# Intra-aortic balloon pump counterpulsation (IABP) for myocardial infarction complicated by cardiogenic shock (Review)

**Unverzagt S, Machemer MT, Solms A, Thiele H, Burkhoff D, Seyfarth M, de Waha A, Ohman EM, Buerke M, Haerting J, Werdan K, Prondzinsky R**


This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 7

http://www.thecochranelibrary.com

## TABLE OF CONTENTS

[Intervention Review]

# Intra-aortic balloon pump counterpulsation (IABP) for myocardial infarction complicated by cardiogenic shock

Susanne Unverzagt[2], Maria-Theresia Machemer[2], Alexander Solms[2], Holger Thiele[3], Daniel Burkhoff[4], Melchior Seyfarth[5], Antoinette de Waha[6], E. Magnus Ohman[7], Michael Buerke[8], Johannes Haerting[2], Karl Werdan[8], Roland Prondzinsky[1]

[1]Cardiology/Intensive Care Medicine, Carl-von Basedow-Klinikum Merseburg, Merseburg, Germany. [2]Institute of Medical Epidemiology, Biostatistics and Informatics, Martin-Luther-University Halle-Wittenberg, Halle/Saale, Germany. [3]Internal Medicine/Cardiology, University of Leipzig, Leipzig, Germany. [4]Medicine, Columbia University Medical School, New York, NY, USA. [5]HELIOS Klinikum Wuppertal, Department of Cardiology, University of Witten-Herdecke, München, Germany. [6]Deutsches Herzzentrum München, Department of Cardiology, Interventional Cardiology Group, München, Germany. [7]Programme for Advanced Coronary Diseases, Division of Cardiovascular Medicine, Duke Heart Center, Ambulatory Care, Durham, NC, USA. [8]Internal Medicine III, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany

Contact address: Roland Prondzinsky, Cardiology/Intensive Care Medicine, Carl-von Basedow-Klinikum Merseburg, Weisse Mauer 42, Merseburg, 06217, Germany. r.prondzinsky@klinikum-saalekreis.de.

**Editorial group:** Cochrane Heart Group.
**Publication status and date:** New, published in Issue 7, 2011.
**Review content assessed as up-to-date:** 19 July 2010.

**Citation:** Unverzagt S, Machemer MT, Solms A, Thiele H, Burkhoff D, Seyfarth M, de Waha A, Ohman EM, Buerke M, Haerting J, Werdan K, Prondzinsky R. Intra-aortic balloon pump counterpulsation (IABP) for myocardial infarction complicated by cardiogenic shock. *Cochrane Database of Systematic Reviews* 2011, Issue 7. Art. No.: CD007398. DOI: 10.1002/14651858.CD007398.pub2.



## ABSTRACT

### Background

Intra-aortic balloon pump counterpulsation (IABP) is currently the most commonly used mechanical assist device for patients with cardiogenic shock due to acute myocardial infarction.

Although there is only limited evidence by randomised controlled trials, the current guidelines of the American Heart Association/ American College of Cardiology and the European Society of Cardiology strongly recommend the use of the intra-aortic balloon counterpulsation in patients with infarction-related cardiogenic shock on the basis of pathophysiological considerations as also non-randomised trials and registry data.

### Objectives

To determine the effect of IABP versus non-IABP or other assist devices guideline compliant standard therapy, in terms of efficacy and safety, on mortality and morbidity in patients with acute myocardial infarction complicated by cardiogenic shock.

### Search strategy

Searches of CENTRAL, MEDLINE and EMBASE, LILACS, IndMed and KoreaMed, registers of ongoing trials and proceedings of conferences were conducted in January 2010, unrestricted by date. Reference lists were scanned and experts in the field contacted to obtain further information. No language restrictions were applied.

### Selection criteria

Randomised controlled trials on patients with myocardial infarction complicated by cardiogenic shock.

**Data collection and analysis**

Data collection and analysis were performed according to a published protocol. Individual patient data were provided for five trials and merged with aggregate data. Summary statistics for the primary endpoints were hazard ratios (HR's) and odds ratios with 95% confidence intervals (CI).

**Main results**

Six eligible and two ongoing studies were identified from a total of 1410 references. Three compared IABP to standard treatment and three to percutaneous left assist devices (LVAD). Data from a total of 190 patients with acute myocardial infarction and cardiogenic shock were included in the meta-analysis: 105 patients were treated with IABP and 85 patients served as controls. 40 patients were treated without assisting devices and 45 patients with LVAD. HR's for all-cause 30-day mortality of 1.04 (95% CI 0.62 to 1.73) provides no evidence for a survival benefit. While differences in survival were comparable in patients treated with IABP, with and without LVAD, haemodynamics and incidences of device related complications show heterogeneous results.

**Authors' conclusions**

Available evidence suggests that IABP may have a beneficial effect on the haemodynamics, however there is no convincing randomised data to support the use of IABP in infarct related cardiogenic shock.

## PLAIN LANGUAGE SUMMARY

**Intra-aortic Balloon counterpulsation in patients with acute myocardial infarction and cardiogenic shock**

Patients with acute myocardial infarction complicated by cardiogenic shock still have a poor prognosis after primary revascularization procedures such as coronary artery bypass grafting or primary percutaneous coronary intervention. Under patho-physiological considerations, the failing heart due to impaired left ventricular function following acute myocardial infarction is the main cause for the development of cardiogenic shock characterized by instable haemodynamics with reduced systolic and mean arterial pressures. The reduced blood pressure leads to hypoperfusion with reduced oxygen supply to vital organs. Following these pathophysiological considerations it seemed to be a consequent therapeutic concept to give haemodynamic support to these haemodynamically instable patients by a mechanical assist device, called intra-aortic balloon pump (IABP). While the balloon becomes in- and deflated synchronal with the beats of the heart, it acts to increase blood flow to the heart as well as reduce the amount of work the heart is doing. This support can be provided for a few hours and up to several days. Recent evidence suggests that certain patients with acute myocardial infarction complicated by cardiogenic shock and treated by thrombolysis may have a benefit from a period of support with the IABP after revascularization by thrombolysis. Nowadays the most preferred revascularization procedure is primary percutaneous coronary intervention. For these patients a few number of heterogeneous randomised trials with only small patient numbers were not able to show convincing evidence, for either benefit or harm, supporting the use of the intra-aortic counterpulsation beyond initial haemodynamic improvements. This present lack of evidence due to a small number of randomised controlled trials with small numbers of patients does not exclude, that there might be clinically significant effects, which only can be proven by larger randomised controlled trials. For this reason a larger multicenter trial (IABP-SHOCK II) has been started in 2009, to clarify the use of the IABP in infarct related cardiogenic shock and its results will provide better evidence at the beginning of 2013.

## BACKGROUND

### Description of the condition

Worldwide, cardiovascular disease is estimated to be the leading cause of death and loss of disability-adjusted life years (Murray 1996). Each year approximately 920,000 people in the United States (US) experience acute myocardial infarction (AMI), and about 150,000 of them die: accounting for 5.1% of all male and 2.5% of female AMI deaths. The estimated direct and indirect 2008 cost of coronary heart disease (ICD/10 codes I20-I25) in the US was $156.4 billion (AHA 2008). In the United Kingdom

about 227,000 myocardial infarctions occur annually and it has been estimated that about 1 million people over 35 years old, have had a myocardial infarction (BHF 2007). Data from the INTERHEART study showed that rates of cardiovascular disease have risen greatly in low-income and middle-income countries with about 80% of the global burden of cardiovascular disease occurring in these countries (Yusuf 2004).

AMI is complicated by cardiogenic shock in 7% to 10% of cases (Goldberg 1999; Hochman 1999). Cardiogenic shock after AMI is a complex syndrome that involves a cascade of acute left ventricular dysfunction, decreased cardiac output, hypotension, and tissue hypoperfusion (Hochman 2007). Subsequently, complicating multi-organ dysfunction might occur due to ischemia/reperfusion and the following inflammatory response. Clinically defined, cardiogenic shock is hypotension (a systolic blood pressure of < 90 mm Hg for at least 30 minutes or the need for supportive measures to maintain a systolic blood pressure of ≥ 90 mm Hg) and end-organ hypoperfusion (cool extremities or a urine output of < 30 ml per hour, and a heart rate of ≥ 60 beats per minute). Haemodynamic criteria include cardiac index (< 1.8 L/min/$m^2$ or < 2.2 L/min/$m^2$ if inotropic drugs are used) and a pulmonary-capillary wedge pressure of at least 15 mm Hg (Forrester 1976a; Forrester 1976b; Hochman 1999). Patients with sustained hypotension, suspected cardiogenic shock or suspected acute heart failure at the time of AMI are at increased risk of death approaching 30% to 70% mortality within 30 days (Ohman 2005b). Fewer than 50% patients with cardiogenic shock survive up to one year (Hochman 2007).

The poor outcome associated with medical management of cardiogenic shock has spurred more aggressive interventional approaches, including thrombolysis, intra-aortic balloon support and early diagnostic angiography with primary percutaneous coronary revascularization (PCI) (Ohman 2005b). Early mechanical revascularization, using either percutaneous coronary intervention or coronary artery bypass graft (CABG) surgery, along with supportive care, improves mid- and long-term survival in these patients when compared with initial medical stabilisation alone (Hochman 2001).

## Description of the intervention

Aortic counterpulsation (intra-aortic balloon pump (IABP)) was introduced in 1968 into clinical practice (Kantrowitz 1968) as a means for supporting patients undergoing surgical revascularization. Initial experience documented that this device had important physiological effects including an improvement of cardiac function and diastolic blood pressure and a reduction in systemic acidosis. More recently, several investigators have also shown enhanced coronary, cerebral and renal perfusion (even microperfusion) with IABP, particularly among patients having percutaneous coronary intervention during cardiogenic shock. However, this impressive physiological profile has not been followed by equally important randomised clinical trial data (Ohman 2001; Werdan 2010a).

During the last years IABP-insertion became safer according to smaller diameters of the balloon catheter and the corresponding insertion sheaths. Nevertheless every additional arterial puncture especially in cases of emergency can lead to IABP related complications such as bleedings, arterial ischemia, venous thrombosis and also infections. For the reason that especially bleeding complications are not always defined and reported according to comparable standards, the evaluation of IABP related complications remains hampered. Studies reporting complication rates are diverse in terms of the indications for aortic counterpulsation, the technique used for insertion (surgical or percutaneous), the duration of use, and the specific definition of a complication (Arafa 1999; Assis 2009; Cohen 2003; Cooper 2008; Dyub 2008; Erdogan 2006; Fuchs 2009; Gjesdal 2009; Kocogullari 2008; Kumbasar 1999; Lewis 2007; Pfeiffer 2005; Riaz 2008; Stone 2003). The presence of peripheral arterial disease (including a history of claudication, femoral bruit, or absent pulses) has been the most consistent and reproducible predictor of complications (Santa-Cruz 2006). Arafa 1999 reported major vascular complications (limb ischemia, aortic dissection, abdominal aorta perforation, bilateral limb ischemia) in 8%, minor vascular complications (hematoma requiring operative revision, haemorrhage treated by IABP-removal, limb ischemia relieved by IABP-removal, local infection and Ischaemic skin loss) in 3% and late vascular complications in 2% (foot drop, pseudoaneurysm, limb ischemia) of patients.

## Why it is important to do this review

IABP is currently the most commonly used mechanical assist device for patients with cardiogenic shock. Its use is encouraged by a class I recommendation in the American Heart Association (AHA)/American College of Cardiology (ACC) and also the European Society of Cardiology (ESC) guidelines for the management of AMI patients with cardiogenic shock (Antman 2004; van de Werf 2008). The Level B in the AHA/ACC and C evidence in the ESC guidelines behind this recommendation can largely be attributed to pathophysiological considerations and benefits observed in registries that predominantly enrolled patients treated with thrombolytic therapy in the pre-PCI era. There are still controversial differences in therapeutic behaviour in the US and European countries with far greater use of IABP in the US than in Europe. In the US with the highest rate of IABP use, the mortality rate was relevant lower than in European countries such as the United Kingdom (Hudson 1999).

In the early 1980s two smaller randomised trials failed to show any benefit of IABP compared with control therapy on infarct size or left ventricular function in patients with myocardial infarction predominantly without cardiogenic shock (Flaherty 1985; O'Rourke 1981). Previous randomised trials of IABP in high-risk patients without cardiogenic shock have suggested a lower mor-

bidity, particularly among the patients with several high-risk features (Ishihara 1991; Ohman 1994). These studies were too small to address mortality, but they favoured a better outcomes with IABP treatment compared to standard therapy without IABP. Randomised trials of IABP in cardiogenic shock are clearly needed, and one was conducted with surrogate endpoints (Prondzinsky 2010) and another was not completed because of physician bias and difficulties in obtaining consent among critically ill patients (Ohman 2005a).

Non-randomised clinical studies have nearly uniformly shown a benefit associated with IABP for patients with cardiogenic shock (Alcan 1983; Forssell 1979; Holmes 1997; Kontovannis 1999; Kovack 1997b; McEnany 1978; Moulopoulos 1986b; Takano 1984; Weiss 1984). However, these studies are subject to selection bias: patients receiving IABP were in general younger, had fewer comorbid illnesses, and were more aggressively treated with cardiac catheterization and revascularization compared with patients not treated with IABP (Hudson 1999; Sanborn 2000). Data from a large, prospective registry suggest little benefit of IABP placement in cardiogenic shock patients treated with primary PCI (Barron 2001) and one trial reported higher mortality rates associated with IABP use in this group of patients (Barron 2001).

Based on a recent publication it seems probable that not all patients in cardiogenic shock benefit from IABP therapy (Hochman 2003) in which the component of inflammation was associated with systemic inflammatory response syndrome and septic organ failure. This begs the question whether IABP may be beneficial in inflammatory conditions and whether IABP may accelerate systemic inflammation by continuous blood cell surface activation.

A systematic review by Field 2007 suggests that preoperative IABP use may be beneficial on mortality and morbidity in specific high risk patients groups undergoing coronary artery bypass surgery.

A systematic review by Sjauw 2009 of intra aortic balloon pump therapy in ST-elevation myocardial infarction performed two separate meta-analyses. The first meta-analysis included seven randomised trials with 1009 patients with STEMI without restriction to patients with cardiogenic shock and the second one uses data from 10,529 STEMI patients from non-randomised trials with cardiogenic shock. A second systematic review by Cheng 2009 performed a meta-analysis of three studies comparing safety and efficacy of IABP with percutaneous left ventricular assist devices (LVADs) and performed meta-analysis of aggregate data to 30-day survival, haemodynamics (CI, MAP and PCWP) and adverse events (leg ischemia, bleeding and sepsis).

The results of this review add some evidence and represents a formal assessment of the cumulative data with meta-analysis of all the evidence for and against the use of IABP in patients with acute myocardial infarction complicated by cardiogenic shock. IABP-insertion in critically ill patients is correlated with some risk complications and these potential risks can only be justified by an acceptable (evidence-based) opportunity of measurable beneficial clinical effects in IABP-treated patients. This could have implications for clinical practice. Two additional studies comparing IABP versus standard without IABP (Arias 2005; Prondzinsky 2010) and subgroups of patients with myocardial infarction and cardiogenic shock of two other studies (Burkhoff 2006; Ohman 2005a) were included. Extensive analyses of 30-days and six-months mortality distribution provide an important opportunity to examine the effects over a prolonged period. Analyses were adjusted for age, sex and diabetes to see whether the observed effects were consistent across different types of patients.

