TITLE: Intra-aortic Balloon Pump for Treatment of Cardiogenic Shock

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INTRA-AORTIC BALLOON PUMP (IABP) FOR TREATMENT OF CARDIOGENIC SHOCK
A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum (CTAF) was asked to assess the evidence for Intra-aortic balloon pump (IABP) as a treatment for cardiogenic shock. This topic is being reviewed now because of a recent publication suggesting that in patients with myocardial infarction (MI) and cardiogenic shock who are planning to undergo revascularization, IABP had no impact on 30 day mortality.\(^1\)

BACKGROUND

Cardiogenic shock is defined as a syndrome of inadequate end organ perfusion. It is defined based on the following hemodynamic parameters: Systolic blood pressure (SBP) <80-90 mm Hg or Mean Arterial Pressure (MAP) 30 mm Hg lower than baseline, with severe reduction in the Cardiac Index (CI) (<1.8 L/min/m\(^2\) without support or <2.0 to 2.2 L/min/m\(^2\) with support) and adequate or elevated filling pressures. The most common cause of cardiogenic shock is acute ST elevation MI. Other causes include acute mitral regurgitation or rupture of either the ventricular septum or the free wall. Cardiogenic shock (CS) can be caused by any acute and severe left or right ventricular dysfunction. In patients with acute ST elevation MI, timely reperfusion is an important goal.
Treatment of Cardiogenic Shock Due To Left Ventricular Dysfunction

Patients with shock should be transported to facilities with cardiac catheterization facilities and capable of revascularization – either Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Graft (CABG). Treatment options include ventilation support to correct hypoxia and acidosis, optimization of intravascular volume, aspirin, intravenous heparin, possible platelet glycoprotein IIb/IIIa inhibitors in those with non-ST segment myocardial infarction (NSTEMI), and insertion of a pulmonary artery catheter if necessary. Additional measures include pharmacologic support including inotropes such as dopamine, mechanical support such as IABP and reperfusion or revascularization with either primary PCI, CABG or thrombolytic treatment for patients not receiving PCI in a timely manner.

Intra-aortic Balloon Pump (IABP)

IABP is a type of mechanical hemodynamic support and it is most widely used circulatory assist device.\textsuperscript{2} It is used in many clinical conditions including cardiogenic shock, intractable angina, low cardiac output after CABG,\textsuperscript{,} adjunctive therapy for patients after fibrinolysis at high risk for restenosis, adjunctive therapy in high risk or complicated angioplasty, prophylaxis in patients with severe left main coronary disease before impending surgery, refractory heart failure as a bridge to further treatment or intractable ventricular arrhythmias as a bridge to further therapy.\textsuperscript{3,\textsuperscript{8}} The CTAF assessment will focus on the use of IABP in the treatment of cardiogenic shock.

There are two parts to the IABP. The first part is a catheter with two lumens. The first lumen allows for distal aspiration/flushing or pressure monitoring. The second lumen contains a balloon that allows for delivery and removal of helium gas. The balloon size ranges from 20 to 50 ccs. There is also a console that has the system for the helium transfer as well as controlling inflation and deflation of the balloon.
The IABP is inserted through the femoral artery and using fluoroscopic guidance, it is advanced so that the distal end is in the proximal descending aorta. There is an external console which initiates and controls pumping. It gets input from the aortic pressure and the EKG. The pump inflation occurs immediately after the aortic valve closes and deflates right before the valve opens. There are software algorithms that can regulate the pump, which means that less staff time is required to supervise its use.

There are two major results of IABP use. When it inflates during diastole, blood gets displaced to the proximal aorta. When it deflates during systole, there is a vacuum effect that reduces afterload thus allowing for more blood to be effectively pumped, reducing systolic pressure, increasing diastolic pressure (increasing coronary blood flow) and
increasing mean arterial pressure. Reductions in afterload and in wall stress lead to decreased myocardial oxygen consumption, which is an important treatment goal in patients with myocardial ischemia.

Diastole: inflation  Systole: deflation

Note: FDA document stated that picture copied from http://www.rcisreview.com/cardiogenicshock.htm

Current Clinical Guidelines

The current guidelines of the American College of Cardiology and the American Heart Association recommend IABP counterpulsation when cardiogenic shock is not quickly reversed with pharmacologic therapy. They recommend IABP as a stabilizing measure for angiography and prompt revascularization. This is a Class I recommendation with level B evidence published initially in 2004 and not changed with the most recent guideline update in 2007. Additional Class I recommendations include that IABP be used in patients with acute MI in the following settings: hypotension (systolic BP less than 90 mm Hg or ≥30 mm Hg below baseline mean arterial pressure) that does not respond to other interventions.
unless further support is limited by patient’s wishes or contraindications or unsuitability for further invasive care, low-output state, cardiogenic shock not quickly reversed with pharmacologic therapy as a stabilizing measure for angiography and prompt revascularization, and recurrent ischemic-type chest discomfort and hemodynamic instability, poor left ventricular function or a large area of myocardium at risk.

