Clinical experience with the intra-aortic balloon pump (IABP) spans >40 years.\(^1\) Physiological studies have demonstrated that the IABP acutely improves systemic hemodynamics, augments coronary flow, reduces myocardial oxygen demand, and can sustain coronary patency after percutaneous revascularization.\(^2\) These sound physiological principles, largely supportive observational data,\(^5\)\(^7\) and a historical lack of alternative percutaneous devices to provide circulatory support led to the widespread use of the IABP in cardiogenic shock secondary to acute myocardial infarction (AMI), ST-segment elevation-acute coronary syndrome without shock and also in high-risk percutaneous coronary intervention (PCI), despite a paucity of adequately powered randomized evidence to support their use. Nearly 5 decades since the introduction of IABP into clinical practice, we finally have randomized data on the efficacy of balloon counterpulsation for each of the 3 above indications.\(^8\)\(^-\)\(^10\) The main clinical applications for counterpulsation and the randomized data for each indication are summarized in the Table.

To the surprise of many who have come to rely on the support and reassurance provided by this device, none of the recent trials reached their primary efficacy end points. Where does that leave us with the IABP? Is it time to abandon ship or is there hope yet for an old friend?

Perhaps the most surprising of these randomized controlled trial (RCT) results was from the most recent trial, IABP-SHOCK II.\(^4\) This multicenter, open-labeled, randomized study enrolled 600 patients with AMI (with or without ST-segment elevation) with cardiogenic shock, if early revascularization was planned. Patients were randomized in a 1:1 ratio to intra-aortic balloon counterpulsation (IABP group) or no intra-aortic counterpulsation (control group). The primary study end point, 30-day all-cause mortality, occurred in a similar proportion of the IABP and control groups (39.7% and 41.3%; relative risk with IABP 0.96; \(P=0.69\)), by an intention-to-treat analysis. There were no significant differences in the multiple secondary end points (including serial assessments of serum lactate, creatinine, C-reactive protein levels, or the Simplified Acute Physiology Score or in the safety end points [including severe or life-threatening bleeding, peripheral ischemic complications, sepsis, and stroke]). Several aspects of this important trial merit further consideration.

The sample size calculation for the IABP-SHOCK II trial was based on an anticipated 30-day mortality of 56% in the control group, giving 80% power to detect a 12% absolute reduction in mortality with IABP insertion. However, the observed mortality rate in the control group was significantly lower than anticipated, which may either indicate 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. Nevertheless, despite the remarkable feat of having randomized 600 patients with cardiogenic shock (twice the number enrolled in the seminal SHOCK trial), the IABP-SHOCK II trial lacks sufficient power to address its primary hypothesis definitively. Given the observed mortality rate of \(<40\%\), >900 patients would have been required to detect the specified treatment effect. However, given that identical mortality rates were observed in the 2 treatment arms of IABP-SHOCK II, it is possible that a larger sample size alone may have failed to reveal a benefit of IABP therapy.

Forty-three patients crossed-over to the alternative treatment strategy in the IABP-SHOCK II trial; 30 patients (10%) who were assigned to the control group underwent IABP insertion, whereas 13 patients (4.2%) assigned to the IABP group did not receive an IABP. The impact of crossover on the overall result of a RCT can be difficult to evaluate and depends on the frequency of crossover, as well as the symmetry of events in this crossover population. A per-protocol analysis of the IABP-SHOCK II data, which excluded all crossover patients, revealed similar results to the primary intention-to-treat analysis. From these 2 published analyses, it seems that the patients in the control group who received IABP insertion had markedly different outcomes to those who crossed-over in the opposite direction; death occurred more often in the first 30 days in IABP group who did not receive IABP insertion (11/13) than in the control group who received IABP therapy (12/30). Given the asymmetrical event rates in the 2 crossover groups, it is possible that excluding these patients may have led to loss of important data and hence an as-treated analysis may have been instructive, although the latter cohort are likely to be prone to selection bias. In addition to the crossover to IABP therapy, some patients in the control group also received percutaneous left ventricular assist devices, which may also have improved the likelihood of survival to 30 days. These considerations are not peculiar to IABP-SHOCK II but exemplify the philosophical and methodological difficulties.