# OBJECTIVES

The primary aim of this review is to evaluate, in terms of efficacy and safety, the effect of IABP versus non-IABP or other assist devices guideline compliant standard therapy on mortality and morbidity in patients with AMI complicated by cardiogenic shock.

# METHODS

## Criteria for considering studies for this review

### Types of studies

Randomised controlled trials with or without blinding and any report of mortality that examined the efficacy of IABP versus standard therapy were included. We accepted cross-over studies. Observational trials were excluded.

### Types of participants

Adult patients (from the age of 18) with a clinical diagnosis of myocardial infarction complicated by cardiogenic shock undergoing PCI, CABG or thrombolysis.

### Types of interventions

IABP versus non-IABP or other assist devices guideline compliant standard therapy. The term standard therapy describes guideline compliant therapies (percutaneous coronary intervention, coronary artery bypass graft surgery or thrombolysis, pharmacological haemodynamic and, as required ventilatory or other organ function support).

### Types of outcome measures

#### Primary outcomes

- All-cause mortality (mortality distribution and rates within the commonly accepted limits of either to discharge, within 30 days, 6 months and 1 year)
- Non-fatal cardiovascular events (reinfarction, reocclusion and subsequent re-revascularization, stroke, recurrent ischemia), (hierarchical lower ranked endpoint).

#### Secondary outcomes

- Haemodynamics (cardiac index (CI), mean arterial pressure (MAP), pulmonary capillary wedge pressure (PCWP)).
- Length of hospital and intensive care unit (ICU) stay.
- Quality of life.
- All IABP-related post-interventional complications.

## Search methods for identification of studies

Searches were conducted to identify published and unpublished randomised controlled trials. Searching for trials included all information available since 1968 (introduction of IABP into clinical practice, Kantrowitz 1968) up to January 2010. No language restrictions were included in the search strategies.

### Electronic searches

The search strategies for the review were constructed by using a combination of subject headings and terms relating to the health condition of interest (myocardial infarction and cardiogenic shock), the intervention (intra-aortic balloon counterpulsation) and the type of study design (randomised trial). We used controlled vocabulary terms and text words and searched different sources of information. The search strategies used are documented in Appendix 1.

The following sources were searched:

1. Health-related electronic bibliographic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library* (Issue 1, 2010), MEDLINE (OVID) (1966 to January 2010, Week 2, searched on 19 January 2010), EMBASE (1980 to January 2010, Week 2, searched on 19 January 2010), LILACS, IndMedand KoreaMed (unrestricted date to January 2010, searched on 20 January 2010). .
2. Registers of ongoing and completed trials:
   - www.controlled-trials.com (searched on 28 January 2010)
   - www.centerwatch.com (searched on 29 January 2010)
   - Benchmark registry (www.datascope.com/ca/pdf/benchmark2_brochure.pdf) and
   - National Research Register (www.controlled-trials.com/mrt/archived (2000-2007).

### Searching other resources

Hand searching included the annual conference proceedings of the following societies: American Heart Association (AHA) (published in Circulation), American College of Cardiology (ACC), European Society of Cardiology (ESC), European Society of Intensive Care (ESICM) and Deutsche Gesellschaft für Kardiologie (all 1968 to 2009).

Members of the Cochrane Heart Group, experts in the field and manufacturers of the device were contacted. In addition, reference lists from eligible trials were scanned and first authors were contacted to obtain further information on study design and to collect individual patient data.

## Data collection and analysis

### Selection of studies

Studies identified through the search strategies described above were screened by titles. In a second step, two authors (SU & MM) independently screened abstracts and keywords. Full articles were taken into account for further assessment if the information given suggests that the study:

- used random or quasi-random allocation to the comparison groups (IABP versus non-IABP)
- included patients with myocardial infarction complicated by cardiogenic shock
- included primary data

Differences in opinion were settled by consensus with a third reviewer (RP). After the exclusion of non-relevant publications and duplicates, the full-text versions of the remaining papers were assessed against the inclusion and exclusion criteria and data were extracted and entered into standardised data extraction forms.The selection process was recorded in a PRISMA flow chart according to Moher 2009.

### Data extraction and management

Two authors (SU & MM) independently extracted details of study population, interventions and outcomes by using a data extraction form, which was designed especially for the topic of this review. Differences in data extraction were resolved by consensus with a third author (RP), referring back to the original article. The data extraction form included the following items:

- General information - title, authors, source, contact address, country, published/unpublished, language and year of publication, sponsoring of trial;
- Trial characteristics - including study design, timing/follow-up, quality assessment as specified above;
- Patients - inclusion and exclusion criteria, sample size, baseline characteristics, similarity of groups at baseline, withdrawals, cross-over and losses to follow-up;

- Interventions - type of standard therapy and comparison assist devices; and
- Outcomes - time to death (hazard ratios [HR] and their 95% confidence intervals [CI]), number of deaths and patients per group, mortality at specific time points (in-hospital, 30 days, 6 months, 1 year), other clinical event outcomes (reinfarction, reocclusion, re-revascularization, stroke, recurrent ischemia), haemodynamics (cardiac index, mean arterial pressure, pulmonary capillary wedge pressure), length of hospital and ICU stay, doses of catecholamines (dobutamine, arterenol , dopamine), IABP-related post-interventional complications.

As this review was planned as an individual patient-data (IPD) meta-analysis, first authors of all eligible trials were contacted and asked to provide IPD and data on missing information. Analyses are based on updated IPD as reliable and the most powerful method to calculate and compare times to death with adjustment to important co-variables (age, sex and diabetes) and haemodynamics (Piedbois 2004).

### Assessment of risk of bias in included studies

The review analyses the results of randomised trials. Two authors (SU & MM) independently assessed the internal validity of eligible studies according to the Cochrane Collaboration risk of bias tool (Higgins 2011). Disagreements were resolved in discussion with RP and HT until consensus was obtained.
Risk of bias was described and judged in six specific domains:

- sequence generation;
- allocation concealment;
- blinding of participants, personnel, and outcome assessors;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias (such as cross-over, early stopping, per protocol analysis).

The domains of sequence generation, allocation concealment and selective outcome reporting were reported by a single entry for each study. For incomplete outcome data two entries were used because assessments generally need to be made separately for different outcomes (mortality and haemodynamics). A blinding of the investigated intervention was judged to be not possible. The description is based on the published study report which was added by mixture of study reports, protocols, published comments on the study and contacts with the investigators. The judgements involve the answers 'yes' (indicates a low risk of bias), 'no' (indicates a high risk of bias) and 'unclear' (if risk of bias is unknown; or if an entry is not relevant to the study).

### Measures of treatment effect

Meta-analysis was conducted on mortality distribution and mortality rates, non-fatal events, haemodynamics (CI, MAP, PCWP) measured within six hours after implantation, length of hospital and ICU stay on the basis of individual patient data.
HR and 95% CI for time to death as primary outcome measures were calculated for five studies with available IPD to describe mortality distribution over 30 days and six months. For these trials, Kaplan-Meier curves and mortality rates at discharge from hospital and 30-days, six months and one year after randomisation were generated. Mortality rates of all eligible trials were compared and odds ratios were calculated. Because of high survival rates, it was not possible to calculate median survival for both treatment groups in one of the included trials. Weighted mean differences were calculated as effect measures for haemodynamics and lengths of hospital stay and odds ratios for IABP related complications. All final effect measures are presented with their 95% CI .
Safety outcome to describe IABP-related post-interventional complications were chosen a posteriori and included the following frequently reported possibly device-related adverse events during support: bleeding, vascular injury, leg or limb ischemia, embolism, infection and thrombocytopenia. The frequencies of these IABP-related complications and non-fatal cardiovascular events are presented in numbers and percentages with corresponding odds ratios.

### Unit of analysis issues

Patients were individually randomised into two groups. The effect of the intervention was measured and analysed on the basis of single measurements for each outcome for each patient.

### Dealing with missing data

If data were not available in the trial report or data collection the investigators were approached to see if the missing data could be provided. Only in one RCT (Arias 2005) hazard ratios and 95% confidence intervals were not calculated because of missing information. The first author was contacted and provided some missing information. He was not able to provide any individual patient data and had no access to the data base. Odds Ratios describe the effect on in-hospital mortality in this trial. All other HR were calculated from individual patient data.

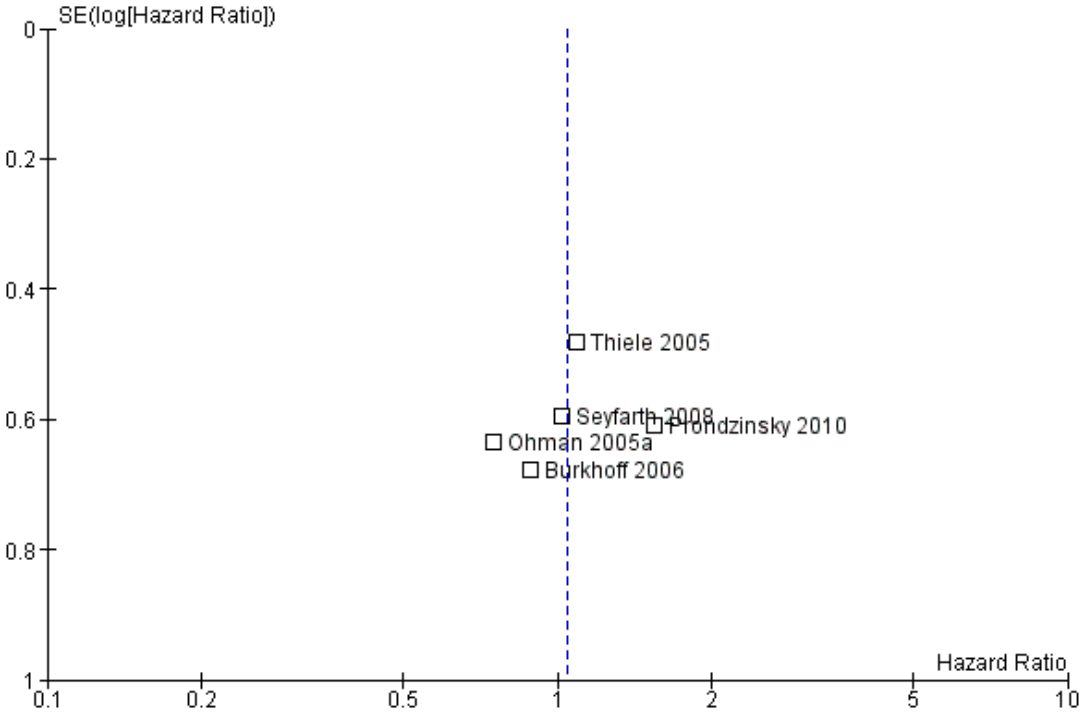
### Assessment of heterogeneity

Heterogeneity was classified on statistical and clinical grounds by two independent reviewers. Inconsistency between studies was quantified by $I^2$ (Higgins 2002). In case of substantial heterogeneity meta-analysis was restricted to subgroups. Independent from the presence of statistical heterogeneity, possible causes were assessed if the differences in outcomes seemed clinically important.

### Assessment of reporting biases

Although every effort was made to identify unpublished studies, publication bias was assessed using funnel plots. It is acknowledged that asymmetry, of which publication bias is one cause, is difficult to detect on the small number of five studies (Figure 1) in case 30 day mortality distribution or four trials in case of in-hospital mortality rates encountered in this systematic review.

**Figure 1. Funnel plot of comparison: IABP versus Control, outcome: all-cause 30-day mortality distribution.**




### Data synthesis

The analysis is based on the intention-to-treat principle. The IPD analysis contains data from all randomised patients with AMI and cardiogenic shock from five of six relevant studies. Analyses of IPD were done using SAS software (Whitehead 2002). First, all trials were analysed individually and finally a stratified Cox model of all trials with different baseline hazard functions in each single trial was used to estimate the overall hazard ratio (one step approach). According to the high heterogeneity between included RCTs (differences in the treatments in the control groups, in pharmacological support, length of follow-up, primary outcome measures, sources of bias) we decided to use the random-effect model for meta-analysis of the relevant studies. The one step meta-analysis as described above and a two step approach (Riley 2010) with separate Cox models in single trials and data synthesis in RevMan gave nearly identical results. We show the results of one-step meta-analyses to describe all-cause mortality distribution in the text and in all additional analyses in Table 1. Data and analysis tables and forest plots display effect estimates and confidence intervals for both individual studies and two-step meta-analyses. IPD was not provided for one study. We reduced our available IPD describing in-hospital-mortality rates to aggregated data and combined aggregate data by the two-stage-approach described in Riley 2007.

Non-fatal cardiovascular events, IABP-related post-interventional complications and all secondary outcome measures were analysed descriptively with RevMan 5.