These current guidelines are based primarily on data from registry studies and until recently there has been concern about the lack of adequately powered randomized controlled trials. These guidelines have been called into question because of a recently published trial showing that IABP use in patients with cardiogenic shock who were planning to undergo early revascularization did not result in a reduction in 30 day mortality.\textsuperscript{1} CTAF is thus evaluating the use of IABP for the treatment of cardiogenic shock.

**TA Criterion 1:** The technology must have final approval from the appropriate government regulatory bodies

Intra-aortic balloon pump devices and systems are regulated by the U.S. Food and Drug Administration (FDA) as Class III devices under FDA regulations 21 CFR 870.3535 but are currently marketed through the 510(k) process for Class II products.\textsuperscript{10} 510(k) approvals over time documented by the FDA\textsuperscript{11} are shown below.

<table>
<thead>
<tr>
<th>Year(s)</th>
<th>Clinical Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to May, 1976</td>
<td>Myocardial infarction (MI) leading to left heart failure and early signs of cardiogenic shock, and interim left ventricular support to permit the performance of emergency coronary artery bypass surgery (CABG).</td>
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<tr>
<td>(Pre-Amendment)</td>
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<tr>
<td>1980 - 1989</td>
<td>510k approvals: Refractory ventricular failure, cardiogenic shock, unstable refractory angina, impending infarction, mechanical</td>
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</table>
complications due to acute myocardial infarction (i.e., ventricular septal defect, mitral regurgitation or papillary muscle rupture), ischemia related intractable ventricular arrhythmias, cardiac support for high risk general surgical patients, and septic shock.

1990 - 1999
510k approvals: Same indications for 1980 - 1989 with the addition of: weaning from cardiopulmonary bypass, support and stabilization during coronary angiography and angioplasty and intraoperative pulsatile flow generation.

2000 - present
Same indications from 1980 - 1999 with the addition of: Prophylactic support in preparation for cardiac surgery, post-surgical myocardial dysfunction, cardiac contusion, mechanical bridge to other assist devices, cardiac support following correction of anatomical defects and support for failed angioplasty and valvuloplasty.

The FDA Circulatory Systems Device Panel met on December 5, 2012 and made the recommendation that IAPB be classified as Class II devices when indicated for acute coronary syndrome, cardiac and non-cardiac surgery, and complications of heart failure (ischemic or non-ischemic etiologies) and Class III (premarket approval) for all other intended uses. No specific timeline was noted for the approval and/or implementation of the FDA recommendations.

**TA criterion 1 is met.**

**TA Criterion 2:** The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials database, Cochrane reviews database and Database of Abstracts of Reviews of Effects (DARE) were searched using the key
words: shock, cardiogenic or cardiogenic shock and intraaortic balloon pumping. The search was performed for the period from database inception through November, 2012. The bibliographies of systematic reviews and key articles were manually searched for additional references and references were requested from the device manufacturer. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full.

Inclusion criteria:

• Study had to evaluate IABP in the treatment of cardiogenic shock
• Study had to measure clinical outcomes
• Included only humans
• Published in English as a peer reviewed article

Studies were excluded if they only focused on non-clinical outcomes.

A total of 263 potentially relevant articles were identified. These 263 abstracts were evaluated and 242 were excluded. Reasons for exclusion included not addressing the study question, not reporting clinical outcomes, not focusing on patients with cardiogenic shock or being a duplicate publication. Of these, 16 published studies were included. A total of nine cohort studies including two registry studies and seven published clinical trials are included in this evaluation.