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**Intra-aortic Balloon Pump Trials**

**Questions, Answers, and Unresolved Issues**

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inherent in predicting and analyzing crossover in randomized trials involving sick patients. Although a variety of post hoc statistical techniques can be used to account for crossover, ultimately, this is probably best addressed prospectively, with the sample size calculated to allow adequate statistical power to analyze the eventual per-protocol population. However, given the difficulty of recruiting sick patients, power calculations in randomized clinical trials will always reflect a trade-off between ideal study design and the feasibility of recruitment within the available resources and timeframe.

In patients presenting with cardiogenic shock, the risk of hemodynamic compromise is greatest during PCI, when balloon occlusion or vessel closure could trigger a spiral of ischemia, reduced contractility, and diminished myocardial perfusion. In this context, balloon counterpulsation is expected to be most effective when inserted before PCI.

However, in IABP-SHOCK II, nearly all (86.6%) patients underwent IABP insertion after PCI, and it is worthy of note that 10 patients assigned to the IABP group died before an IABP could be inserted, presumably during PCI. Although there was no statistically significant difference between the minority (n=80) who received IABP insertion before PCI and the overall cohort, it remains unclear whether preprocedural IABP insertion may have provided greater benefit than observed in this trial.

All-cause mortality at 6 and 12 months are secondary end points in the IABP-SHOCK II trial. Given that the overall event rate was lower than expected, longer-term outcome data would be of great interest, as this may allow accrual of further clinical events, which in turn may provide further statistical power to exclude a type 2 error and detect a clinically important treatment effect. The importance of longer-term

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**Table. Randomized Control Trials of Intra-aortic Balloon Counterpulsation**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Trial</th>
<th>n</th>
<th>Inclusion</th>
<th>Principal End Point</th>
<th>Results (IABP vs Control Group)</th>
<th>Timing of IABP Insertion</th>
<th>Crossover From Control to IABP</th>
<th>Bleeding Rates</th>
<th>Vascular Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk PCI (excluding shock/AMI)</td>
<td>Perera et al4</td>
<td>301</td>
<td>LVEF≤30% BCIS Jeopardy score ≥8</td>
<td>Composite of death, AMI, CVA or further revascularization at hospital discharge (capped at 28 days)</td>
<td>15.2% vs 16%; OR, 0.94; 95% CI, 0.51-1.76; P=0.85</td>
<td>Pre-PCI 12.0</td>
<td>19.2% vs 11.3%; OR, 1.86; 95% CI, 0.93-3.79; P=0.06 (at hospital discharge, capped at 28 days)</td>
<td>3.3% vs 0%; P=0.06 (at hospital discharge, capped at 28 days)</td>
<td></td>
</tr>
<tr>
<td>AMI-without shock</td>
<td>Ohman et al4</td>
<td>182</td>
<td>STE-ACS or NSTE-ACS Cardiac catheterization within 24 h of symptoms</td>
<td>All-cause mortality at follow-up (median 51 mo)</td>
<td>27.8% vs. 38.7%, HR 0.66; 95% CI 0.44 - 0.98; P=0.039</td>
<td>Post-PCI 8.1</td>
<td>2% vs 1%</td>
<td>5% vs 2%</td>
<td></td>
</tr>
<tr>
<td>Stone et al12</td>
<td>437</td>
<td>STE-ACS or NSTE-ACS+urgent catheterization revealing an occluded vessel with regional LV dysfunction</td>
<td>Composite of death, reinfarction, infarct-related artery reocclusion, stroke, new-onset heart failure, or sustained hypotension</td>
<td>28.9% vs 29.2%; P=0.95</td>
<td>Post-PCI 11.5</td>
<td>36% vs 27%; P=0.05 (in-hospital)</td>
<td>0.5% vs 0.4%; P=1.0 (in-hospital; requiring surgical intervention)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>van’t Hof et al13</td>
<td>238</td>
<td>STE-ACS Primary PCI</td>
<td>Composite of death, nonfatal reinfarction, stroke or EF≤30% at 6 mo</td>
<td>26% vs. 26%; P=0.94</td>
<td>Post-PCI 31.4</td>
<td>3% vs 4%</td>
<td>3.1% in the IABP group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patel et al9</td>
<td>337</td>
<td>anterior STE-ACS Primary PCI</td>
<td>Infarct size as a percentage of LV mass</td>
<td>42.1% vs 37.5%; P=0.07</td>
<td>Pre-PCI 8.5</td>
<td>3.1% vs 1.7%; P=0.49 (at 30 days)</td>
<td>4.3% vs 1.1%; P=0.09 (at 30 days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI complicated by cardiogenic shock</td>
<td>Thiele et al5</td>
<td>600</td>
<td>STE-ACS or NSTE-ACS Early PCI Cardiogenic shock</td>
<td>30-d mortality</td>
<td>39.7% vs 41.3%; P=0.69</td>
<td>Operator discretion (86.6% after PCI)</td>
<td>10.0</td>
<td>3.3% vs 4.4%; P=0.51 (severe/ life-threatening)</td>
<td>4.3% vs 3.4%; P=0.53 (surgical vascular repair)</td>
</tr>
</tbody>
</table>