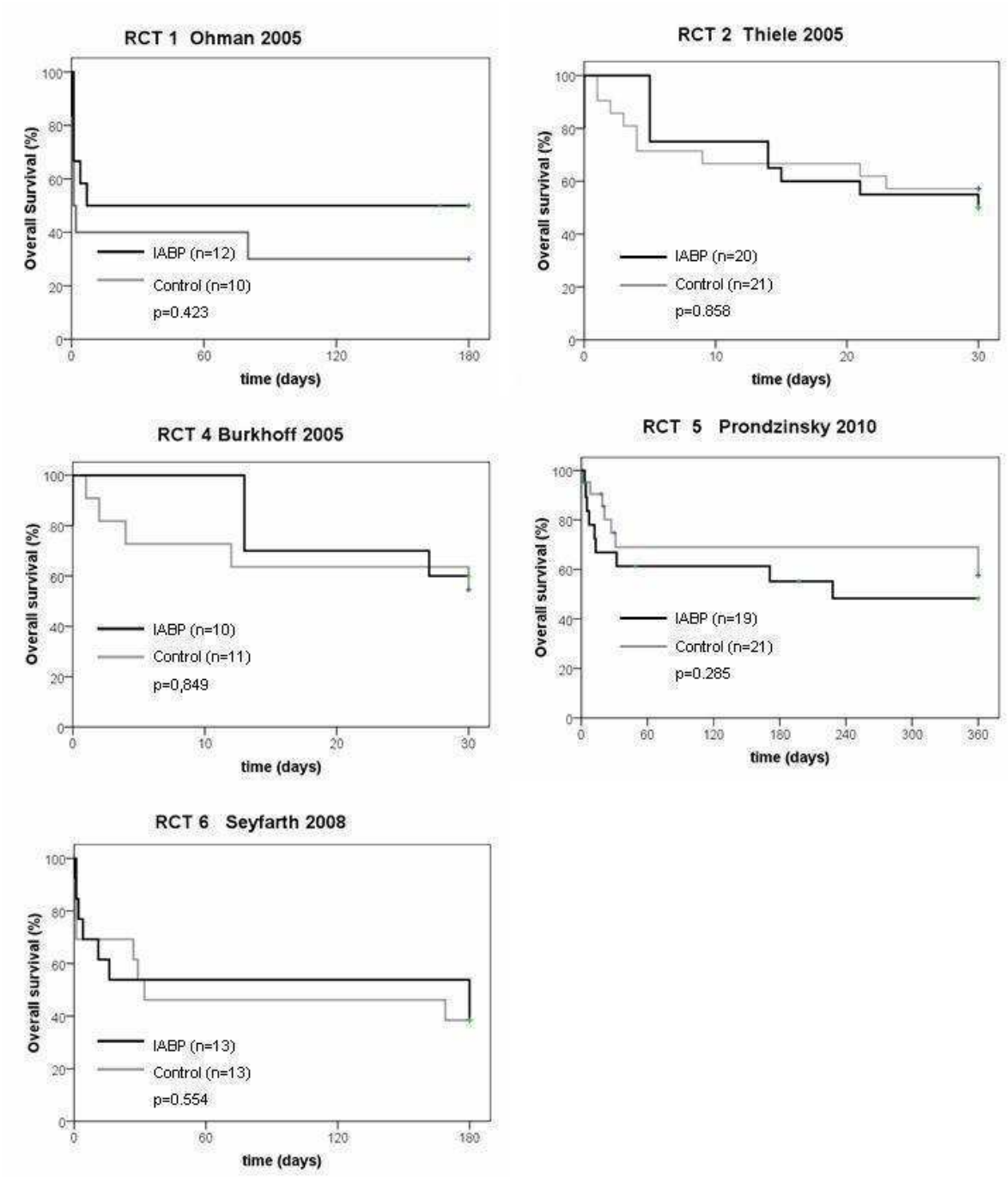
**Table 1. Mortality distribution - additional information**

| Lengths of follow up | adjustment factors | model | Subgroup analysis | HR, 95%CI |
|---|---|---|---|---|
| All-cause 30-day mortality | no | one-step meta-analysis | no | 1.04, 95% CI 0.62-1.73 |
| All-cause 30-day mortality | no | two-step meta-analysis | no | 1.04, 95% CI 0.62-1.74 |
| All-cause 30-day mortality | age, sex | one-step meta-analysis | no | 1.04, 95% CI 0.62-1.75 |
| All-cause 30-day mortality | age, sex, diabetes | one-step meta-analysis | no | 1.05, 95% CI 0.60-2.84 |
| All-cause 30-day mortality | no | one-step meta-analysis | male | 1.08, 95% CI 0.56-2.06 |
| All-cause 30-day mortality | no | one-step meta-analysis | female | 0.90, 95% CI 0.35-2.30 |
| All-cause 30-day mortality | no | one-step meta-analysis | <75 years | 1.11, 95% CI 0.63-1.36 |
| All-cause 30-day mortality | no | one-step meta-analysis | ≥75 years | 0.76, 95% CI 0.19-2.98 |
| All-cause 6-month mortality | no | one-step meta-analysis | no | 0.93, 95% CI 0.49-1.77 |
| All-cause 6-month mortality | no | two-step meta-analysis | no | 0.93, 95% CI 0.49-1.77 |
| All-cause 6-month mortality | age, sex | one-step meta-analysis | no | 0.96, 95% CI 0.50-1.83 |
| All-cause 6-month mortality | age, sex, diabetes | one-step meta-analysis | no | 0.93, 95% CI 0.49-1.78 |

### Dealing with the proportional hazards assumption

The elementary assumption in the Cox Proportional Hazards Model demands a constant effect (or a constant quotient of the hazards over the observation period). Most of study data do not satisfy this assumption (Figure 2).To test the extent of this infraction a gamma frailty model (Duchateau 2008) was applied. This analysis showed only a weak influence on the parameter estimation and we proceeded executing the analysis as preplanned with the Cox Proportional Hazards Model.

**Figure 2. Mortality distribution of patients with myocardial infarction complicated by cardiogenic shock on the basis of individual patient data of five studies included**



### Subgroup analysis and investigation of heterogeneity

Stratified analyses were restricted to preplanned prognostic factors age (<75 vs. ≥75 years) and sex to find differences in survival under IABP support.

### Sensitivity analysis

Sensitivity analyses were performed to explore the influence of including/excluding certain types of studies. Due to the few number of heterogeneous included studies and different sources of bias we restricted our analyses to the preplanned influence of standard therapy (PCI versus thrombolytic therapy) and added a sensitivity analysis to investigate the influence of different types of controls (with or without other LVAD).

## RESULTS

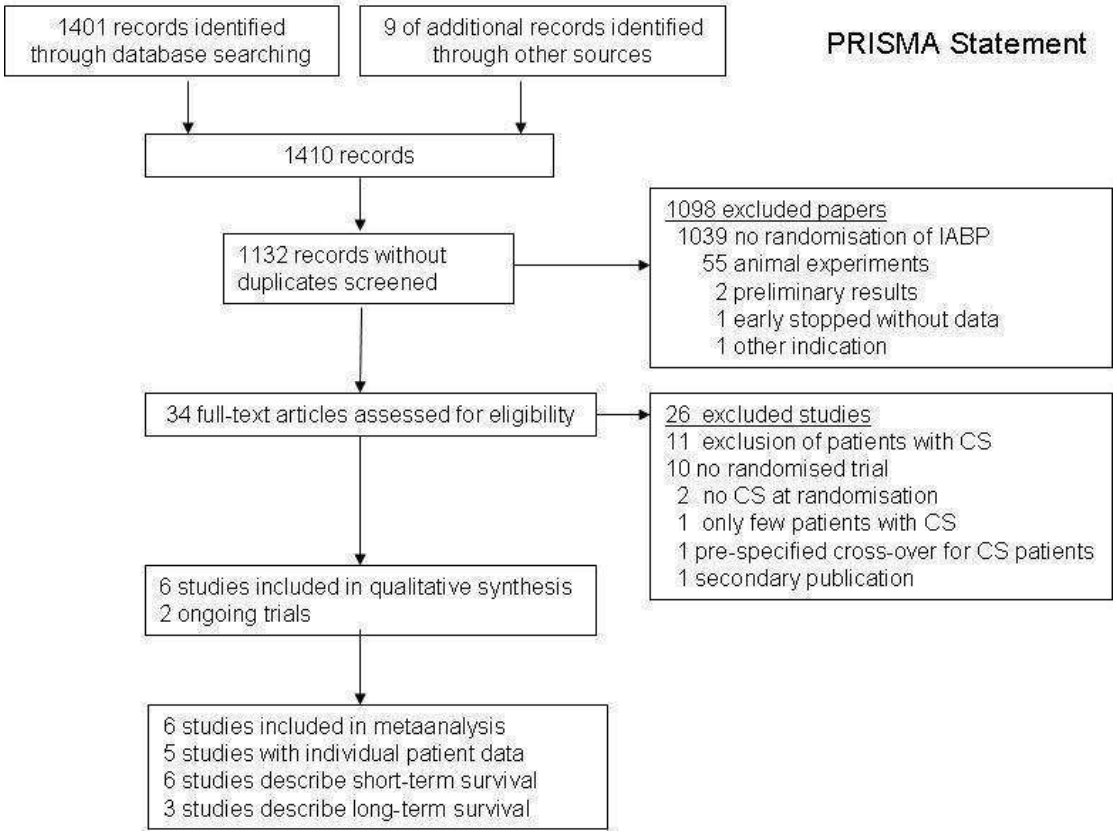
### Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

### Results of the search

Having used the above search strategies to identify potentially relevant references, a total of 1410 references were identified (CENTRAL 5, MEDLINE 757, EMBASE 639 and other 9). Thirty four studies were thought to be of relevance and full papers were assessed against the in- and exclusion criteria. Of these only six met our pre-defined inclusion criteria and two studies are ongoing (see Characteristics of ongoing studies). The remaining studies are listed in Characteristics of excluded studies. This process was recorded in a PRISMA flow chart (Figure 3).

**Figure 3. PRISMA statement to document the search process**



### Included studies

Six eligible studies with a total of 190 patients with AMI and cardiogenic shock were identified for the comparison IABP versus no IABP (Arias 2005; Burkhoff 2006; Prondzinsky 2010; Ohman 2005a; Seyfarth 2008; Thiele 2005). Two studies are ongoing and plan to include 984 patients in cardiogenic shock or with haemodynamic instability (IABP Shock II; RECOVER II Trial). Four studies were conducted in Germany (IABP Shock II; Prondzinsky 2010; Seyfarth 2008; Thiele 2005), two studies in the United States (Burkhoff 2006; RECOVER II Trial), one study in Mexico (Arias 2005) and one study in the United States, Australia and Europe (Ohman 2005a). Most patients had Caucasian or Hispanic ethnicity.

Authors of all included studies provided additional information. Individual patient data from five studies with 150 patients were collected in a database. Each study characteristic is presented briefly in tabular form (please see Characteristics of included studies and Characteristics of ongoing studies). Below a more comprehensive assessment of included studies is given.

Ohman 2005a randomised between 1996 and 1999 57 patients in a multicenter open label trial into two groups, a control group (27) and an intervention group (30). Analysis and descriptions are restricted to 22 patients with suspected cardiogenic shock in Killip Class IV (12 in the intervention group and 10 in the control group). The intervention group got IABP up to three hours after starting fibrinolysis by standard or sheathless technique. Patients received IABP for 48 hours at a rate of 1:1 and were weaned gradually over 12 hours before pump removal. In total 3/10 (33%) of patients with cardiogenic shock from the control group crossed over to emergency IABP and 3/12 (25%) of patients from the intervention group did not receive IABP. Mean duration of support was 53±30 hours in the intervention group. Myocardial revascularization was performed using fibrinolytic therapy (all patients), PCI (23%), stent implantation (14%) or bypass surgery (18%). Pharmacological support with intravenous heparin was prespecified, use of other medications and procedures were left to the discretion of physicians.During the first 30 days 6/12 patients (50%) died in the intervention and 6/10 patients (60%) in the control group (OR 0.67, 95% CI 0.12 to 3.64). Six months after randomisation a total of 6/11 patients (55%) in the intervention group and 7/10 patients (70%) in the control group had died (OR 0.51, 95%CI 0.09 to 3.11). The resulting HRs of all-cause 30-day mortality distribution (HR 0.75, 95%CI 0.28 to 2.00) and 6-month mortality distribution (HR 0.62, 95% CI 0.19 to 2.02, log-rank P=0.42) (Figure 2) slightly favour the intervention with IABP but does not reach statistical significance. Adjustments for age, sex and diabetes showed only little influence on these results. 2/12 patients (17%) suffered from strokes in the intervention group and no re-infarctions were documented as non-fatal cardiovascular events during hospital stay. There were only one related complications in the control group (limb ischemia). Only clinical endpoints and no haemodynamic parameters or information about in-hospital stay and intensive care requirement were provided. The trial was early stopped because of missed enrolment goal.

Thiele 2005 randomised between 2000 and 2003 41 patients in a single centre open label trial into two groups, a control group (21) and an intervention group (20). The inclusion criteria were myocardial infarction complicated by cardiogenic shock. The intervention group got IABP percutaneously according to standard procedures (initially on a pumping ratio of 1:1 with 100% balloon inflation), the control group got treatment with a percutaneous LVAD (TandemHeart). One patient with rapid haemodynamic improvement did not receive LVAD. Mean duration of support with IABP was 84 ± 54 hours in the intervention group and 77 ± 47 hours with TandemHeart in the control group. Myocardial revascularization was performed using PCI (plus stenting) (95% of patients) and bypass surgery (5%). Pharmacological support on the basis of heparin, dopamine and dobutamine, diuretics and fluids was given according to standard intensive care guidelines. All patients with PCI were started with aspirin and clopidogrel. Mortality during the first 30 days included 9/20 patients (45%) in the intervention and 9/21 patients (43%) in the control group (OR 1.09, 95%CI 0.32 to 3.75). The hazard ratio of all-cause 30-day mortality distribution (HR 1.09, 95% CI 0.44 to 2.79, log rank P = 0.86) (Figure 2) reflects no significant difference between groups. Adjustments for age, sex and diabetes showed only little influence on these results. During hospital stay 10/20 patients from the intervention group died (50%) (in-hospital-mortality rate, OR 1.33, 95% CI 0.39 to 4.57). Three patients with four non-fatal cardiovascular events were documented during in-hospital stay: One patient with reinfarction and one with recurrent ischemia in the intervention group and one patient with reocclusion and subsequent re-revascularization in the control group. Pre-implantation cardiac index was noted to fall in the intervention group (1.62 ± 0.37 to 1.19 ± 0.84 L/min/$m^2$ post implantation, P = 0.058) and to rise in the control group (1.71 ± 0.38 to 2.32 ± 0.59 L/min/$m^2$ post implantation, P < 0.001). Pre- implantation MAP was noted to rise in the intervention (65 ± 14 to 72 ± 12 mm Hg post implantation, P = 0.003) as well as in the control group (62 ± 14 to 76 ± 13 mm Hg post implantation, P < 0.001). Pre-implantation PCWP was noted to fall in the intervention (25.1 ± 6.1 to 21.6 ± 5.8 mm Hg post implantation, P = 0.028) as well as in the control group (20.8 ± 4.2 to 15.9 ± 3.8 mm Hg post implantation, P < 0.001). Length of in-hospital stay was 12 ± 14 days in the intervention group and 13 ± 13 days in the control group. There were some possibly related complications in both treatment groups. 5/20 patients (25%) from the intervention and 18/21 patients (86%) from the control group suffered from moderate or severe bleeding. No patient from the intervention group but 7/21 patients (33%) from the control group developed limb ischemia after implantation of a 17 French arterial cannula. 12/20 patients (60%) from the intervention group and 14/21 patients (66%) from the control group suffered from infections. One pa-

tient from the intervention group suffered from embolism and one patient from the control group developed thrombocytopenia.

Arias 2005 randomised between 2001 and 2003 40 patients in a single-centre open label trial into two groups. The authors analysed patients in a control group (9) and an intervention group (31): 27.5% of patients crossed over to IABP. The inclusion criteria were myocardial infarction complicated by cardiogenic shock. The intervention group got IABP percutaneously with fluoroscopy of Arrow AutoCAT 2 WAVE® IABP. Myocardial revascularization was performed using PCI. Pharmacological support was given on the basis of inotropics (dopamine and dobutamine), vasopressors, analgesic and anticoagulant agents. In-hospital mortality rates from the coronary station included 10/31 deaths (32%) in the intervention group and 5/9 deaths (56%) in the control group. The resulting OR (0.38, 95%CI 0.08 to 1.73) slightly favours the intervention with IABP but does not reach statistical significance.

