCI Registry 45  |  | 0.76 (0.08, 8.81)  | 8.56 |
AMC CS  |  | 1.41 (0.14, 13.72)  | 5.83 |
ALKK-PCI Registry 46  |  | 2.93 (0.18, 46.97)  | 2.21 |
Mahmoudi et al 44  |  | 5.15 (0.24, 109.15)  | 2.09 |
Brodie et al 38  |  | 2.86 (1.15, 7.10)  | 18.00 |
Stub et al 43  |  | 0.63 (0.13, 3.16)  | 15.75 |
Subtotal (I²=0.0%, P=0.704)  |  | 1.72 (0.93, 3.19)  | 63.29 |
Overall (I²=0.0%, P=0.636)  |  | 1.71 (1.04, 2.82)  | 100 |

Figure 4 Forest plots of the safety endpoints of the included trials.

Notes: The odds ratio (OR) of severe bleeding requiring blood transfusion (A) and stroke (B) associated with IABP use versus no IABP use stratified by different dual regimens. Weights are from random effects analysis.

Abbreviations: CI, confidence interval; IABP, intra-aortic balloon pump; RCT, randomized controlled trial; ID, identification.
Society of Cardiology guidelines strongly recommended IABP as a bridge to reperfusion for patients suffering from AMI complicated by CS, recommendations derived from several observational clinical trials. However, these recommendations have been challenged because of several recent meta-analyses and RCTs, which demonstrated that IABP for patients with AMI complicated by CS was not associated with reduced mortality, but with high potential risks of major bleeding and stroke. The IABP-SHOCK II trial, a randomized, open-label, multicenter trial involving 600 patients with CS following AMI who underwent early revascularization, demonstrated that IABP did not increase either 6- or 12-month survival rates compared with no IABP use. Moreover, the IABP SHOCK trial demonstrated that

Figure 5 (Continued)
### C

| Study ID               | Midterm mortality | OR (95% CI) | % weight |
|------------------------|-------------------|-------------|----------|
| No reperfusion         |                   |             |          |
| Flaherty et al\(^{15}\) | 2.33 (0.37, 14.61) | 100         |
| Subtotal (P=NA%, P=NA) | 2.33 (0.37, 14.61) | 100         |
| ERV alone              |                   |             |          |
| IABP-SHOCK II\(^{7,8}\) | 0.94 (0.67, 1.30)  | 14.38       |
| Vijayalakshmi et al\(^{26}\) | 7.97 (0.38, 167.53) | 5.82       |
| Gu et al\(^{29}\)     | 0.29 (0.10, 0.87)  | 12.23       |
| Gu et al\(^{41}\)     | 0.38 (0.16, 0.90)  | 13.09       |
| Stub et al\(^{15}\)   | 1.54 (1.02, 2.33)  | 14.24       |
| AMC CS\(^{44}\)       | 2.31 (1.36, 3.93)  | 13.99       |
| Dziewierz et al\(^{45}\) | 0.81 (0.25, 2.60)  | 11.99       |
| Brodie et al\(^{36}\) | 13.63 (9.11, 20.40)| 14.26       |
| Subtotal (P=95.0%, P=0.000) | 1.43 (0.56, 3.69)  | 100         |
| TT alone               |                   |             |          |
| #TACTICS\(^{19}\)     | 0.50 (0.11, 2.24)  | 16.03       |
| Kovack et al\(^{38}\) | 0.23 (0.07, 0.81)  | 22.89       |
| #GUSTO-I\(^{44}\)    | 0.50 (0.23, 1.07)  | 61.40       |
| Kono et al\(^{28}\)   | (Excluded)        | 0.00        |
| Subtotal (P=0.0%, P=0.574) | 0.42 (0.23, 0.76)  | 100         |
| TT+ERV                |                   |             |          |
| #GUSTO-I\(^{44}\)    | 2.00 (0.69, 5.76)  | 77.55       |
| TACTICS\(^{19}\)     | 1.38 (0.19, 9.83)  | 22.45       |
| Subtotal (P=0.0%, P=0.742) | 1.84 (0.72, 4.67)  | 100         |