Randomized control trials of intra-aortic balloon pump (IABP) use during percutaneous coronary intervention (PCI). The table only includes data from trials that randomly assigned patients to IABP support or PCI without planned IABP insertion and enrolled ≥100 patients.

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; CI, confidence interval; CVA, cerebrovascular accident; HR, hazard ratio; LVEF, left ventricular ejection fraction; NSTE, no ST-segment elevation (on ECG); OR, odds ratio; and STE, ST-segment elevation (on ECG).
follow-up was demonstrated in the original SHOCK trial\textsuperscript{14} and the more recent RCT on elective IABP therapy, Balloon pump-assisted Coronary Intervention Study (BCIS-1)\textsuperscript{10} (Figure). In the SHOCK trial, which compared early revascularization with a strategy of initial medical stabilization for patients presenting with cardiogenic shock, no significant difference was found between the treatment arms in the occurrence of the primary end point, 30-day mortality. However, the mortality trend observed at 30 days did reach statistical significance at 6 months (a prespecified time point), in favor of early revascularization; a result that has profoundly influenced contemporary management of cardiogenic shock. BCIS-1 was a multicenter RCT that randomly assigned 301 patients with severe ischemic cardiomyopathy to receive elective IABP before PCI or to undergo PCI without planned IABP support. There was no difference in the frequency of Major Adverse Cardiac and Cerebrovascular Events (MACCE) at hospital discharge (capped at 28 days), although procedural complications occurred less often in the elective IABP group and 12% of patients assigned to have PCI without IABP support required rescue IABP insertion because of hemodynamic instability. A numeric difference in mortality was noted at 6 months, which failed to reach significance on account of the low number of events at that stage. Longer-term follow-up allowed accrual of more events. A hundred deaths had occurred at a median interval of 51 months after randomization (overall mortality was 33%). Significantly fewer deaths occurred in the IABP group compared with controls (hazard ratio, 0.66; 95% confidence interval, 0.44–0.98; \(P=0.039\)). The hazard ratio was noted to remain relatively constant throughout the duration of follow-up, suggesting that the difference in mortality is likely to have been attributable to elective IABP therapy at the time of PCI, rather than a later effect, and that the progressive accrual of events provided sufficient power to detect this treatment effect. Although the mechanism of benefit remains unclear, no systematic differences were found between the treatment groups (in baseline or revascularization characteristics) that might confound interpretation of the observed difference in outcome.\textsuperscript{11}

Counterpulsation Reduces Infarct Size Pre-PCI (CRISP) is the third of the recent RCT addressing the use of IABP\textsuperscript{9} This trial examined the role of the IABP in anterior ST-segment elevation-acute coronary syndrome without cardiogenic shock. It was a multicenter randomized trial, including 337 patients, who were randomized in a 1:1 ratio to either IABP before PCI or PCI alone. There was no difference in the infarct size assessed by cardiac MRI, the primary end point of the trial. A statistically nonsignificant trend to an increase in infarct size was observed in the IABP group, compared with the control group. Although it is possible that this may relate to treatment assignment (via a mechanism that is unclear), this observation may also have been affected by the fact that more patients in the control group were unable to undergo MRI because of death or clinical instability, compared with the IABP group.
which in turn could have led to a degree of selection bias. As with IABP-SHOCK II and BCIS-1, a proportion (8.5%) of patients in the control arm required rescue IABP insertion, primarily because of the onset of severe hypotension or cardiogenic shock. All-cause mortality at 6 months, a prespecified secondary end point, was numerically less frequent in the elective IABP group, although the number of events was too low to allow meaningful statistical comparison (1.9% versus 5.2%; \( P=0.12 \)). The exploratory composite end point of death, shock, or new worsening heart failure also occurred less often in the IABP group (5% versus 12%; \( P=0.03 \)). Longer-term clinical follow-up of this cohort is currently being undertaken, and it remains to be seen whether these trends reach statistical significance with accrual of further events. Post-hoc analysis of baseline and procedural characteristics is also being planned, with a view to identifying a subgroup of the overall cohort who may derive benefit from elective IABP insertion even in the absence of hemodynamic compromise.