Burkhoff 2006 randomised between 2002 and 2004 33 patients in a multicenter open label trial into two groups, a control group (19) and an intervention group (14). Of the 33 randomised patients, 21 were diagnosed with AMI (10 in the intervention group and 11 in the control group). Additionally, nine patients were treated in the roll-in phase, five of them with AMI: 36% of patients from the intervention group were bridged to another therapy after enrolment (four patients to LVAD, one patient to PCI) and 37% of patients from the control group were bridged to another therapy (three patients to LVAD, one patient to extracorporeal membrane oxygenation, two patients to PCI with stenting placement, one patient to mitral valve repair). The intervention group got conventional treatment with IABP, the control group got treatment with a percutaneous LVAD (TandemHeart). Most patients (67%) entered the study on IABP but still met haemodynamic criteria for cardiogenic shock. Mean duration of support with IABP was 75 ± 95 hours in the intervention group and 61 ± 45 hours with TandemHeart in the control group. Myocardial revascularization was performed for patients with myocardial infarction using PCI (85% of patients), bypass surgery (12%) or LVAD (4%). Pharmacological support on the basis of pressor, inotropic and pharmacologic agents based on physician's standard of care. Mortality of CS and AMI patients during the first 30 days included 4/10 patients (40%) in the intervention and 4/11 patients (36%) in the control group (OR 1.17, 95% CI 0.20 to 6.80). The resulting HR of all-cause 30-day mortality distribution (HR 0.88, 95% CI 0.23 to 3.31, log rank P = 0.85) (Figure 2) reflects no significant difference between groups. Adjustments for age and sex showed no influence on these results. Pre-defined haemodynamic success criteria (no death during support or within 24 hours of device removal, CI $\geq$ 2.2 L/min/$m^2$, PCWP $\leq$ 24 mm Hg, and MAP $\geq$ 70 mm Hg reflecting the average values during support) were satisfied in 14% of all randomised patients in the intervention group compared with 37% of patients in the control group. Most of the patients entered the study already on IABP and were then randomised to continued IABP or switch to TandemHeart. Therfore pre-IABP haemodynamic information are not available and we decided not to include haemodynamic parameters from this trial. There were some possibly related complications in both treatment groups. In the intervention group there was one need for surgical intervention related to treat device related adverse event (7.1%) and one device-related removal because of any problem (7.1%). In the control group there was one instance of device failure (5.3%). On average, patients in the intervention group experienced 2.6 events per patient (1.2 serious) compared with 3.1 events (1.3 serious) per patient in the control group. There were no specific adverse events that related to the performance of the transseptal puncture or insertion of the transseptal cannula. 2/14 patients (14%) from the intervention and 8/19 patients (42%) from the control group suffered from bleeding. 2/14 patients (14%) from the intervention and 4/19 patients (21%) from the control group developed leg ischemia. No patient from the intervention but 3/19 patients (16%) from the control group suffered from cannulation site infection. 3/14 patients (21%) from the intervention and 3/19 patients (16%) from the control group suffered from thrombocytopenia. According to the great number of detected neurologic dysfunction, a proper discrimination between device-related and shock-induced symptoms was not performed.

Prondzinsky 2010 randomised between 2003 and 2004 45 patients in a single centre open label trial into two groups, a control group (22) and an intervention group (23). Of the intervention group, four patients were excluded (two patients did not fulfil the shock criteria; in one patient, the time from MI to shock was $\geq$ 48 hrs; and for one patient, no post-randomisation data was available for technical reasons). Among the 22 patients randomised to control group, one patient was excluded because he did not fulfil the criteria for cardiogenic shock. The intervention group got IABP percutaneously according to standard procedures via the femoral artery using an 8-French sheath immediately after PCI. Aortic counterpulsation was continued for a minimum of 48 hours. Mean duration of support with IABP was 45 ± 34 hours in the intervention group and 184 hours in the one cross-over patient in the control group. Myocardial revascularization was performed using PCI in 90% (in 85 % plus stenting) of patients. Pharmacological support was given on the basis of inotropic and vasopressor agents, aspirin, glycoprotein-IIb-/IIIa-receptor-blocker, heparin according to standard intensive care guidelines. Mortality during the first 30 days included 6/19 patients (32%) in the intervention and 5/21 patients in the control group (24%) (OR 1.48, 95% CI 0.37 to 5.96). During hospital stay 7/19 patients (37%) died in the intervention and 6/21 patients (29%) in the control group (OR 1.46, 95% CI 0.39 to 5.51). Six months after randomisation a total of 8/17 patients in the intervention group (47%) and 6/18 patients in the control group (33%) had died (OR 1.78, 95% CI 0.45 to 6.97). One year after randomisation a total of nine patients (56%) in the intervention and six patients (33%) in the control group had died (OR 2.57, 95% CI 0.64 to 10.34). The HRs of all-cause 30-day mortality distribution (HR 1.55, 95% CI 0.47 to 5.08) and

6-month mortality distribution (HR 1.66, 95% CI 0.57 to 4.79, log-rank P = 0.28) (Figure 2) reflects no significant difference between groups. Adjustments for age, sex and diabetes showed only little influence on these results. Eleven patients (28%) with 22 non-fatal cardiovascular events were documented during in-hospital stay: In the intervention group one patient had reinfarction and recurrent ischemia and two patients (11%) had reocclusion and subsequent re-revascularization. Alternatively, eight patients (38%) had reocclusion and subsequent re-revascularization in the control group. Mean cardiac index was noted to stay nearly constant on the intervention group with a high variability of post-interventional values (2.32 ± 0.57 to 2.93 ± 1.42 L/min/$m^2$post intervention, P = 0.93) as well as in the control group (1.73 ± 0.37 to 2.44 ± 0.67 L/min/$m^2$ post intervention, P = 0.23). Mean MAP showed comparable low changes and high variability in the intervention group (81 ± 11 to 76 ± 16 mm Hg post intervention, P = 0.64) as well as in the control group (83 ± 17 to 80 ± 16 mm Hg post intervention, P = 0.46). Mean PCWP showed no changes but high variability in the intervention group (20.1 ± 5.3 to 20.9 ± 4.4 mm Hg post intervention, P = 0.96) and on a lower level in the control group (14.9 ± 5.6 to 16.2 ± 5.1 mm Hg post intervention, P = 0.78). Length of in-hospital stay were 18 ± 14 days in the intervention group and 29 ± 29 days in the control group. Length of intensive care requirement were 8 ± 7 days in the intervention and 14 ±12 days in the control group (P = 0.06), respectively. There was only one possibly related complication (leg ischemia) in the intervention group. No patient developed other complications as bleeding, vascular injury, embolism, infection or thrombocytopenia that could be attributed to IABP use.

Seyfarth 2008 randomised between 2004 and 2007 26 patients in a two-center open label trial into two groups, a control group (13) and an intervention group (13). The intervention group got conventional treatment with IABP, the control group got treatment with a percutaneous LVAD (Impella). One patient assigned to the control group died before implantation and did not receive LVAD. The assigned device was implanted in both groups after revascularization therapy via the access site. As long as the assigned device was implanted, heparin was given intravenously adjusted to a partial thromboplastin time of 60 to 80 seconds . Mean duration of support with IABP was 26 ± 19 hours in the intervention group and 27 ± 16 hours with Impella in the control group. Myocardial revascularization was performed using PCI (92% of patients) or CABG (8%). Pharmacological support was given on the basis of positive inotropic drugs and vasopressors (remaining unchanged over 30 min after implantation of devices) without further regulations by protocol. Mortality during the first 30 days included 6/13 patients (46%) in the intervention and 6/13 patients (46%) in the control group (OR 1.00, 95% CI 0.21 to 4.67). During hospital stay 5/13 patients (38%) in the intervention and 7/13 patients (54%) in the control group had died (OR 0.54, 95% CI 0.11 to 2.55). Six months after randomisation a total of 6/13 patients (46%) in the intervention and 8/13 patients (62%) in the control group had died (OR 0.54, 95% CI 0.11 to 2.55). The resulting HR of all-cause 30-day mortality distribution (HR 0.99, 95% CI 0.31 to 3.15) and 6-month mortality distribution (HR 0.72, 95% CI 0.24 to 2.13, log-rank P = 0.55) (Figure 2) reflects no significant difference between groups. Adjustments for age, sex and diabetes showed only little influence on these results. During in-hospital stay no patients with non-fatal cardiovascular events were documented in the intervention group but one patient (4%) with three non-fatal cardiovascular events (reinfarction, reocclusion and subsequent revascularization) was reported in the control group. The primary endpoint of the study was the change of cardiac index 30 minutes after implantation. Pre- implantation cardiac index remained stable in the intervention group (1.73 ± 0.59 to 1.84 ± 0.71 L/min/$m^2$ post implantation, P = 0.25) and was noted to rise in the control group (1.71 ± 0.45 to 2.20 ± 0.64 L/min/$m^2$ post implantation, P = 0.003). Pre-implantation MAP remained stable in the intervention group (72 ± 17 to 71 ± 22 mm Hg post implantation, P = 0.79) and was noted to rise in the control group (78 ± 16 to 87 ± 18 mm Hg post implantation, P = 0.039). Pre-implantation PCWP tended to decrease in the intervention group (21.9 ± 6.6 to 20.2 ± 5.5 mm Hg post implantation, P = 0.08) as well as in the control group (22.1 ± 8.1 to 19.3 ± 4.7 mm Hg post implantation, P = 0.09). Length of in-hospital stay was 18 ± 11 days in the intervention group and 14 ± 4 days in the control group. There were 3/13 patients with complications (infection in 23% of patients) in the intervention group, one patient with bleeding and one patient with acute limb ischemia requiring surgery after device explantation in the control group. No complication could be directly attributed to the use of the devices.

### Participants

The age of the patients in the study population of all trials ranges from 33 to 84 years, the median age in the single trial ranges from 64 to 69 years. The proportion of male patients was between 65% and 81%. Between 16% and 54% of participants had diabetes, the percentage of participants with previous infarction was between 22.5% and 58%. The distribution of other baseline characteristics and haemodynamic parameters of patients included in the randomised controlled trials are presented in Characteristics of included studies.

Patients were included into eligible randomised trials between 1996 and 2007. Between two and 35 patients were included per year (median inclusion of 14 patients per year). Burkhoff 2006 randomised 33 patients with cardiogenic shock due to acute myocardial infarction in 70% of patients or decompensated chronic heart failure in most of the remaining patients. We restricted our survival analysis to the individual patients with acute myocardial infarction (10 IABP patients and 11 TandemHeart patients). In the study by Ohman 2005a patients with myocardial infarction complicated by hypotension, suspected cardiogenic shock or heart failure were included for randomisation. At time of randomisa-

tion, 22 patients (39%) had Killip class IV. We restricted our analysis to these patients with cardiogenic shock (12 IABP patients and 10 patients in the control group without IABP). In total, 190 patients were included for meta-analysis, of whom 105 patients were treated with IABP and 85 were treated without IABP.

#### Interventions

Three studies which included 102 patients with AMI and cardiogenic shock compared the intervention IABP versus standard treatment without IABP (Arias 2005; Ohman 2005a; Prondzinsky 2010) and three studies with 88 randomised patients compared the intervention IABP with percutaneous left assist devices. Two of these studies with 62 patients compared IABP versus TandemHeart (Burkhoff 2006; Thiele 2005) and one study with 26 patients compared IABP versus Impella (Seyfarth 2008). The TandemHeart LVAD (TandemHeart, Cardiac Assist, Pittsburgh, PA, USA) is a percutaneous left atrial-to femoral arterial LVAD, driven by a low-speed centrifugal continuous flow pump (Thiele 2001). The Impella LVAD (Impella LP2.5, Abiomed Europe GmbH, Aachen, Germany) is a catheter-based, impeller-driven, axial flow pump which pumps blood directly from the left ventricle into the ascending aorta (Henriques 2006). In this review the intervention group includes all treatment groups with patients randomised to get IABP and the control group include all treatment groups without IABP.

Combining results of all trials, mean duration of support with IABP was 59±57 hours in the intervention group. Myocardial revascularization was performed using PCI in all studies. 85% of patients were revascularized with PCI and 81% with PCI and stenting. Only few patients (5%) and only one study (Ohman 2005a) with thrombolytic therapy as standard was found.

#### Outcomes

Primary data was available to perform a meta-analysis on mortality distribution and mortality rates at discharge from hospital, 30-days, six months and one year after randomisation, haemodynamics, length of hospital and ICU stay and IABP-related complications. Possible IABP-related complications were reported in different ways and a pooled analysis was only possible for bleeding, vascular injury, leg or limb ischemia, embolism, infection and thrombocytopenia. Complications in the single trials are described in Included studies . It was not possible to compare quality of life due to lack of data. Time of follow-up varied between time in coronary unit with 10 to 15 days (Arias 2005), 30 days (Burkhoff 2006; Thiele 2005), six months (Ohman 2005a; Seyfarth 2008) and one year (Prondzinsky 2010).

### Excluded studies

Most randomised trials on IABP excluded patients with cardiogenic shock (Christenson 1997a; Christenson 1997b; Christenson 1997c; Christenson 1999; Christenson 2003; Flaherty 1985; Kono 1996; Ohman 1994; Perera 2009; Stone 1997; Vijayalakshmi 2007) or pre-specified cross-over to IABP in case of cardiogenic shock (Van 't Hof 1999). Ten of the investigated trials did not use a randomised allocation (Anderson 1997; Barron 2001; Bengtson 1992; Kovack 1997a; Moulopoulos 1986a; Sanborn 2000; Stomel 1994; Vis 2007a; Vis 2007b; Waksman 1993) and in two trials, patients had no cardiogenic shock at time of randomisation (Li 2007; Marra 2002). In one trial (O'Rourke 1981) only four patients suffered from cardiogenic shock. Causes for exclusion are presented briefly in tabular form (please see Characteristics of excluded studies).

### Risk of bias in included studies

All trials were published in peer-reviewed journals. Five trials acknowledged the support of either Datascope (Ohman 2005a; Prondzinsky 2010); Cardiac Assist (Burkhoff 2006; Thiele 2005) or Abiomed Europe GmbH (Seyfarth 2008). Datascope is one of the manufacturers of the IABPs, Cardiac Assist of the TandemHeart LVAD and Abiomed Europe GmbH developed the Impella LVAD. The range of the number of included participants was 26 to 57. Three trials compared IABP versus percutaneous LVAD, three trials to standard treatment without IABP. In five trials the analysis was done by intention-to-treat (Burkhoff 2006; Ohman 2005a; Prondzinsky 2010; Seyfarth 2008; Thiele 2005). Figure 4 and Figure 5 present risk of bias in the six eligible studies and summarizes risk of bias.

**Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**

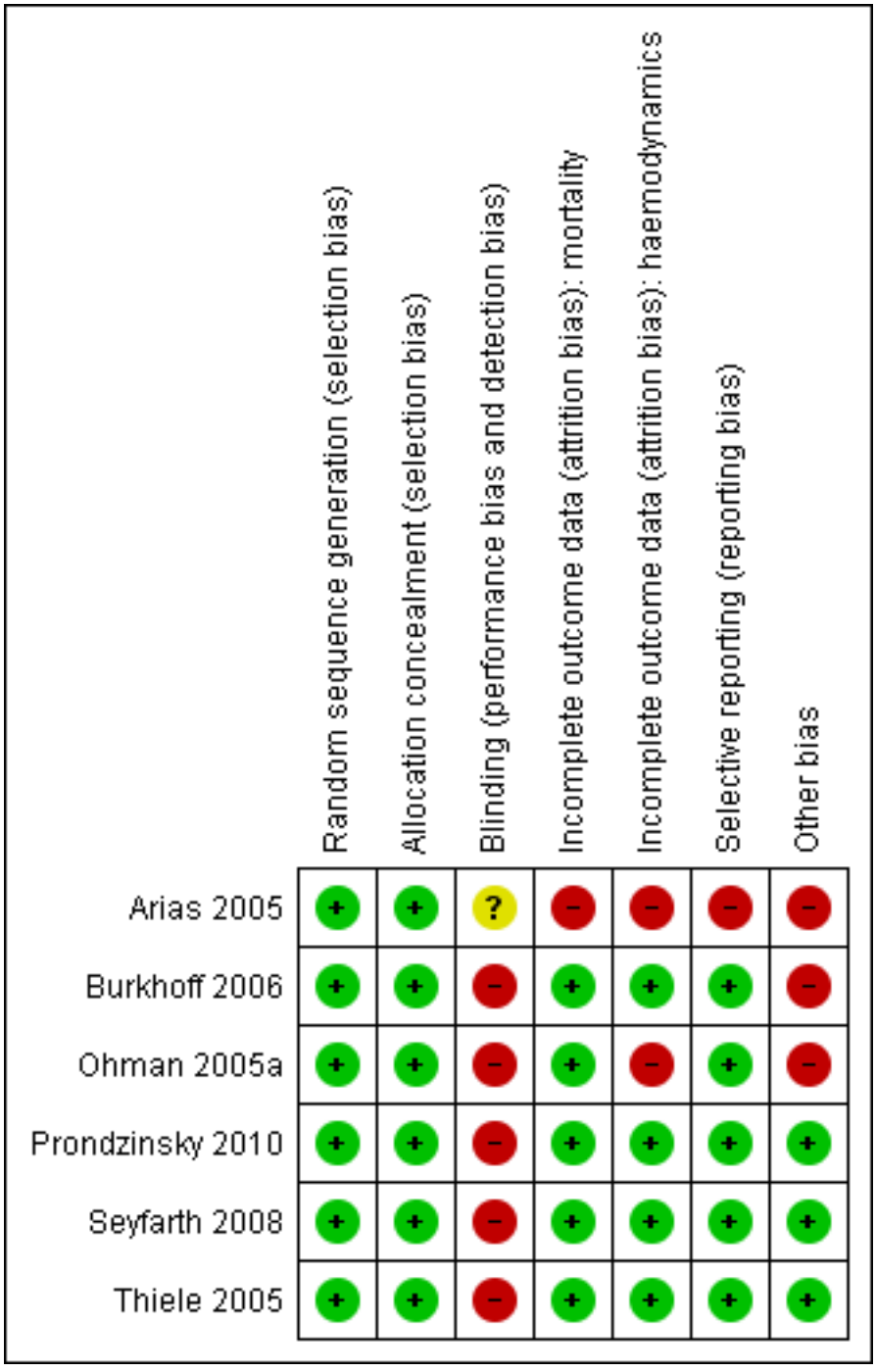
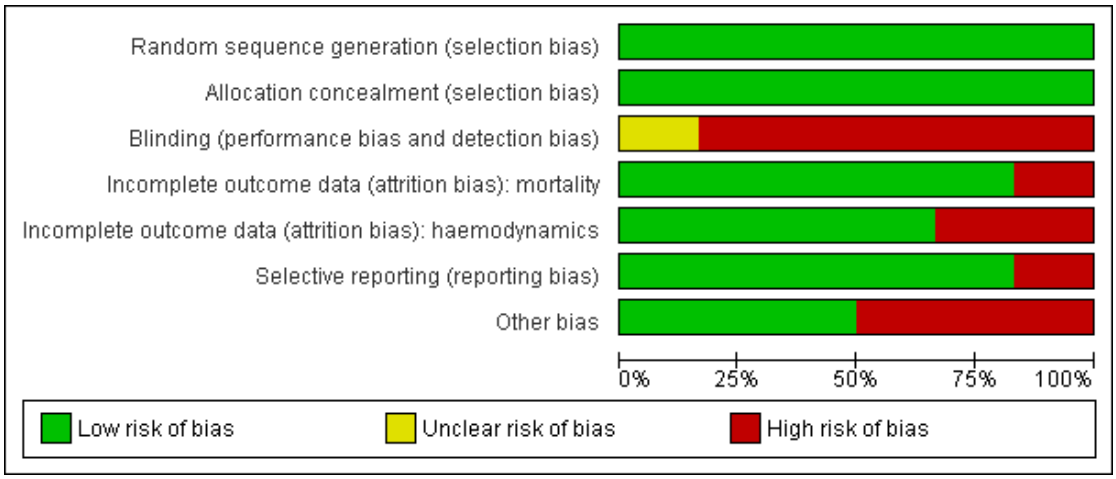


**Figure 5. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**




### Sequence generation

In all trials currently included in this review the method of method of sequence generation was provided by the author. All trials used random tables. One trial used random number tables without further restriction (Thiele 2005), one trial used a stratified randomisation (Arias 2005) and four trials used a blocked randomisation technique (Burkhoff 2006; Ohman 2005a; Prondzinsky 2010; Seyfarth 2008).

### Allocation

In all trials currently included in this review the method of allocation concealment was either described in the text or this information was provided by the author. Adaequate methods of allocation (opaque sealed envelopes or central telephone allocation) were described in all studies. Five trials used opaque sealed envelopes, and in one, a central telephone allocation system was used (Ohman 2005a).

### Blinding

Only one trial described a blinding in the study without further detailed information (Arias 2005). Blinding of the intervention to study personal was not possible rendering the risk of differential behaviour of health care providers in all trials. Unblinding of outcome assessment of investigated objective (especially all-cause mortality) outcomes is unlikely to introduce bias.

### Incomplete outcome data

All-cause mortality and haemodynamics were investigated.
Arias 2005 restricted reporting of all-cause mortality to in-hospital mortality. Complete 30-day follow up data were available in five studies. Six-months follow-up data of all-cause mortality distribution were available in three trials (Ohman 2005a; Prondzinsky 2010; Seyfarth 2008 ) with missing follow-up data of 5/83 (5.5%) patients. Only in one of these studies (Prondzinsky 2010) survival status of 5/40 patients (12.5%) was missed on reasons for missing outcome data unlikely to be related to true outcome (censoring after discharge from hospital).
Haemodynamic post interventional data were reported in four trials with follow-up times ranging from 30 minutes to 28 days. Individual patient data of three trials (Prondzinsky 2010; Thiele 2005; Seyfarth 2008 ) were included into the analysis. Follow-up information was lost in 11/106 patients (10.4%, cardiac index), 5/106 (4.7%, mean arterial pressure) and 16/106 (15.1%, pulmonary capillary wedge).

### Selective reporting

Key outcomes mortality, haemodynamic and adverse events were reported in five of six trials. We missed information about course of haemodynamics after randomisation in Arias 2005.

### Other potential sources of bias

In three studies (Arias 2005; Burkhoff 2006; Ohman 2005a ) important deviations from the study plan, which are possible reasons for bias, were documented: high cross-over rates, early stopping and the inclusion of patients with IABP at randomisation. Cross-over rates were high in these three studies: Arias 2005 reported the results of the per-protocol (PP) analysis with cross over of 11/20 patients to the intervention group. Only results of the per-protocol (PP) analysis were available. These results are restricted to the analysis of in-hospital mortality rates. In Ohman 2005a 3/10 patients (33%) from the control crossed over to the intervention group and 3/12 (25%) from the intervention to control group. The results of the intention-to-treat and per-protocol analysis do not show relevant differences: During the first 30 days 6/12 patients (50%) died in the group randomised to IABP and 6/10 patients (60%) in the group randomised to non-IABP (ITT analysis). From the non-survivors, 5/12 patients (42%) died in the group treated with IABP and 7/10 patients (70%) in the group treated without IABP (PP analysis). The resulting Odds Ratios are 0.67, 95% CI 0.12 to 3.64 (ITT analysis) and 0.30, 95% CI 0.05 to 1.80 (PP analysis). In Burkhoff 2006 5/14 patients (36%) randomised to IABP and 7/19 patients (37 %) from the control group with LVAD were bridged to another therapy, no patient was bridged to IABP. The overall proportion of cross-over compared with observed event risk is to low to have a clinically relevant impact on the intervention effect estimate on mortality. Most patients (66%) in Burkhoff 2006 were enrolled after failure of IABP before enrolment and randomisation but all patients still met haemodynamic criteria for CS. The trial was stopped early on the recommendation of the Data Safety Monitoring Board.
Being aware of these methodological restrictions, we nevertheless decided to include all studies with randomisation of patients with our indication because of the limited number of trials available for this comparison. Risk of bias tables of all single trials are given in detail in Characteristics of included studies.

## Effects of interventions

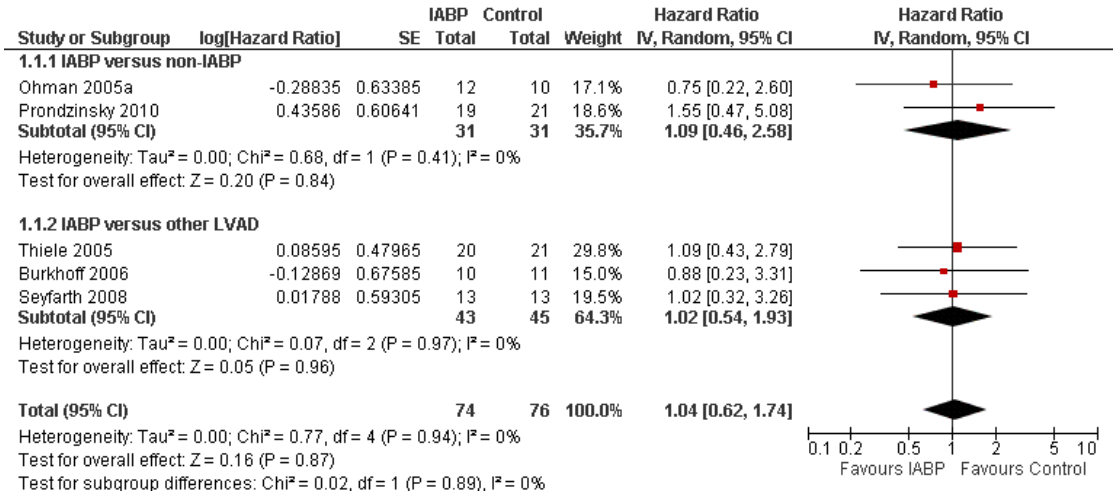
### Primary outcome measures:

#### (a) All-cause mortality

#### 30-days all cause mortality

Combining across all trials, five trials with 150 patients (Burkhoff 2006; Ohman 2005a; Prondzinsky 2010; Thiele 2005; Seyfarth 2008) reported 31/74 (42%) deaths in the intervention compared with 30/76 (39%) deaths in the control group (Analysis 1.3). The hazard ratio indicated no difference in mortality distribution between groups (HR 1.04, 95% CI 0.62 to 1.73, Figure 6).This result was consistent whether a one or a two-step approach was used. Adjustments to age, sex and diabetes does not change the result (Table 1). There was no substantial heterogeneity observed in these analyses.

**Figure 6. Forest plot of comparison: IABP versus Control, outcome: all-cause 30-day mortality distribution.**



A preplanned analysis according to the types of revascularization also showed no differences between groups. Most patients in five studies (Arias 2005; Burkhoff 2006; Prondzinsky 2010; Seyfarth 2008; Thiele 2005) were revascularized by PCI and in Ohman 2005a patients were revascularized with thrombolytic therapy. An additional sensitivity analysis comparing standard without IABP to other LVAD shows no influence on the results. The two studies (Ohman 2005a; Prondzinsky 2010) comparing IABP to standard treatment without IABP did not later the results. A preplanned subgroup analysis investigated the influence of prognostic factors age and sex to all-cause mortality on the basis of individual patient data. Combining results across all trials, 22/50 (44%) men and 9/24 (38%) women died in the intervention and 21/53 (40%) men and 10/23 women (43%) in the control group. 25/58 (43%) of patients < 75 years and 6/16 (38%) of patients ≥ 75 years died in the intervention and 27/68 (40%) and 4/8 (50%) in the control group, respectively (Table 1).

**In-hospital all cause mortality**

Meta-analysis was conducted on four trials with 147 patients to describe in-hospital mortality rates (Arias 2005; Thiele 2005; Prondzinsky 2010; Seyfarth 2008). Combining across trials, 32/83 patients (39%) died in the intervention and 27/64 patients (42%) in the control group (OR 0.88, 95% CI 0.44 to 1.76) (Analysis 1.4).

**Six-months all cause mortality**

Meta-analysis was conducted on three trials with 83 patients to describe all-cause six month mortality distribution (Ohman 2005a; Prondzinsky 2010; Seyfarth 2008). Combining across trials, 20/42 patients (48%) died in the intervention and 21/41 patients (51%) in the control group ( Analysis 1.5). The hazard ratio of 0.93 (95% CI 0.49 to1.77) indicated no difference between groups , even when adjustments were made for age, sex and diabetes or a one- or two step approach was used Table 1). There was no substantial heterogeneity observed in these analysis.

A preplanned analysis according to the types of revascularization also showed no differences between groups. Most patients in Prondzinsky 2010 and Seyfarth 2008 were revascularized by PCI and in Ohman 2005a patients were revascularized with thrombolytic therapy. An additional sensitivity analysis comparing standard without IABP or other LVAD did not later the results.

**One-year all cause mortality**

One-year mortality information is available from 34 patients of one trial (Prondzinsky 2010). 9/16 patients (56%) died in the intervention and 6 /16 patients (38%) in the control group (OR 2.14, 95% CI 0.52 to 8.81).

**(b) Non-fatal cardiovascular events**

Data were available in up to four trials with 129 patients (Ohman 2005a; Prondzinsky 2010; Seyfarth 2008; Thiele 2005). Reported results are combined across trials. 2/64 patients (3.1%) from the intervention and 1/65 patient (1.5%) from the control group suffered from reinfarction, 2/64 patients (3.1%) from the intervention and 0/65 patients from the control group had a stroke. Reocclusion and subsequent re-revascularization were reported in three trials with 107 patients ( Prondzinsky 2010; Seyfarth 2008; Thiele 2005). Altogether, 2/52 patients (3.8%) from the intervention and 10/55 patients (18.2%) from the control group had re-occlusion and subsequent re-revascularization. Recurrent ischemia were reported in two trials with 81 patients ( Prondzinsky 2010; Thiele 2005). 2/39 patients (5.1%) from the intervention and 0/42 patients from the control group had recurrent ischemia (Table 2).