Details of the cohort studies are described in Table 1. Five of them were retrospective studies. One was a prospective multicenter study, and three were registry studies. The largest retrospective study had 200 patients and the remaining four studies had less than 70 patients each. The three registry studies were significantly larger with sample sizes ranging from 292 to 23,180 patients.
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>N</th>
<th>Inclusion Criteria</th>
<th>Intervention</th>
<th>Mean Age</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moulopoulos, 1986</td>
<td>Retrospective, single center</td>
<td>49</td>
<td>Systolic pressure &lt;80 and Urine output</td>
<td>IABP (n=34) Usual care (N=15)</td>
<td>60 (intervention) 61 (control)</td>
<td>10/34 treated with IABP survived more than a month 0/15 who did not receive IABP survived</td>
<td>Patients seen before 1985</td>
</tr>
<tr>
<td>Bengston, 1992</td>
<td>Case series, single center</td>
<td>200</td>
<td>Acute MI and cardiogenic shock</td>
<td>IABP vs no IABP</td>
<td>64 (IABP) vs 67 (no IABP)</td>
<td>In hospital mortality 48% among those with IABP and 57% in those with no IABP: NS</td>
<td>One or many subgroup analyses</td>
</tr>
<tr>
<td>Waksman, 1993</td>
<td>Retrospective, single center</td>
<td>41</td>
<td>Acute MI and cardiogenic shock</td>
<td>IABP (n=20) vs no IABP (n=21)</td>
<td>65.6 (IABP) 67.8 (no IABP)</td>
<td>In hospital survival (46% for IABP vs 19%; p&lt;0.05) One year survival: 38% IABP vs 10%; p&lt;0.05</td>
<td></td>
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<tr>
<td>Stomel, 1994</td>
<td>Retrospective single center</td>
<td>64</td>
<td>Acute MI and cardiogenic shock</td>
<td>1. TL (N=13) 2. IABP (N=29) 3. TL and IABP (N=22)</td>
<td>66 (TL) 67 (IABP) 65 (TL and IABP)</td>
<td>Survival to hospital discharge: Group 1: 23% vs Group 2: 28% vs Group 3: 68%; p=0.005</td>
<td>May be some patient overlap with Kovack study</td>
</tr>
<tr>
<td>Kovack, 1997</td>
<td>Retrospective, two centers</td>
<td>46</td>
<td>Acute MI and cardiogenic shock undergoing thrombolysis</td>
<td>1. IABP (n=27) 2. No IABP (n=19)</td>
<td>62 (IABP) 64 (no IABP)</td>
<td>Survival to community hospital discharge: (Group 1: 93% vs Group 2: 37%) Higher one year survival for IABP (67% vs 32%; p=0.019)</td>
<td>Maybe be some patient overlap with Stomel study</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>N</td>
<td>Inclusion Criteria</td>
<td>Intervention</td>
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<tr>
<td>GUSTO I, anderson, 1997</td>
<td>Prospective, multicenter</td>
<td>310</td>
<td>Acute MI and cardiogenic shock</td>
<td>IABP (n=68) vs no IABP (n=248)</td>
<td>64 (IABP)</td>
<td>68 (no IABP)</td>
<td>In hospital mortality: 48% IABP vs 59% no IABP: p=0.12 30 day mortality: 47% IABP vs 60% no IABP: p=0.06 one year mortality: 57% IABP vs 67% no IABP: p=0.04</td>
</tr>
<tr>
<td>SHOCK registry Sanborn, 2000</td>
<td>Registry, multicenter</td>
<td>856</td>
<td>Acute MI with cardiogenic shock</td>
<td>1. TT/no IABP (n=285) 2. IABP only: n=279 3. TT only (n=132) TT and IABP: n=160</td>
<td>73 (Grp 1)</td>
<td>66 (Grp 2) 71 (Grp 3) 63 9Grp 4)</td>
<td>In hospital mortality lower with IABP (50% vs 72%: p=0.001) In hospital mortality by group: TT plus IABP 47% vs IABP only 52% vs TT only 63% vs no TT/no IABP 77%: p=0.001) Benefit in those treated with IABP regardless of TT</td>
</tr>
<tr>
<td>NRMI-2, Barron, 2001</td>
<td>Registry, multicenter</td>
<td>23,180</td>
<td>Acute MI with cardiogenic shock</td>
<td>IABP (N=7,268) No IABP (n=15,912)</td>
<td>67 (IABP)</td>
<td>74 (No IABP)</td>
<td>In those who received thrombolytic therapy, IABP associated with reduced hospital mortality (67% vs 49%). No benefit in those treated with primary angioplasty Trend toward reduced mortality in those treated with IABP and TT</td>
</tr>
<tr>
<td>AMC CS cohort Sjauw, 2009; Vis, 2006; Engstrom, 2010; Vis, 2007</td>
<td>Single center, registry</td>
<td>292</td>
<td>Acute MI with cardiogenic shock all undergoing PCI</td>
<td>IABP 199 No IABP 93</td>
<td></td>
<td></td>
<td>30 day mortality: 47% IABP vs 28% no IABP</td>
</tr>
</tbody>
</table>
TL: Thrombolysis
TT: Thrombolytic Therapy
MI: Myocardial Infarction
NS: Non Significant
Table 2: Trials of IABP for the Treatment of Cardiogenic Shock