On the basis of BCIS-1, CRISP-AMI, and IABP-SHOCK II, it is clear that the risk of major adverse complications associated with PCI in the context of acute or chronic severe left ventricular impairment cannot be ameliorated by a strategy of routine elective IABP insertion. However, there is a signal that a subset of this heterogeneous cohort may benefit from pre-PCI elective IABP insertion. Although the need for rescue IABP in itself cannot be regarded as proof of efficacy of the device, it is worthy of note that \( \approx \)10% of patients assigned to control therapy in each of these 3 trials required bailout IABP therapy. A smaller than anticipated (but nevertheless clinically important) potential treatment effect means that, despite the laudable collective achievement, these randomized trials lack the power to exclude a definitive beneficial impact of elective IABP therapy; a drawback that can partly be addressed by increasing the length of follow-up, but also indicates the need for ongoing registry data, with a view to generating a risk stratification system that may allow prospective identification of patients who may benefit from elective, upfront IABP insertion. These may be patients with extreme left ventricular dysfunction, elevated filling pressures, and an extensive amount of myocardium at risk, where there is a risk of prolonged peri-procedural ischemia on account of the complexity of planned PCI or the acuity of presentation.

What these trials and contemporary registries of IABP also tell us is that counterpulsation is broadly a safe treatment, with acceptably low rates of device-related complications (as summarized in the Table). It is particularly noteworthy that there was no significant difference in the incidence of vascular complications or device-related bleeding between patients receiving IABP therapy or those assigned to the control group even in the setting of AMI or cardiogenic shock, emergent situations which would have required rapid IABP insertion. The CRISP-AMI trial also elegantly demonstrated that IABP insertion can be carried out rapidly even in the context of AMI, with no significant delay in the time to reperfusion, compared with those who received primary PCI without IABP support.

We should consider the possibility that the negative findings from the RCTs to date may be because the IABP did not provide sufficient hemodynamic support in these scenarios, particularly in cardiogenic shock. Percutaneous left ventricular assist devices, such as the Impella device, represent an alternative or adjunctive means of providing circulatory support but at present, there is no evidence that these devices provide enhanced clinical benefit compared with IABP or that the increased risk of vascular complications associated with their use would justify their potentially superior hemodynamic profiles.\(^{16,17} \) There is a pressing need for an adequately powered, carefully designed trial of percutaneous assist devices in cardiogenic shock, compared with IABP therapy. Another interesting group is the subset of patients with extensive myocardial infarction (without shock) and persistent ischemia, despite adequate epicardial reperfusion (no-reflow phenomenon). In these patients, with ongoing pain and persistent ST-segment elevation, temporary unloading of the left ventricle might improve the likelihood of recovery of the endangered myocardium. Outside the context of acute coronary syndromes, patients with advanced heart failure are another population for whom IABP is often considered, as a stabilization strategy or as a bridge to transplant or surgical ventricular assist device.\(^{18} \)

The role of IABP or percutaneous LVAD for this indication has not been evaluated in a large-scale RCT to date.

In the meantime, it is our view that institutions undertaking high-risk PCI in hemodynamically stable patients or those in shock, should have access to IABP therapy and should have in place algorithms that allow timely selection of patients at risk of deterioration, for escalation to percutaneous left ventricular assist device therapy or more advanced circulatory support, as required. In parallel, there is also a need for a bedside to bench approach, to further understand the physiological basis of action of counterpulsation and left ventricular support devices in each of these high-risk settings, to provide mechanistic explanations for the results observed in these RCTs, enable prospective distinction of responders from nonresponders and aid individualization of circulatory support in the future.\(^{19–21} \)

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Key Words: acute myocardial infarction, shock, cardiogenic, counterpulsation, high-risk percutaneous coronary intervention, intra-aortic balloon pump, left ventricular assist devices, mortality.
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