**Table 2. Frequency of non-fatal events**

| study | event | Control group | IABP | | Control | | Odds Ratio (95%CI) |
|---|---|---|---|---|---|---|---|
| | | | Events | Total | Events | Total | |
| Ohman 2005 | reinfarction | non-IABP | 0 (0.0%) | 12 | 0 (0.0%) | 10 | not estimable |
| Prondzinsky 2010 | reinfarction | non-IABP | 1 (5.3%) | 19 | 0 (0.0%) | 21 | 3.49 (0.13-90.86) |
| Thiele 2005 | reinfarction | other LVAD | 1 (5.0%) | 20 | 0 (0.0%) | 21 | 3.31(0.01-86.06) |
| Seyfarth 2008 | reinfarction | other LVAD | 0 (0.0%) | 13 | 1 (7.7%) | 13 | 0.31 (0.01-8.30) |
| **Total events** | **reinfarction** | | **2 (3.1%)** | **64** | **1 (1.5%)** | **65** | not estimated |
| Ohman 2005 | stroke | non-IABP | 2 (16.7%) | 12 | 0 (0.0%) | 10 | 5.00 (0.21-117.21) |

**Table 2. Frequency of non-fatal events** (*Continued*)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Prondzinsky 2010 | stroke | non-IABP | 0 (0.0%) | 19 | 0 (0.0%) | 21 | not estimable |
| Thiele 2005 | stroke | other LVAD | 0 (0.0%) | 20 | 0 (0.0%) | 21 | not estimable |
| Seyfarth 2008 | stroke | other LVAD | 0 (0.0%) | 13 | 0 (0.0%) | 13 | not estimable |
| **Total events** | **stroke** | | **2 (3.1%)** | **64** | **0 (0.0%)** | **65** | not estimated |
| Prondzinsky 2010 | reocclusion and re-revascularization | non-IABP | 2 (10.5%) | 19 | 8 (38.1%) | 21 | 0.09 (0.01-0.81) |
| Thiele 2005 | reocclusion and re-revascularization | other LVAD | 0 (0.0%) | 20 | 1 (4.8%) | 21 | 0.33 (0.01-8.30) |
| Seyfarth 2008 | reocclusion and re-revascularization | other LVAD | 0 (0.0%) | 13 | 1 (0.0%) | 13 | 0.31 (0.01-8.30) |
| **Total events** | **reocclusion and re-revascularization** | | **2 (3.9%)** | **52** | **10 (18.2%)** | **55** | **0.32 (0.03-3.25)** |
| Prondzinsky 2010 | recurrent ischemia | non-IABP | 1 (5.3%) | 19 | 0 (0.0%) | 21 | 3.49 (0.13-90.86) |
| Thiele 2005 | recurrent ischemia | other LVAD | 1 (5.0%) | 20 | 0 (0.0%) | 21 | 3.31 (0.13-86.06) |
| **Total events** | **recurrent ischemia** | | **2 (5.1%)** | **39** | **0 (0.0%)** | **42** | **3.40 (0.34-34.04)** |

## Secondary outcome measures:

### (a) Haemodynamics (cardiac index, mean arterial pressure, pulmonary capillary wedge)

#### Cardiac index

Cardiac index measured after device implantation was available on 95 patients from three eligible studies (Prondzinsky 2010; Seyfarth 2008; Thiele 2005). Cardiac index showed substantial heterogeneity ($I^2$ = 85%) between trials. To explore heterogeneity, a subgroup analysis according to the comparison group was conducted and showed relevant differences according to comparison groups (non-IABP versus other LVAD) on the results. In Prondzinsky 2010, patients randomised to IABP (n = 16) had higher mean cardiac indices compared to control group patients (n = 14) without any assist devices (mean difference (MD) 0.49 L/min/$m^2$, 95% CI -0.29 to 1.27). In contrast, combining the results of two trials, patients randomised to IABP (n = 32) had lower mean cardiac indices compared to control group patients (n = 32) with LVAD (MD -0.75 L/min/$m^2$, 95% CI -1.51 to 0.00).

#### Mean arterial pressure

Mean arterial pressure (MAP) after device implantation was available on 101 patients from three eligible studies. Combining across all trials, patients in the intervention group (n = 50) showed lower mean MAP values post implantation compared to control group patients (n = 51) (MD -5.1 mm Hg, 95% CI -10.9 to 0.66) with low heterogeneity between trials.

**Pulmonary capillary wedge**

Pulmonary capillary wedge (PCWP) after device implantation was available on 90 patients from three eligible studies. Combining across all trials, patients in the intervention group (n = 45) showed higher mean PCWP values post implantation compared to control group patients (n = 45) (MD 3.9 mm Hg, 95% CI 1.1 to 6.7) with moderate heterogeneity between trials ($I^2$ = 44%). To explore heterogeneity a subgroup analysis according to the comparison group (non-IABP or other LVAD) was conducted but a difference according to comparison groups was not stated.

#### (b) Length of hospital and intensive care unit (ICU) stay

Information about length of hospital stay is available from three trials with 77 patients (Prondzinsky 2010; Seyfarth 2008; Thiele 2005) and information about intensive care requirement is available only from 40 patients of one trial (Prondzinsky 2010). Combining across all trials, patients from the intervention groups (n = 38) stayed a shorter mean time in hospital control group patients (n = 39) (MD -4.7 days, 95% CI -10.8 to 1.5) with low heterogeneity between trials (Analysis 1.9). Prondzinsky 2010 showed a corresponding benefit in intensive care requirement with a shorter mean time in the intervention group (n=19) compared to patients in the control group (n = 21) (-6.2 days, 95% CI -12.3 to -0.07).

#### (c) Quality of life

No results were available from included studies.

#### (d) All IABP-related post-interventional complications

Possible IABP related complications were described heterogeneously in the trials. Analyses display frequencies of possibly related complication as moderate or severe bleeding, vascular injury, leg or limb ischemia, embolism, infection and thrombocytopenia. In detail, high incidence of complications in control groups has to be attributed to interventions with other LVAD. In consequence, frequency in the intervention group, in control groups with LVAD and without LVAD are analysed separately (Table 3). Reported results are combined across trials. Up to five trials (Burkhoff 2006; Prondzinsky 2010; Ohman 2005a; Seyfarth 2008 and Thiele 2005) reported the frequency of post-interventional complications. 7/78 patients (9.0%) from the intervention but 0/31 patient in the control group without LVAD and 27/53 patients (51% ) from the control group with LVAD suffered from moderate or severe bleeding. . 0/33 patients in the intervention and 0/21 patients in the control group without LVAD but 2/19 patients (10%) from the control group with LVAD suffered from vascular injury.

**Table 3. Frequency of IABP-related complications**

| study | event | Control group | IABP | | Control | | Odds Ratio (95%CI) |
|---|---|---|---|---|---|---|---|
| | | | Events | Total | Events | Total | |
| Ohman 2005 | bleeding | non-IABP | 0 (0.0%) | 12 | 0 (0.0%) | 10 | not estimable |
| Prondzinsky 2010 | bleeding | non-IABP | 0 (0.0%) | 19 | 0 (0.0%) | 21 | not estimable |
| **Total events** | **bleeding** | **non-IABP** | **0 (0.0%)** | **31** | **0 (0.0%)** | **31** | not estimable |
| Burkhoff 2006 | bleeding | other LVAD | 2 (14.3%) | 14 | 8 (42.1%) | 19 | 0.23 (0.04-1.32) |
| Seyfarth 2008 | bleeding | other LVAD | 0 (0.0%) | 13 | 1 (7.7%) | 13 | 0.31 (0.01-8.30) |
| Thiele 2005 | bleeding | other LVAD | 5 (25%) | 20 | 18 (85.7%) | 21 | 0.06 (0.01-0.27) |
| **Total events** | **bleeding** | **other LVAD** | **7 (14.9%)** | **47** | **27 (50.9%)** | **53** | **0.12 (0.04-0.36)** |

**Table 3. Frequency of IABP-related complications** (*Continued*)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Prondzinsky 2010 | vascular injury | non-IABP | 0 (0.0%) | 19 | 0 (0.0%) | 21 | not estimable |
| Burkhoff 2006 | vascular injury | other LVAD | 0 (0.0%) | 14 | 2 (10.5%) | 19 | 0.24 (0.01-5.44) |
| Ohman 2005 | leg or limb ischemia | non-IABP | 0 (0.0%) | 12 | 1 (10.0%) | 10 | 0.28 (0.01-7.57) |
| Prondzinsky 2010 | leg or limb ischemia | non-IABP | 1 (5.3%) | 19 | 0 (0.0%) | 21 | 3.49 (0.13-90.86) |
| **Total events** | **leg or limb ischemia** | **non-IABP** | **1 (3.2%)** | **31** | **1 (3.2%)** | **31** | not estimated |
| Burkhoff 2006 | leg or limb ischemia | other LVAD | 2 (14.3%) | 14 | 4 (21.1%) | 19 | 0.63 (0.10-4.01) |
| Seyfarth 2008 | leg or limb ischemia | other LVAD | 0 (0.0%) | 13 | 1 (7.7%) | 13 | 0.31 (0.01-8.30) |
| Thiele 2005 | leg or limb ischemia | other LVAD | 0 (0.0%) | 20 | 7 (33.3%) | 21 | 0.05 (0.00-0.89) |
| **Total events** | **leg or limb ischemia** | **other LVAD** | **2 (4.3%)** | **47** | **12 (22.6%)** | **53** | **0.28 (0.06-1.34)** |
| Prondzinsky 2010 | embolism | non-IABP | 0 (0.0%) | 19 | 0 (0.0%) | 21 | not estimable |
| Thiele 2005 | embolism | other LVAD | 1 (5.3%) | 20 | 0 (0.0%) | 21 | 3.31 (0.13-86.06) |
| Prondzinsky 2010 | infection | non-IABP | 0 (0.0%) | 19 | 0 (0.0%) | 21 | not estimable |
| Burkhoff 2006 | infection | other LVAD | 0 (0.0%) | 14 | 3 (15.8%) | 19 | 0.16 (0.01-3.42) |
| Seyfarth 2008 | infection | other LVAD | 3 (23.1%) | 13 | 0 (0.0%) | 13 | 9.0 (0.42-194.07) |
| Thiele 2005 | infection | other LVAD | 12 (60%) | 20 | 14 (33.3%) | 21 | 0.75 (0.21-2.68) |
| **Total events** | **infection** | **other LVAD** | **15 (31.9%)** | **47** | **17 (32.1%)** | **53** | not estimated |
| Prondzinsky 2010 | thrombocytopenia | non-IABP | 0 (0.0%) | 19 | 0 (0.0%) | 21 | not estimable |
| Burkhoff 2006 | thrombocytopenia | other LVAD | 3 (21.4%) | 14 | 3 (15.8%) | 19 | 1.45 (0.25-8.58) |

**Table 3. Frequency of IABP-related complications** (*Continued*)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Thiele 2005 | thrombocy-topenia | other LVAD | 0 (0.0%) | 20 | 1 (4.8%) | 21 | 0.33 (0.01-8.67) |
| **Total events** | **thrombocy-topenia** | **other LVAD** | **3 (8.8%)** | **34** | **4 (10.0%)** | **40** | not estimated |

3/78 patients (3.8%) from the intervention and 1/31 patient (3.2%) from the control group without LVAD and 12/53 patients (23%) from control groups with LVAD had leg or limb ischemia. Embolism was reported in two trials, 1/40 patient (2.5%) from the intervention but no patient from control groups suffered from embolism. 15/66 patients (23%) from the intervention and 0/21 patient from the control group without LVAD but 17/53 patients (32%) from the control group with LVAD suffered from infection. Thrombocytopenia was reported in three trials. 3/53 patients (5.7%) from the intervention group and 0/21 patient from the control group without LVAD but 4/40 patients (10%) from the control group with LVAD suffered from thrombocytopenia .

randomised to IABP had higher mean cardiac index than patients without assist devices and lower mean cardiac index than patients with LVAD. Patients in the IABP group showed lower mean arterial pressure values and higher mean pulmonary capillary wedge pressure. A higher incidence of complications was observed in control groups with other LVADs especially in the frequency of moderate and severe bleeding compared to the intervention group with IABP. Two additional studies are ongoing and designed to include more than 600 patients in cardiogenic shock (IABP-Shock trial) and up to 384 patients with haemodynamic instability. The IABP SHOCK II Trial is designed as a randomised controlled trial and was powered for mortality. A predefined interim-analysis will be performed after 271 patients; the final data might be available at the beginning of 2013 to answer the questions for clinically significant beneficial or harmful effects of IABP support.

# DISCUSSION

## Summary of main results

Data from six eligible small studies with a total of 190 patients with AMI and cardiogenic shock identified to compare IABP versus no IABP could not show convincing evidence for either benefit or harm supporting the use of the intra-aortic counterpulsation. Each of these analysed studies on its own is too small to be sufficiently powered to investigate those beneficial or harmful effects of IABP support beyond initial haemodynamic improvements; but even the aggregated study population of all included trials with 190 patients remains to small in total and does allow to draw definite clues regarding the effects of IABP support.

Three trials compared IABP to standard treatment and three to other percutaneous LVAD. Combining the result of all six trials, in the intervention and control arm 42% and 39% of patients died during the first 30 days and 48% and 51% of patients died during 6 months after randomisation, respectively. Hazard ratios of all-cause mortality distribution provide no evidence for a survival benefit. Adjustments to age, sex and diabetes and investigation in subgroups (IABP vs. non-IABP and IABP vs. other LVAD) confirm these results. While differences in survival were comparable in patients treated with IABP, with and without LVAD, haemodynamics show heterogeneous results. Post implantation, patients

## Quality of the evidence

The results of this meta-analysis are limited by several issues concerning the number of trials, the number of patients in each trial and in total, the heterogeneity of included patients at baseline and the fact that IABP has been compared to no-IABP and to other LVADs:

a) Although patient numbers in total are small it can be looked upon as positive aspect that all included trials had been performed by different investigators at different institutions, so that a bias due to repeated single-centre experiences can be excluded.

b) All these analysed trials have been conducted properly under the conditions of prospective randomised controlled trials, so that we believe this meta-analysis can contribute valuable data to estimate the effects of the IABP support in infarct-related cardiogenic shock, although these trials were not planned and calculated under the terms of mortality. One limitation with a great impact on clues which can be drawn is the fact that there are only a few trials in infarct-related cardiogenic shock which even showed only small sample volumes.

More specifically there are points of concern within the most of the included and analysed studies.