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>N</th>
<th>Inclusion Criteria</th>
<th>Intervention</th>
<th>Outcomes</th>
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</thead>
<tbody>
<tr>
<td>IABP vs Usual Care</td>
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<tr>
<td>O’Rourke, 1981</td>
<td>RCT in two centers</td>
<td>30</td>
<td>Acute MI complicated by heart failure (4 had CGS)</td>
<td>IABP vs standard therapy</td>
<td>Hospital mortality</td>
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<td></td>
<td>Mortality at follow-up</td>
</tr>
<tr>
<td>Ohman, 2005 TACTICS</td>
<td>Randomized, multicenter</td>
<td>57</td>
<td>Acute MI complicated by hypotension and eligible for fibrinolytic therapy</td>
<td>Fibrinolytic therapy vs fibrinolytic therapy plus 48 hours IABP</td>
<td>All cause mortality at six months</td>
</tr>
<tr>
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<td></td>
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<td></td>
<td>Secondary endpoints included in hospital reinfarction, in-hospital safety events, in-hospital stroke, in hospital death or non-fatal MI, new CHF and 30 day mortality</td>
</tr>
<tr>
<td>Prondizinsky, 2010 SHOCK</td>
<td>Randomized controlled open label</td>
<td>45</td>
<td>Acute MI and CS and undergoing PCI</td>
<td>IABP vs no IABP</td>
<td>APACHE II scores</td>
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<td>Hemodynamic values</td>
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<td>Inflammatory markers</td>
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<td></td>
<td>BNP</td>
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<tr>
<td>Thiele, 2012 SHOCK II</td>
<td>Randomized, multicenter, open-label</td>
<td>600</td>
<td>AMI and CS and planning to have revascularization</td>
<td>IABP vs no IABP</td>
<td>30 day mortality</td>
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<td></td>
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<td></td>
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<td></td>
<td>Major bleeding, peripheral ischemic complications, sepsis and stroke</td>
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<tr>
<td>IABP vs Percutaneous Left Ventricular Assist Devices (LVAD)</td>
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<tr>
<td>Thiele, 2005</td>
<td>Randomized, single center, open label</td>
<td>41</td>
<td>Revascularized AMI with CS with intended PCI</td>
<td>IABP vs Tandem Heart LVAD</td>
<td>Cardiac power index and hemodynamic outcomes</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Secondary outcomes: complications and severe bleeding</td>
</tr>
<tr>
<td>Burkhoff, 2006</td>
<td>Randomized, multicenter, open label</td>
<td>33</td>
<td>CS caused by AMI or decompensated CHF</td>
<td>IABP vs Tandem Heart LVAD</td>
<td>Cardiac index and hemodynamic variables</td>
</tr>
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<td>Secondary endpoints: Overall survival</td>
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<td>Adverse events</td>
</tr>
<tr>
<td>Seyfarth, 2008</td>
<td>Randomized multicenter, open-label</td>
<td>26</td>
<td>AMI complicated by CS</td>
<td>IABP vs Impella LP2.5</td>
<td>Change in cardiac index from baseline to 30 minutes later</td>
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<td>Secondary endpoint: 30 day mortality</td>
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</tbody>
</table>

AMI: Acute Myocardial Infarction  
CHF: Congestive Heart Failure  
APACHE: Acute Physiology and Chronic Health Evaluation  
CS: Cardiogenic Shock  
PCI: Percutaneous Coronary Intervention  
BNP: Brain Natriuretic Peptide
<table>
<thead>
<tr>
<th>Study</th>
<th>Mean Age</th>
<th>Length of Follow-Up</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Rourke, 1981</td>
<td>60 (IABP) 54 (Control)</td>
<td>15 months</td>
<td>Hospital mortality: 50% IABP vs 44% standard therapy; p=0.05 Follow-up mortality 57% vs 62%; p=0.09</td>
<td>No significant benefit Small study with limited power Only 4 patients had CS</td>
</tr>
<tr>
<td>Ohman, 2005 TACTICS</td>
<td>67 (Fibrinolysis) 68 (Fibrinolysis plus IABP)</td>
<td>6 months</td>
<td>No difference in primary end point between groups (34% for combined treatment vs 43% for fibrinolysis alone) Trend toward benefit of IABP in those with Killip Class III or IV (6 month mortality 39% vs 80% for fibrinolysis alone: p=0.05)</td>
<td>9/27 patients in the fibrinolysis group got an IABP Small study with limited power</td>
</tr>
<tr>
<td>Prodinsky, 2010 SHOCK</td>
<td>64.2</td>
<td>4 days</td>
<td>Change in APACHE II score: 2.4 point reduction in IABP group vs 2.8 in standard therapy group: NS Hospital mortality: 36.8% in IABP group and 28.6% in standard treatment group (NS) No significant difference in cardiac index between groups BNP drop at day 2 and 3 greater in IABP group</td>
<td>No difference in clinical outcomes (APACHE score and hospital mortality) between the two groups</td>
</tr>
<tr>
<td>Thiele, 2012 SHOCK II</td>
<td>70 (IABP group) 69 (control)</td>
<td>30 days</td>
<td>30 day mortality: 39.7% in IABP group vs 41.3% control (RR 0.96: 95% C.I.: 0.79-1.17: p=0.69) Major bleeding 3.3% IABP vs 4.4% control: p=0.51 Peripheral ischemic complications: 4.3% IABP vs 3.4%; p=0.53) Sepsis (15.7% IABP vs 20.5%; p=0.15) Stroke (0.7% vs 1.7%; p=0.28)</td>
<td>No reduction in the primary outcome of 30 day mortality in patients with AMI and CS who were to undergo PCI</td>
</tr>
<tr>
<td>Study</td>
<td>Mean Age</td>
<td>Length of Follow-Up</td>
<td>Results</td>
<td>Comments</td>
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<tr>
<td>IABP vs Percutaneous Left Ventricular Assist Device (LVAD)</td>
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<td></td>
</tr>
<tr>
<td>Thiele, 2005²⁷</td>
<td>63 (LVAD) 66 (IABP)</td>
<td>30 days</td>
<td>30 day mortality IABP 45% vs LVAD 43%</td>
<td>More complications with VAD</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Limb ischemia and bleeding more in LVAD group</td>
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<td></td>
<td>Ischemia 7 vs 0: p=0.009</td>
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<td></td>
<td></td>
<td></td>
<td>Bleeding 19 vs 8: p=0.002</td>
<td></td>
</tr>
<tr>
<td>Burkhoff, 2006²⁸</td>
<td>66 (LVAD) 60 (IABP)</td>
<td>30 days</td>
<td>No difference in 30 day survival between the two groups (64% IABP vs 53% Tandem Heart; NS)</td>
<td>Tandem Heart improved hemodynamics more than IABP but no difference in survival Small study</td>
</tr>
<tr>
<td>Seyfarth, 2008²⁹</td>
<td>65 (LVAD) 67 (IABP)</td>
<td>30 days</td>
<td>30 day mortality 46% in both groups</td>
<td>Cardiac index was increased with VAD but no effect on mortality</td>
</tr>
</tbody>
</table>