### D

| Study ID               | Opportunity for IABP insertion | OR (95% CI) | % weight |
|------------------------|--------------------------------|-------------|----------|
| Pre-reperfusion        |                                |             |          |
| Li et al\(^{27}\)     | 0.45 (0.04, 5.39)              | 2.16        |
| Gu et al\(^{41}\)     | 0.32 (0.13, 0.77)              | 17.08       |
| Gu et al\(^{29}\)     | 0.44 (0.18, 1.10)              | 16.04       |
| BCIS-1\(^{10}\)       | 0.61 (0.38, 0.99)              | 57.09       |
| CRISP AMI\(^{30}\)    | 0.36 (0.09, 1.34)              | 7.63        |
| Subtotal (P=0.0%, P=0.738) | 0.49 (0.34, 0.71)              | 100         |
| Post-reperfusion       |                                |             |          |
| TACTICS\(^{19}\)      | 0.63 (0.21, 1.83)              | 24.49       |
| Kovack et al\(^{25}\) | 0.23 (0.07, 0.81)              | 21.94       |
| French et al\(^{40}\) | 2.47 (0.97, 6.24)              | 26.61       |
| Van’t Hof et al\(^{35}\) | 1.40 (0.57, 3.45)              | 26.96       |
| Subtotal (P=70.4%, P=0.018) | 0.90 (0.35, 2.31)              | 100         |

Figure 5 Forest plots of the subgroup analysis of the included trials.

Notes: The odds ratio (OR) of in-hospital all-cause mortality (A) and long-term all-cause mortality (B) among the patients suffering from AMI complicated by CS, as well as midterm all-cause mortality (C) and the long-term mortality associated with different opportunities of IABP insertion vs no IABP use (D) according to reperfusion strategy and IABP insertion associated with IABP use versus no IABP use stratified by different dual regimens. (C): Different groups of patients from the TACTICS trial received the corresponding reperfusion; (D): Different groups of patients from the GUSTO-I trial received the corresponding reperfusion. Weights are from random effects analysis.

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; ERV, emergency revascularization; TT, thrombolytic therapy; CS, cardiogenic shock; IABP, intra-aortic balloon pump; ID, identification; NA, not available.
IABP insertion exerted only modest or even no effects on the acute physiology and chronic health evaluation II score as a marker of disease severity, improvements in cardiac index, reduced inflammation, or reduced plasma brain natriuretic peptide levels compared with medical therapy alone. In summary, the current data did not support IABP as a routine treatment for patients with AMI regardless of whether the patients suffered from AMI complicated by CS, which called the above-mentioned guidelines into question. On the other hand, all these over-mentioned meta-analyses for IABP application did not include all available relevant citations and there was none of them grouped meticulously which might cover the beneficial efficacy of IABP on special patients. Therefore, we carried out this updated, comprehensive meta-analysis to explore which patients could benefit mostly from IABP insertion.

In spite of the advances in early revascularization, the mortality rate of patients suffering from AMI complicated by CS remains high; IABP was empirically preferred with respect to the treatment of these patients. The thrombolysis and counterpulsation to improve survival in myocardial infarction (TACTICS) trial demonstrated that IABP insertion for patients with AMI complicated by either hypotension or severe heart failure who were receiving thrombolysis was not associated with a significant risk reduction on 6-month mortality, but was associated with increased survival rates for patients in Killip classes III or IV (39% for combined therapy versus 80% for fibrinolysis alone). The data from the present study demonstrated the superior effects of IABP in patients suffering from AMI, particularly those complicated with CS, findings consistent with results of two previous meta-analyses. IABP may be the optimal choice for specific patients with AMI, but not for all patients with AMI.