There was a frequent cross-over in several trials:

Ohman 2005a*:* 33% of patients from the control group with car-

diogenic shock crossed over to emergency IABP. 25% of the intervention group with cardiogenic shock did not receive IABP.
Thiele 2005*:* One patient with rapid haemodynamic improvement did not receive the assigned LVAD.
Arias 2005*:* 27.5% of patients assigned to the control group crossed over to IABP and were analysed in this group.
Burkhoff 2006*:* This multicenter-trial with only a small sample volume stopped recruitment earlier than initially intended. Futhermore, different therapeutic strategies were performed in the patients included. Moreover there was also a complex cross-over situation: 37% of patients from the control group were bridged to another therapy (3 patients to LVAD, 1 patient to extracorporeal membrane oxygenation, 2 patients to PCI with stenting placement, 1 patient to mitral valve repair).
Prondzinsky 2010*:* One patient of the control group was treated with IABP.
Seyfarth 2008*:* One patient assigned to the control group died before implantation and did not received the LVAD.
c) Under the limited number of included trials there was one trial (Ohman 2005a) which included patients with acute decompensated heart failure and haemodynamically instable patients, at the same time. In this case only individual patient data eligible according to the criteria of CS could be extracted and evaluated.
d) Another limitation is given by the fact that only three RCTs compared IABP support versus a control without any device giving haemodynamic support. Three trials compared the IABP support to other assist devices as Tandem-Heart or the Impella system.
e) For the limited number of three trials comparing IABP to no IABP, individual patient data of only two of the three trials were available. One trial included patients being revascularized by thrombolysis and the other by PCI. Indeed in this meta-analysis there were only 40 patients, revascularized by the present state of the art by primary PCI and compared to a no IABP control group.
f) Although there has been shown a favourable trend in haemodynamics for IABP support compared to no IABP controls, it has to be stated that haemodynamics have only little impact on prognosis in infarct related cardiogenic shock (Lim 2003; Prondzinsky 2010). While the effect of IABP-timing in field of cardiac surgery had been discussed during the last years (Ramnarine 2005) this discussion currently had been continued in the field of cardiogenic shock (Abdel-Wahab 2010). As shown by Lim and coworkers the haemodynamics in critically ill CS-patients are less predictive than expected. These surprising findings might be explained in particular by the effect of timing. Haemodynamic stabilization under the terms of CS has to be achieved as soon as possible before the potential multiorgan dysfunction syndrome (MODS) or multiorgan failure (MOF) is established. A haemodynamic stabilization under the terms of established MOF shows no impact on prognosis any more, while after the onset of multiorgan failure, MOF shows the leading prognostic impact for outcome.
g) An additional limitation has to be seen in the patient groups themselves. While patients with acute NSTEMI or STEMI can be described very well regarding their baseline conditions, haemodynamic instable cardiogenic shock patients show a broader variation at baseline. Recently, it has been published that multiorgan failure (MOF) and systemic inflammation (SIRS) have the greatest impact on prognosis in infarct-related cardiogenic shock (Prondzinsky 2010). Nevertheless the most baseline data available only provide limited information for the quantifiable estimation of MOF and inflammation at baseline; they are mostly based on socio-demographic and haemodynamic data to assess baseline comparability, so that full comparability of all included patients under these conditions cannot be assured due to the limited size of included studies.
h) Here we refer to section b), where major concerns regarding the issue of cross-over designs are explained.
i) The duration of IABP support differed in the intervention group between the trials from 26±19 up to 84±54 hours.· The different duration of IABP support may reflect different patient populations regarding the degree of haemodynamic instability but may also indicate treatment algorithms for management for cardiogenic shock, regarding inotropic and vasopressor support as also IABP weaning.
j) As shown by the OASIS-5 Trial (Yusuf 2006) outcome in haemodynamically stable patients with acute coronary syndromes is obviously driven by the (intervention-related) bleeding rate. Therefore it would have been very helpful if the assessment of complications, respectively bleedings in all analysed trials were performed in a comparable way i.e. by the TIMI-bleeding definition. Therefore the bleeding related impact on outcome could not be determined. It cannot be excluded that bleedings counteract the trends of favourable haemodynamics in the intervention group.
k) Abdel-Wahab 2010 performed a retrospective analysis of 48 patients with cardiogenic shock and found more favourable results for those CS patients in whom the IABP support had been initiated prior to primary PCI. Indeed the issue of timing IABP support in primary PCI has not been investigated in detail. Therefore it can not be excluded that an earlier initiation of IABP support might have impact outcome, due to earlier improved macro-circulation preventing multiorgan dysfunction or failure.
Although there is currently a strong recommendation for the use of intra-aortic counterpulsation under the conditions of cardiogenic shock by the American College of Cardiology and American Heart Association (ACC/AHA) and also the European Society of Cardiology (ESC), the utilization rate of adjunctive IABP support in STEMI complicated by cardiogenic shock remains low (20% to 39%).This gap of strong recommendation predominantly based on non-randomised trials and registries on one hand and restricted guideline adherence in daily clinical practice on the other hand might be related to our findings that the therapeutic effects seem to be limited to improved haemodynamics, which apparently could not be transferred into improved outcome. Additionally our findings showed an increased rate of bleedings under intra-aortic

counterpulsation. On the background that bleedings, especially major bleedings, show a strong relationship to poor outcome in ACS-patients, the findings of our review might explain, why the majority of clinicians exercise restraint against IABP support in cardiogenic shock.

### Agreements and disagreements with other studies or reviews

#### Other randomised studies

During the last decades several prospective randomised controlled trials (Flaherty 1985; Kono 1996; O'Rourke 1981; Stone 1997; Van 't Hof 1999) with IABP support in ST-segment elevation myocardial infarction (STEMI) without cardiogenic shock have been performed. These trials recently have been investigated and analysed in a meta-analysis (Sjauw 2009). This meta-analysis included seven randomised trials with 1009 patients of STEMI. IABP neither showed a 30-day survival benefit nor improved left ventricular function, while the IABP support was associated with higher stroke and bleeding rates. Another review compared the results of randomised trials comparing percutaneous LVAD with IABP on the basis of three available trials (Cheng 2009) and stated that 'although use of percutaneous LVAD resulted in a better haemodynamic profile compared with IABP counterpulsation, this did not translate into improved 30-day survival' but patients treated with LVAD tended to have a higher incidence of leg ischemia and device-related bleeding.

#### Other non-randomised studies

Sjauw 2009 conducted a second meta-analysis in nine cohort studies with 10,529 patients with STEMI and cardiogenic shock (Anderson 1997; Barron 2001; Bengtson 1992; Kovack 1997a; Moulopoulos 1986a; Stomel 1994; Vis 2007a; Vis 2007b; Waksman 1993). In this meta-analysis, the subgroup treated with thrombolysis showed an 18% decrease in 30-day mortality under IABP-support. These findings are limited by higher revascularization rates compared to patients without IABP support. As shown by Hochman 1999 revascularization of the infarct related artery in infarct related CS shows relevant impact on outcomes. Additionally there was a bias towards younger age in the IABP group. For this reason the reported beneficial effects for IABP supported in AMI patients undergoing IABP support after thrombolysis have to be interpreted very carefully. In contrast to these beneficial findings the National Registry for Acute Myocardial Infarction (Spencer 2001) showed an increased mortality rate under IABP support after revascularization using percutaneous coronary intervention. These data led to an increasing increased mortality rate of 6% under IABP support in the meta-analysis by Sjauw 2009. Also in the light of these mixed and controversial data of non-randomised trials the strong recommendation for IABP support especially in PCI patients is not evidence based.

This review adds some evidence from two additional studies ( Arias 2005; Prondzinsky 2010) and subgroups of patients with myocardial infarction and cardiogenic shock of two other studies ( Burkhoff 2006; Ohman 2005a) and represents a formal assessment of mortality distribution.

## AUTHORS' CONCLUSIONS

### Implications for practice

At present there is no robust and convincing evidence to support the use of IABP in infarct related cardiogenic shock if revascularized by primary PCI. The present body of evidence is represented by a small number of heterogeneous randomised trials with only small patient numbers. Even the meta-analysis including all available data from 190 patients does not allow definite conclusions about the potential beneficial or harmful clinical effects of IABP support beyond initial hemodynamical improvement. Using the present annual rates of cardiogenic shock Thiele 2009 calculated that approximately 70.000-96.000 patients in the US and Europe with infarct related cardiogenic shock do not receive the guideline recommended IABP support. Regarding the lack of evidence for IABP support in cardiogenic shock, the present recommendations should be re-examined. In recognition of a large body of evidence for IABP-support in CS generated by non-randomised trials, which is in contrast to the lack of evidence in a small number of randomised controlled trials, IABP support should no longer be strongly recommended by the guidelines in every case of infarct related cardiogenic shock and should be supported as an individual treatment option based on the personal experience and decision of the investigator and the particular circumstances of the individual treatment situation (Werdan 2010b). Especially in cases of recognizable increased IABP-related risks, such as vascular damage or local bleedings, the recommendation for IABP-support needs to be relativized. Another argument is an economical considerations: strong guideline recommendations should be limited to clear evidence of therapeutic superiority and proven cost-effectiveness. If both points are a matter of debate it can not be surprising that there will be a gap between recommendation and daily clinical practice.

### Implications for research

According to the recently reported data (Prondzinsky 2010) systemic inflammation substantially contributes to outcome in cardiogenic shock. Though it is common that the first phase of cardiogenic shock is accompanied by compensatory vasoconstriction, recent studies have shown that during the following phases of cardiogenic shock inappropriate vasodilation induced by inflammation seems to be the key for understanding the persisting haemodynamic instability as reflected by increasing rates of inotropes

and vasopressors (Debrunner 2008; Geppert 2002; Geppert 2006; Hochman 2003; Kohsaka 2006; Seely 2000).

In consequence, subgroups of patients and the phases of cardiogenic shock regarding systemic inflammation and multiorgan failure clearly have to be defined to allow a better discrimination of patient groups. Only the consequent quantifiable evaluation of inflammation and organ failure will allow a reliable interpretation of further trials, to detect beneficial or harmful effects on outcome in different subgroups.

These future trials should investigate the contribution of IABP-support to all cause mortality. Additionally these trials also should examine the therapeutic and prognostic effect of IABP support according to different phases of CS.

## ACKNOWLEDGEMENTS

The excellent support from the Cochrane Heart Group and the German Cochrane Centre was very much appreciated.

We would like to acknowledge Beth Fraulo for collaboration in the collection of individual patient data and Dr. Eduardo Arias who provided unpublished information. We thank Andreas Wiencke and Katharina Hirsch for support in statistical analysis regarding Frailty models and Doris Gerlach for the support as librarian.

## REFERENCES

### References to studies included in this review

**Arias 2005** *{published data only}*
Arias EA, González-Chon O, García-López SMC, Chacón MA, Noriega-Iriondo F, Vega RE, et al.Impact of the intra-aortic balloon pump in the mortality due to cardiogenic shock secondary to acute myocardial infarction [Spanish] [Impacto delbalón intra–aórtico de contrapulsación en la mortalidad por choque cardiogénico secundario a infarto agudo delmiocardio]. *Archivos de Cardiologia de Mexico* 2005;**75**(3):260–6.

**Burkhoff 2006** *{published data only}*
Burkhoff D, Cohen H, Brunckhorst C, O'Neill WW. A randomized multicenter clinical study to evaluate the safety and efficacy of the TandemHeart percutaneous ventricular assist device versus conventional therapy with intraaortic balloon pumping for treatment of cardiogenic shock. *American Heart Journal* 2006;**152**(3):469.e1–8.

**Ohman 2005a** *{published data only}*
Ohman EM, Nanas J, Stomel RJ, Leesar MA, Nielsen DWT, O'Dea D, et al.Thrombolysis and counterpulsation to improve survival in myocardial infarction complicated by hypotension and suspected cardiogenic shock or heart failure: results of the TACTICS Trial. *Journal of Thrombosis & Thrombolysis* 2005;**19**(1):33–9.

**Prondzinsky 2010** *{published data only}*
Prondzinsky R, Lemm H, Swyter M, Wegener N, Unverzagt S, Carter JM, et al.Intra-aortic balloon counterpulsation in patients with acute myocardial infarction complicated by cardiogenic shock: The prospective, randomized IABP SHOCK Trial for attenuation of multiorgan dysfunction syndrome. *Critical Care Medicine* 2010;**38**(1):1–9.

**Seyfarth 2008** *{published data only}*
Seyfarth M, Sibbing D, Bauer I, Fröhlich G, Bott-Flügel L, Byrne R, et al.A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. *Journal of the American College of Cardiology* 2008;**52**(19):1584–88.

**Thiele 2005** *{published data only}*
Thiele H, Sick P, Boudriot E, Diederich K-W, Hambrecht R, Niebauer J, et al.Randomized comparison of intra-aortic balloon support with a percutaneous left ventricular assist device in patients with revascularized acute myocardial infarction complicated by cardiogenic shock. *European Heart Journal* 2005;**26**(13):1276–83.

### References to studies excluded from this review

**Anderson 1997** *{published data only}*
Anderson RD, Ohman EM, Holmes DR, Col I, Stebbins AL, Bates ER, et al.Use of intraaortic balloon counterpulsation in patients presenting with cardiogenic shock: observations from the GUSTO-I Study. Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries. *Journal of the American College of Cardiology* 1997;**30**(3):708–15.

**Barron 2001** *{published data only}*
Barron HV, Every NR, Parsons LS, Angeja B, Goldberg RJ, Gore JM, et al.The use of intra-aortic balloon counterpulsation in patients with cardiogenic shock complicating acute myocardial infarction: data from the National Registryof Myocardial Infarction 2. *American Heart Journal* 2001;**141**:933-9.

**Bengtson 1992** *{published data only}*
Bengtson JR, Kaplan AJ, Pieper KS, Wildermann NM, Mark DB, Pryor DB, et al.Prognosis in cardiogenic shock after acute myocardial infarction in the interventional era. *Journal of the American College of Cardiology* 1992;**20**:1482-9.

**Christenson 1997a** *{published data only}*
Christenson JT, Simonet F, Badel P, Schmuziger M. Evaluation of preoperative intra-aortic balloon pump support in high risk coronary patients. *European Journal of Cardio-Thoracic Surgery* 1997;**11**(6):1097–103.

**Christenson 1997b** *{published data only}*

Christenson JT, Simonet F, Badel P, Schmuziger M. The effect of preoperative intra-aortic balloon pump support in patients with coronary artery disease, poor left-ventricular function (LVEF < 40%), and hypertensive LV hypertrophy. *Thoracic & Cardiovascular Surgeon* 1997;**45**:60–4.

**Christenson 1997c** *{published data only}*

Christenson JT, Badel P, Simonet F, Schmuziger M. Preoperative intraaortic balloon pump enhances cardiac performance and improves the outcome of redo CABG. *Annals of Thoracic Surgery* 1997;**64**:1237–44.

**Christenson 1999** *{published data only}*

Christenson JT, Simonet F, Badel P, Schmuziger M. Optimal timing of preoperative intraaortic balloon pump support in high-risk coronary patients. *Annals of Thoracic Surgery* 1999;**68**:934–8.

**Christenson 2003** *{published data only}*

Christenson JT, Licker M, Kalangos A. The role of intra-aortic counterpulsation in high-risk OPCAB surgery: A prospective randomized study. *Journal of Cardiac Surgery* 2003;**18**(4):286–94.

**Flaherty 1985** *{published data only}*

Flaherty JT, Becker LC, Weiss JL, Brinker JA, Bulkley BH, Gerstenblith G, et al.Results of a randomized prospective trial of intraaortic balloon counterpulsation and intravenous nitroglycerin in patients with acute myocardial infarction. *Journal of the American College of Cardiology* 1985;**6**(2): 434–46.

**Kono 1996** *{published data only}*

Kono T, Morita H, Nishina T, Fujita M, Onaka H, Hirota Y, et al.Aortic counterpulsation may improve late patency of the occluded coronary artery in patients with early failure of thrombolytic therapy. *Journal of the American College of Cardiology* 1996;**28**(4):876–81.

**Kovack 1997a** *{published data only}*

Kovack PJ, Rasak MA, Bates ER, Ohman EM, Stomel RJ. Thrombolysis plus aortic counterpulsation: improved survival in patients who present to community hospitals with cardiogenic shock. *Journal of the American College of Cardiology* 1997;**29**(7):1454-8.

**Li 2007** *{published data only}*

Li JL, Xue H, Wang BS, Zhang HY, Yin LH, Shun WD, et al.Effect of prolonged intra-aortic balloon pumping in patients with cardiogenic shock following acute myocardial infarction. *Medical Science Monitor* 2007;**13**(6):CR270–4.