LVAD: Left Ventricular Assist Device(s)
Details of the seven randomized trials and the outcomes measured are described in Table 2. There were four trials comparing IABP with usual care\textsuperscript{1,24,26} and three trials comparing IABP with left ventricular assist devices\textsuperscript{27,29}. A total of 732 patients were included in the studies comparing IABP with usual care: 600 of these came from the SHOCK II Trial. A total of 100 patients were included in three trials comparing IABP with LVAD - the largest study had 41 participants and the smallest had 26 participants.

Measured clinical outcomes included in hospital, 30 day and 6 month mortality, complications such as bleeding or limb ischemia and APACHE II scores. Many of the smaller trials also included hemodynamic outcomes, such as change in cardiac index, inflammatory markers and brain natriuretic peptide (BNP) as primary outcomes.

Level of Evidence: 1,2, 3

TA Criterion 2 is met.

TA Criteria 3: The technology must improve net health outcomes.

The majority of the evidence supporting the use of IABP in cardiogenic shock comes from cohort studies and registry studies. Five retrospective cohort studies or case series, all published in the 1980s or 1990s included a total of 400 patients\textsuperscript{12,16}. Two hundred of these patients came from a single study\textsuperscript{13}. All included participants with acute MI and cardiogenic shock. Most studies compared patients who received IABP vs no IABP, but one study compared patients who received thrombolysis alone, IABP alone or thrombolysis and IABP\textsuperscript{15}. All studies evaluated either in hospital or 30 day mortality. In all of the studies, those who received IABP were slightly younger. Mortality was lower with IABP use in all studies, although this reduction was not statistically significant in all of the studies.
The majority of the evidence supporting use of IABP comes from prospective or registry studies. There is one prospective study reporting observational results from a clinical trial\textsuperscript{17} and three registry studies.

In the GUSTO-I trial, 41,021 patients were randomized to receive four different thrombolytic regimens for the treatment of acute MI.\textsuperscript{30} Prospective data on diagnosis, treatment and outcomes were collected. These data included whether or not patients with cardiogenic shock received IABP. A total of 315 patients developed cardiogenic shock. Information on IABP status was not available for five of them, leaving 310 patients available for analysis. IABP was placed in 68 patients (22%). There were trends toward a reduction in 30 day mortality with IABP use (48% vs 59%;\textit{p} = 0.12) and a significant reduction in one year mortality (67% vs 57%;\textit{p} = 0.04). However, there were more adverse events and more bleeding in the IABP group.

In the SHOCK Trial Registry, patients with cardiogenic shock complicating acute MI were prospectively registered at 36 different institutions.\textsuperscript{19} Patients were treated (based on physician choice) with one of four treatments: thrombolytic therapy (TT) alone, IABP alone, both IABP and TT, or neither IABP or TT. A total of 1,190 patients were enrolled in the SHOCK Trial Registry and 884 of them had cardiogenic shock due to predominant LV failure. Twenty-six patients had the IABP placed before the onset of shock and two patients had incomplete data, leaving 856 patients available for analysis. As in the earlier cohort studies, there were age differences among the groups. Those treated with TT and IABP were significantly younger than patients in any of the other groups. Other risk factors (e.g. previous MI, CHF, renal insufficiency or PVD) were also less common in the TT plus IABP group. Those who were treated with IABP had a lower in hospital mortality than those who did not receive IABP (50% vs 72%;\textit{p} = 0.001). In addition, there was a significant reduction in mortality among the four different treatment groups (47% TT/IABP; 52% IABP only; 63% TT only and 77% no IABP/no TT:\textit{p} < 0.001). Although investigators
attempted to adjust for confounders, those who received IABP tended to be healthier at baseline, which could have influenced the results.