In fact, the observed reductions in mortality secondary to IABP usage may be balanced by the increased rates of stroke and severe bleeding. More and more evidence, including the results from our study, has demonstrated that IABP insertion is associated with a higher incidence of severe bleeding and stroke. Four risk factors for complications following IABP insertion were identified from the Benchmark Registry: age ≥ 75 years, female sex, peripheral arterial disease, and body surface area < 1.65 m². In the meta-analysis published by Sjauw et al., a significantly increased rate of stroke secondary to IABP use was observed in patients suffering from AMI. Restricting activity due to IABP insertion for long periods may promote the development of venous thrombosis, resulting in an increased risk of all-cause death among affected patients. Moreover, several studies have demonstrated that major bleeding was associated with an increased risk of death, indicating that bleeding was dangerous not only because of the hemorrhaging itself but also because it forced the discontinuation of the IABP and necessary antiplatelet therapy, resulting in higher rates of thrombotic events. Thiele et al. pointed out that the higher in-hospital mortality in the AMI patients complicated with CS might depend on hemodynamic deterioration, multiorgan dysfunction, or systemic inflammatory response syndrome. One more possible related point was that some of the included patients were too serious to receive the implantation of IABP before their deaths or even had no access to implant this equipment in time if they were initially treated in a peripheral center. In contrast, the lower long-term mortality among these patients might be due to the successful insertion of IABP which positively affected myocardial recovery following AMI. Therefore, it may be more useful to determine which patients benefit most from IABP insertion, as opposed to studying the complications of IABP use.

In contrast to the recommendations of the ACC/AHA (2012) guidelines, the SHOCK trial demonstrated that a higher rate of in-hospital mortality was observed among the patients suffering from AMI complicated by CS associated with IABP insertion following reperfusion compared with no IABP use (36.8% vs 28.6%). However, the balloon pump-assisted coronary intervention study (BCIS-1) trial demonstrated that IABP insertion before reperfusion may result in a significantly reduced risk of long-term mortality among these patients. Therefore, a subgroup analysis was conducted in our study to address this controversy and determine the ideal opportunity for IABP insertion, as well as which patients may benefit most from IABP insertion. IABP usage was associated with a lower risk of mortality when inserted before reperfusion, a finding consistent with those of previous studies. Early IABP insertion promoted hemodynamic stability and reduced myocardial oxygen demand, which may be important in patients suffering from AMI complicated by CS. Our results indicated that IABP insertion was associated with feasible benefits with respect to long-term survival in patients with AMI, particularly patients suffering from AMI complicated by CS and patients receiving thrombolytic therapy.

Several questions remained unanswered. First, there were not enough data to assess the optimal duration of IABP insertion for patients without severe complications, as well as for which patients the IABP may be removed at an earlier time. Most of current literature regarding the efficacy of IABP use consented to a duration of ~48 hours, although no
absolute benefits regarding survival rates were demonstrated. A second dilemma involved the ideal opportunity for IABP insertion in patients with AMI complicated by hemodynamic compromise. The ACC/AHA (2012) guidelines recommend implantation at the completion of reperfusion. Third, divergence regarding specifics about the reperfusion strategies was observed. Both ERV alone and TT alone demonstrated potential benefits in patients with AMI in this meta-analysis. Therefore, powerful randomized clinical trials comparing IABP use and no IABP use in patients suffering from AMI complicated by CS focusing on the optimal duration of IABP, most suitable time for IABP insertion, and more precise reperfusion strategies must be performed to guide clinical decision making.

Limitations
This study had several limitations. First, this meta-analysis was not based on individual patient data, and the small sample size of several included RCTs also made the evaluation of IABP’s efficacy easily influenced. Second, different studies used different endpoint definitions, which may have been the source of bias. Third, the lack of other potential confounding factors, such as the time of IABP insertion, duration of IABP placement, insertion details, including technology and choice of sheath with different sizes, as well as reperfusion strategies, did not allow us to explore the effects of IABP on patients with AMI or the underlying mechanisms of these effects. Additionally, there was no uniform or clear follow-up period.

Conclusion
IABP insertion is associated with feasible benefits with respect to long-term survival in patients with AMI, particularly those suffering from CS and receiving thrombolytic therapy, at the cost of higher risk of severe bleeding and stroke.

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Author contributions
Z-GF and X-FG were involved in the design, literature searching, assessment of study quality, and drafted the manuscript. Disagreements were resolved by L-WC. X-BL and M-XS revised critically the manuscript. Z-GF and X-FG performed statistical analysis and critically revised the manuscript. QJ, HZ, and Y-ZR constructed the maps. S-LC and N-LT critically revised original study design and the manuscript. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure
The authors report no conflicts of interest in this work.

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