The National Registry of Myocardial Infarction 2 (NRMI 2), a large registry of patients with AMI, is sponsored by Genentech and was started in 1994. Patients are enrolled in the cohort if they are diagnosed with an AMI at a participating hospital. They were included in this analysis if they had cardiogenic shock or if cardiogenic shock developed during their AMI hospitalization. A total of 23,180 patients met inclusion criteria for this analysis. Of these, 7,268 patients (31%) had an IABP inserted. The average age of patients who received an IABP was 67 years, in contrast to 74.1 years for those who did not receive an IABP. In addition, those who received IABP were less likely to have a history of CHF and stroke and were more likely to have received reperfusion therapy. The main outcome was in-hospital mortality. IABP was associated with a significant reduction in mortality among patients who received thrombolytic therapy (67% vs 49%) but was not associated with a mortality reduction among patients treated with primary angioplasty (45% vs 47%). In multivariate analyses, controlling for confounders, IABP in conjunction with thrombolytic therapy decreased the odds of death by 18% (OR 0.82; 95% C.I. 0.72 - 0.93). Again, those who received IABP were healthier at baseline, which again could potentially influence the results.

Finally, among a cohort of 3,038 patients with STEMI treated with PCI and registered in a database in the Netherlands, 292 patients had STEMI complicated by cardiogenic shock. A total of 199 patients had IABP placed and 93 patients had no IABP. Thirty day mortality was 47% in the IABP group vs 28% in the no IABP group. Again, since this was not a randomized controlled trial, there is the possibility of unmeasured confounders.
Potential Benefits

Since cardiogenic shock complicating AMI has such a poor prognosis, the main potential benefit of IABP use in cardiogenic shock is the reduction in mortality. As detailed above, the majority of the nonrandomized comparative studies have shown at least a trend toward a mortality reduction in at least some subgroups. Thus the potential for decreased mortality in a disease where mortality risk is so high is the main potential benefit.

Potential Harms

There are two categories of complications for IABP use. They include vascular and nonvascular events. Vascular complications directly related to the IABP are the major risk associated with IABP use. The most common vascular complications include limb and visceral ischemia, laceration requiring surgical repair and major hemorrhage. Arterial dissection can also occur and requires immediate removal of the IABP.

Nonvascular complications include cholesterol embolization which can sometimes result in loss of a limb, sepsis, especially if the balloon is left in place for more than seven days and balloon rupture. Balloon rupture most often occurs when the balloon pumps against a calcified plaque. Cerebral ischemia and resulting CVA can occur when the IABP has been placed too proximally or when a thrombus has been dislodged. Risk factors for complications include older age, peripheral arterial disease, female sex, diabetes mellitus, hypertension, prolonged support, large catheter size (>9.5 French), body surface area <1.8 m² and cardiac index <2.2 L/min/m². Complications can be decreased by using a sheathless technique and using a smaller balloon size.
Summary

In summary, cardiogenic shock complicating AMI is a serious condition with a high mortality rate. Five small retrospective studies have shown a mortality reduction with IABP. In addition, one prospective observational study of an RCT and three registry studies also suggest a mortality benefit in some if not all subgroups. In all of the studies, those who received an IABP have been younger, and in many cases healthier than those who did not receive an IABP. Although all investigators attempted to adjust for age, disease severity and other confounders, there remains the possibility of unmeasured confounders. The risks associated with IABP use (both vascular and non-vascular) are potentially significant. However, weighing the benefits of a mortality reduction against the risks, IABP does provide net health benefits.

TA Criterion 3 is met.

TA Criterion 4: The technology must be as beneficial as any of the established alternatives.

Four randomized controlled trials have compared the addition of IABP to usual care for the treatment of cardiogenic shock.\textsuperscript{124-26} In the earliest study\textsuperscript{24} 30 patients with early MI complicated by heart failure were randomized to receive IABP (n=14) or standard therapy (n=16). New York Heart Association (NYHA) Functional class also did not differ between the two groups at follow-up. Standard therapy included oxygen, diuretics as needed, heparin, morphine, and lidocaine. Patients who had cardiogenic shock (n=4) received pressors as needed. Hospital mortality was similar in the two groups (7/14 vs 7/16) Overall, there was no clear benefit from the addition of IABP, although all patients had
heart failure, only four of the 30 patients had cardiogenic shock, which limit the conclusions that can be drawn from this study.

In the next study, 57 patients with MI complicated by sustained hypotension or shock were randomized to receive fibrinolysis alone or fibrinolysis with the addition of IABP. The primary endpoint was all cause mortality at six months. Participants in the intervention group had the IABP inserted as soon as possible after randomization and it was left in place for 48 hours. Of the 27 patients assigned to fibrinolysis alone, nine deteriorated and had an IABP inserted. At six months, there was no difference in mortality between the two groups (34% IABP vs 43% fibrinolysis alone: NS). Patients with worse heart failure (Killip class III or IV) showed a trend toward greater benefit with IABP (six month mortality 39% with IABP vs 80% for fibrinolysis alone; p = 0.05).

The third study was the IABP Cardiogenic Shock Trial, a single center randomized controlled study conducted in Germany. Participants were 45 patients with an acute MI complicated by cardiogenic shock and treated with revascularization. IABP plus conventional treatment was compared to conventional treatment alone (vasopressors and or inotropes) and the main outcomes were hemodynamic: cardiac output, pulmonary capillary wedge pressure, pulmonary artery pressure, systemic vascular resistance, pulmonary vascular resistance, cardiac power index, left ventricular stroke work index, heart rate and mean arterial pressure over 96 hours. Since many patients with cardiogenic shock can progress to the multiple organ dysfunction syndrome (MODS) and death caused by organ failure, and since the Acute Physiology and Chronic Health Evaluation (APACHE) score has previously been found to be helpful in predicting likelihood of progressing to MODS, APACHE scores were measured as indicators of prognosis. The main clinical outcome measured was change in APACHE score from baseline to day 4. The APACHE score fell by 2.4 points in the standard therapy group compared with 2.8 points in the IABP group, a difference that was not statistically significant. Hospital mortality was also similar in the two groups (36.8% IABP vs 28.6% standard therapy. In this study, which primarily
focused on hemodynamic outcomes, there were no differences in clinical outcomes between patients treated with standard therapy alone vs those who were treated with standard therapy and IABP.

The IABP-SHOCK II trial was designed as a large prospective multicenter, randomized, open-label, controlled trial with the goal of addressing the question of whether IABP in addition to early revascularization either by PCI or CABG can improve outcomes of patients with cardiogenic shock. The primary outcome was defined as 30 day all-cause mortality. Secondary outcomes included hemodynamic outcomes and laboratory parameters as well as safety assessments. Safety outcomes included major bleeding, peripheral ischemic complications, sepsis and stroke. There is an additional planned follow-up at six and 12 months. Recently the main results of the IABP SHOCK II trial were published. A total of 600 patients with AMI and cardiogenic shock, all of whom were going to receive revascularization, were randomized to receive IABP or no IABP. All were expected to receive revascularization and received the best available medical therapy. A total of 301 patients were randomized to IABP and 299 patients were randomized to usual care. The main outcome was 30 day mortality. At 30 days 119/300 analyzed patients in the IABP group (39.7%) had died vs 123/298 analyzable patients (41.3%) in the control group (RR 0.96 : 95% C.I. 0.79,1.17). For safety outcomes, there were no differences in the rates of major bleeding (3.3 % vs 4.4%; p = 0.51), peripheral ischemic complications (4.3% vs 3.4%; p = 0.53), sepsis (15.7% vs 20.5%; p=0.15) or stroke (0.7% vs 1.7%; p = 0.28). Other measures including time to hemodynamic stabilization, ICU length of stay, necessary dose and duration of catecholamine therapy and renal function also did not differ between the two groups. Six month and twelve month outcomes have not yet been published. This trial did have several limitations. First, because of the nature of the intervention, it could not be blinded. Second, investigators did not measure many of the intermediate measures that have been measured in other trials such as additional hemodynamics and inflammatory markers, but since the main focus is on clinical outcomes, this is less relevant. Third, the overall mortality rate was slightly lower than has been seen in other studies of
patients with AMI and cardiogenic shock, suggesting that these patients may have milder shock, and potentially limiting generalizability. Finally, to date, only 30 day outcomes have been reported. Despite its limitations, this is the largest and most rigorous study assessing the role of IABP in the treatment of AMI complicated by cardiogenic shock, in patients in whom revascularization is planned, and the study found no difference between standard therapy and standard therapy with IABP in the primary endpoint of 30 day mortality.

Left ventricular assist devices (LVAD) with circulatory support have been shown to improve hemodynamic parameters, improve tissue oxygenation and reverse cardiogenic shock. Three small studies have compared IABP with LVAD in patients with cardiogenic shock. These comparative studies assume that IABP is the “standard of care” to which LVAD should be compared. Each of the three studies was small, and together they included only 100 patients. Although some studies showed that hemodynamic parameters improved more with LVAD, none of the studies showed any difference between groups in clinical outcomes of survival.

In summary, only four RCTs have compared the use of IABP to usual care. The three smaller studies did not show any differences in clinical outcomes and the one large study (IABP-SHOCK II) showed no difference in any measured 30 day clinical outcomes with the use of IABP. Thus the current evidence does not suggest that the use of IABP is superior to the established alternative for the treatment of AMI complicated by cardiogenic shock.

Three studies have compared IABP to LVAD. All these studies were small and did not show any differences in clinically significant outcomes, but most importantly since these studies considered IABP the “standard of care,” they did not address the more important question of whether or not IABP should be used in the treatment of AMI complicated by cardiogenic shock.

**TA Criterion 4 is not met.**
TA Criterion 5: The improvement must be attainable outside the investigational settings.

Since an improvement has not yet been shown in the investigational setting, it is not possible to attain an improvement outside the investigational setting.

TA Criterion 5 is not met.

Summary

In summary, IABP for the treatment of cardiogenic shock is currently recommended by the American Heart Association (AHA), but its use has been called into question. The bulk of the supportive evidence comes from registry studies, where those who received IABP had better outcomes than those who did not receive IABP. Despite adjusting for known confounders, there remains the possibility of unmeasured confounders and or selection bias. In the main RCT that was large enough to show a statistically significant difference, and which evaluated the use of IABP for treatment of AMI complicated by CS in patients who are planning to undergo revascularization, there was no reduction in the primary outcome of 30 day mortality with IABP use. Thus, there is currently no evidence from randomized trials that IABP in patients with AMI and CS reduces mortality.
DRAFT RECOMMENDATION

It is recommended that the use of IABP for the treatment of cardiogenic shock does not meet CTAF Criteria 4 or 5 for safety, efficacy and improvement in health outcomes.

This is the first time CTAF has reviewed this technology.
RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Technology Evaluation Center (BCBS TEC)

No reports or assessments were found on this topic at the BCBS TEC website.

Canadian Agency for Drugs and Technology in Health (CADTH)

No reports or assessments were found on this technology at the CADTH website.

National Institute for Health and Clinical Excellence (NICE)

No reports or assessments were found on this technology at the NICE website.

Centers for Medicaid and Medicare Services (CMS)

There is no National Coverage Determination (NCD) code for this technology. Local coverage policies are used to determine coverage. CMS released a document on November 27, 2012 on Potential NCD Topics which listed IAPB as one of the potential topics CMS may consider for further evaluation for NCD development. http://www.cms.gov/medicare-coverage-database/details/medicare-coverage-document-details.aspx?MCDId=19

American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) Task Force on Practice Guidelines


Under Section 8: Complications after STEMI: Recommendations, Class IIa, it states that “The use of intra-aortic balloon pump counterpulsation can be useful for patients with cardiogenic shock after STEMI who do not quickly stabilize with pharmacological therapy.194–197,197a (Level of Evidence: B)”
American College of Cardiology Foundation (ACCF), American Heart Association (AHA) Task Force on Practice Guidelines, and the Society for Cardiovascular Angiography and Interventions (SCAI)

ACCF, AHA, and SCAI jointly published the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. Under Section 5.6. Percutaneous Hemodynamic Support Devices: Recommendation, CLASS IIb states that “Elective insertion of an appropriate hemodynamic support devices as an adjunct to PCI may be reasonable in carefully selected high-risk patients. (Level of Evidence: C)….and that IAPB is frequently used as an adjunct to PCI in hemodynamically unstable patients.”

American College of Cardiology (ACC)

ACC was invited to provide feedback to the draft assessment and to provide testimony at the CTAF public meeting.

The Society of Cardiovascular Angiography and Interventions (SCAI)

SCAI was invited to provide feedback to the draft assessment and to provide testimony at the CTAF public meeting.

The Society of Critical Care Medicine

SCCM was invited to provide feedback to the draft assessment and to provide testimony at the CTAF public meeting.
ABBREVIATIONS

AHA: American Heart Association
AMI: Acute Myocardial Infarction
APACHE: Acute Physiology and Chronic Health Evaluation
CABG: Coronary Artery Bypass Graft
CHF: Congestive Heart Failure
CI: Cardiac Index
CI: Confidence Interval
CS: Cardiogenic Shock
CVA: Cerebrovascular Accident
DARE: Database of Abstracts of Reviews of Effects
GUSTO: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
ICU: Intensive Care Unit
L/min/m²: Liters per minute per meter squared
LV: Left Ventricle or Ventricular
LVAD: Left Ventricular Assist Device(s)
MAP: Mean Arterial Pressure
MI: Myocardial Infarction
MODS: Multiple Organ Dysfunction Syndrome
NRMI 2: National Registry of Myocardial Infarction 2
NS: Non-significant
NSTEMI: Non-ST Segment Myocardial Infarction
NYHA: New York Heart Association
OR: Odds Ratio
PCI: Percutaneous Coronary Intervention
PVD: Peripheral Vascular Disease
SBP: Systolic Blood Pressure
SHOCK: The SHould we emergently revascularize Occluded Coronaries in cardiogenic shock Trial

STEMI: ST Segment Myocardial Infarction

TL: Thrombolysis

TT: Thrombolytic Therapy
REFERENCES


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