**Marra 2002** *{published data only}*

Marra C, De Santo LS, Amarelli C, Della Corte A, Onorati F, Torella M, et al.Coronary artery bypass grafting in patients with severe left ventricular dysfunction: a prospective randomized study on the timing of perioperative intraaortic balloon pump support. *International Journal of Artificial Organs* 2002;**25**(2):141–6.

**Moulopoulos 1986a** *{published data only}*

Moulopoulos S, Stamatelopoulos S, Petrou P. Intraaortic balloon assistance in intractable cardiogenic shock. *European Heart Journal* 1986;**7**(5):396-403.

**O'Rourke 1981** *{published data only}*

O'Rourke MF, Norris RM, Campbell TJ, Chang VP, Sammel NL. Randomized controlled trial of intraaortic balloon counterpulsation in early myocardial infarction with acute heart failure. *American Journal of Cardiology* 1981;**47**:815–20.

**Ohman 1994** *{published data only}*

* Ohman EM, George BS, White CJ, Kern MJ, Gurbel PA, Freedman RJ, et al.Use of aortic counterpulsation to improve sustained coronary artery patency during acute myocardial infarction. Results of a randomized trial. The Randomized IABP Study Group. *Circulation* 1994;**90**(2): 792–9.

Talley JD, Ohman EM, Mark DB, George BS, Leimberger JD, Berdan LG, et al.Economic implications of the prophylactic use of intraaortic balloon counterpulsation in the setting of acute myocardial infarction. The Randomized IABP Study Group. *American Journal of Cardiology* 1997; **79**(5):590–4.

**Perera 2009** *{published data only}*

Perera D, Stables R, Booth J, Thomas M, Redwood S. The balloon pump-assisted coronary intervention study (BCIS-1): rationale and design. *American Heart Journal* 2009;**158** (6):910–6.

**Sanborn 2000** *{published data only}*

Sanborn TA, Sleeper LA, Bates E, Jacobs AK, Boland J, French JK, et al.Impact of thrombolysis, intra-aortic balloon pump counterpulsation, and their combination in cardiogenic shock complicating acute myocardial infarction: a report from the SHOCK Trial Registry. SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK?. *Journal of the American College of Cardiology* 2000;**36**:1123–9.

**Stomel 1994** *{published data only}*

Stomel RJ, Rasak M, Bates ER. Treatment strategies for acute myocardial infarction complicated by cardiogenic shock in a community hospital. *Chest* 1994;**105**:997-1002.

**Stone 1997** *{published data only}*

Stone GW, Marsalese D, Brodie BR, Griffin JJ, Donohue B, Costantini C, et al.A prospective, randomized evaluation of prophylactic intraaortic balloon counterpulsation in high risk patients with acute myocardial infarction treated with primary angioplasty. Second Primary Angioplasty in Myocardial Infarction (PAMI-II) Trial Investigators. *Journal of the American College of Cardiology* 1997;**29**(7):1459–67.

**Van 't Hof 1999** *{published data only}*

Van 't Hof AWJ, Liem AL, de Boer MJ, Hoorntje JCA, Suryapranata H, Zijlstra F. A randomized comparison of intra-aortic balloon pumping after primary coronary angioplasty in high risk patients with acute myocardial infarction. *European Heart Journal* 1999;**20**(9):659–65.

**Vijayalakshmi 2007** *{published data only}*

Vijayalakshmi K, Kunadian B, Whittaker VJ, Wright RA, Hall JA, Sutton A, et al.Intra-aortic counterpulsation does not improve coronary flow early after PCI in a high-risk group of patients: observations from a randomized trial to

explore its mode of action. *Journal of Invasive Cardiology* 2007;**19**(8):339–46.

**Vis 2007a** ***{published data only}***
Vis MM, Sjauw KD, van der Schaaf RJ, Baan J Jr, Koch KT, DeVries JH, et al.In patients with ST-segment elevation myocardial infarction with cardiogenic shock treated with percutaneous coronary intervention, admission glucose level is a strong independent predictor for 1-yearmortality in patients without a prior diagnosis of diabetes. *American Heart Journal* 2007;**154**:1184-90.

**Vis 2007b** ***{published data only}***
Vis MM, Sjauw KD, van der Schaaf RJ, Koch KT, Baan J Jr, Tijssen JG, et al.Prognostic value of admission hemoglobin levels in ST-segment elevation myocardial infarction patients presenting with cardiogenic shock. *American Journal of Cardiology* 2007;**99**:1201-2.

**Waksman 1993** ***{published data only}***
Waksman R, Weiss AT, Gotsman MS, Hasin Y. Intra-aortic balloon counterpulsation improves survival in cardiogenic shock complicating acute myocardial infarction. *European Heart Journal* 1993;**14**(1):71–4.

## References to ongoing studies

**IABP Shock II** ***{published data only}***
NCT 00491036. Intraaortic Balloon Pump in Cardiogenic Shock II. http://www.controlled-trials.com/mrct/trial/389565/IABP (accessed 28 January 2010).

**RECOVER II Trial** ***{published data only}***
NCT00972270. Trial Using Impella LP 2.5 System in Patients With Acute Myocardial Infarction Induced Hemodynamic Instability. http://www.controlled-trials.com/mrct/trial/629451/IABP (accessed 28 January 2010).

## Additional references

**Abdel-Wahab 2010**
Abdel-Wahab M, Saad M, Kynast J, Geist V, Sherif MA, Richardt MA, et al.Comparison of hospital mortality with Iitra-aortic balloon counterpulsation insertion before versus after primary percutaneous coronary intervention for cardiogenic shock complicating acute myocardial infarction. *American Journal Cardiology* 2010;**105**(7):967–71.

**AHA 2008**
American Heart Association. *Heart Disease and Stroke Statistics - 2008 Update*. Dallas, Texas: American Heart Association, 2008.

**Alcan 1983**
Alcan KE, Stertzer SH, Wallsh E, DePasquale NP, Bruno MS. The role of intra-aortic balloon counterpulsation in patients undergoing percutaneous transluminal coronary angioplasty. *American Heart Journal* 1983;**105**(3):527–30.

**Antman 2004**
Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al.ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction--executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *Journal of the American College of Cardiology* 2004;**44**(3):671–719.

**Arafa 1999**
Arafa OE, Pedersen TH, Svennevig JL, Fosse E, Geiran OR. Vascular complications of the intraaortic balloon pump in patients undergoing open heart operations: 15-year experience. *Annals of Thoracic Surgery* 1999;**67**:645–51.

**Assis 2009**
Assis RB, Azzolin K, Boaz M, Rabelo ER. Complications of intra-aortic balloon in a cohort of hospitalized patients: implications of nursing care. *Revista Latino-Americana de Enfermagem* 2009;**17**(5):658–63.

**BHF 2007**
British Heart Foundation. *Coronary Heart Disease Statistics*. London: British Heart Foundation, 2007.

**Cheng 2009**
Cheng JM, den Uil CA, Hoeks SE, van der Ent M, Jewbali LSD, van Domburg RT, et al.Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials. *European Heart Journal* 2009;**30**(17):2102–8.

**Cohen 2003**
Cohen M, Urban P, Christenson JT, Joseph DL, Freedman RJ Jr, Miller MF, et al.Contemporary utilization and outcomes of intraaortic balloon counterpulsation in acute myocardial infarction: the benchmark registry. *Journal of the American College of Cardiology* 2003;**24**(19):1763–70.

**Cooper 2008**
Cooper HA, Thompson E, Panza JA. The role of heparin anticoagulation during intra-aortic balloon counterpulsation in the coronary care unit. *Acute Cardioac Care* 2008;**10**(4):214–20.

**Debrunner 2008**
Debrunner M, Schuiki E, Minder E, Straumann E, Naegeli B, Mury R, et al.Proinflammatory cytokines in acute myocardial infarction with and without cardiogenic shock. *Clinical Research in Cardiology* 2008;**97**(5):298–305.

**Duchateau 2008**
Duchateau L, Janssen P. *The Frailty Model*. Springer Science+Business Media, LLC, 2008.

**Dyub 2008**
Dyub AM, Whitlock RP, Abouzahr LL, Cinà CS. Preoperative intra-aortic balloon pump in patients undergoing coronary bypass surgery: a systematic review and metanalysis. *Journal of Cardiac Surgery* 2008;**23**(1):79–86.

**Erdogan 2006**
Erdogan HB, Goksedef D, Erentug V, Polat A, Bozbuga N, Mansuroglu D, et al.In which patients should sheathless IABP be used? An analysis of vascular complications in 1211 cases. *Journal of Cardiac Surgery* 2006;**21**(4):342–6.

**Field 2007**
Field ML, Rengarajan A, Khan O, Spyt T, Richens D. Preoperative intra aortic balloon pumps in patients undergoing coronary bypass grafting. *Cochrane Database of Systematic Reviews* 2007, Issue 1. [DOI: 10.1002/14651858.CD004472.pub2]

**Forrester 1976a**
Forrester JS, Diamond G, Chatterjee K, Swan HJ. Medical therapy of acute myocardial infarction by application of hemodynamic subsets (first of two parts). *New England Journal of Medicine* 1976;**295**(24):1356–62.

**Forrester 1976b**
Forrester JS, Diamond G, Chatterjee K, Swan HJ. Medical therapy of acute myocardial infarction by application of hemodynamic subsets (second of two parts). *New England Journal of Medicine* 1976;**295**(25):1404–13.

**Forssell 1979**
Forssell G, Nordlander R, Nyquist O, Schenk-Gustavsson K. Intraaortic balloon pumping in the treatment of cardiogenic shock complicating acute myocardial infarction. *Acta Medica Scandinavica* 1979;**206**(3):189–92.

**Fuchs 2009**
Fuchs S, Kornowski R, Teplitsky I, Brosh D, Lev E, Vaknin-Assa H, et al.Major bleeding complicating contemporary primary percutaneous coronary interventions ? incidence, predictors, and prognostic implications. *Cardiovascular Revascularization Medicine* 2009;**10**(2):88–93.

**Geppert 2002**
Geppert A, Steiner A, Zorn G, Delle-Karth G, Koreny M, Haumer M, et al.Multiple organ failure in patients with cardiogenic shock is associated with high plasma levels of interleukin-6. *Critical Care Medicine* 2002;**30**(9):1987–94.

**Geppert 2006**
Geppert A, Dorninger A, Delle-Karth G, Zorn G, Heinz G, Huber K. Plasma concentrations of interleukin-6, organ failure, vasopressor support, and successful coronary revascularization in predicting 30-day mortality of patients with cardiogenic shock complicating acute myocardial infarction. *Critical Care Medicine* 2006;**34**(8):2035–42.

**Gjesdal 2009**
Gjesdal O, Gude E, Arora S, Leivestad T, Andreassen AK, Gullestad L, et al.Intra-aortic balloon counterpulsation as a bridge to heart transplantation does not impair long-term survival. *European Journal of Heart Failure* 2009;**11**(7):709–14.

**Goldberg 1999**
Goldberg RJ, Samad NA, Yarzebski J, Gurwitz J, Bigelow C, Gore JM. Temporal trends in cardiogenic shock complicating acute myocardial infarction. *New England Journal of Medicine* 1999;**340**(15):1162–9.

**Henriques 2006**
Henriques JP, Remmelink M, Baan J Jr, van der Schaaf RJ, Vis MM, Koch KT, et al.Safety and feasibility of elective high-risk percutaneous coronary intervention procedures with left ventricular support of the Impella Recover LP 2.5. *American Journal of Cardiology* 2006;**97**:990-2.

**Higgins 2002**
Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**:1539–58.

**Higgins 2011**
Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. The Cochrane Collaboration.

**Hochman 1999**
Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, et al.Early revascularization in acute myocardial infarction complicated by cardiogenic shock. *New England Journal of Medicine* 1999;**341**(9):625–34.

**Hochman 2001**
Hochman JS, Sleeper LA, White HD, Dzavik V, Wong SC, Menon V, et al.One-year survival following early revascularization for cardiogenic shock. *JAMA* 2001;**285**(2):190–2.

**Hochman 2003**
Hochman JS. Cardiogenic shock complicating acute myocardial infarction: expanding the paradigm. *Circulation* 2003;**107**:2998–3002.

**Hochman 2007**
Hochman 2007, Apolito R. The calm after the storm. Long-term survival after cardiogenic shock. *Journal of the American College of Cardiology* 2007;**50**(18):1759–60.

**Holmes 1997**
Holmes DR Jr, Califf RM, Van de Werff F, Berger BP, Bates ER, Simoons ML, et al.Difference in countries' use of resources and clinical outcome for patients with cardiogenic shock after myocardial infarction: results from the GUSTO trial. *Lancet* 1997;**349**(9045):75–8.

**Hudson 1999**
Hudson MP, Granger CB, Stebbins AL. Cardiogenic shock survival and use of intraaortic balloon counterpulsation: results from the GUSTO I and III trials. *Circulation* 1999;**100**(Suppl):I370.

**Ishihara 1991**
Ishihara M, Sato H, Tateishi H, Uchida T, Dote K. Intraaortic balloon pumping as the postangioplasty strategy in acute myocardial infarction. *American Heart Journal* 1991;**122**(2):385–9.

**Kantrowitz 1968**
Kantrowitz A, Tjonneland S, Freed PS, Phillips SJ, Butner AN, Sherman JL Jr. Initial clinical experience with intraaortic balloon pumping in cardiogenic shock. *JAMA* 1968;**203**:135–40.

**Kocogullari 2008**
Kocogullari CU, Emmiler M, Ayva E, Cekirdekct A. IABP-Related vascular complications: who is responsible ? the patient, the surgeon or the sheath? Part I: sheath-related complications. *Advances in Therapy* 2008;**25**(3):225–30.

**Kohsaka 2006**
Kohsaka S, Menon V, Lowe AM, Lange M, Dzavik V, Sleeper LA, et al.Systemic inflammatory response syndrome after acute myocardial infarction complicated by cardiogenic shock. *Archives of Internal Medicine* 2005;**165** (14):1643–50.

**Kontovannis 1999**
Kontoyannis DA, Nanas JN, Kontoyannis SA, Stamatelopoulos SF, Moulopoulos SD. Mechanical ventilation in conjunction with the intra-aortic balloon pump improves the outcome of patients in profound cardiogenic shock. *Intensive Cate Medicine* 1999;**25**(8): 835–8.

**Kovack 1997b**
Kovack PJ, Rasak MA, Bates ER, Ohman EM, Stomel RJ. Thrombolysis plus aortic counterpulsation: improved survival in patients who present to community hospitals with cardiogenic shock. *Journal of the American College of Cardiology* 1997;**29**(7):1454–8.

**Kumbasar 1999**
Kumbasar SD, Semiz E, Sancaktar O, Yalçinkaya S, De ğ er N. Mechanical complications of intra-aortic balloon counterpulsation. *International Journal of Cardiology* 1999; **70**(1):69–73.

**Lewis 2007**
Lewis PA, Mullany DV, Townsend S, Johnson J, Wood L, Courtney M, et al.Trends in intra-aortic balloon counterpulsation: comparison of 669 record Australian dataset with the multinational Benchmark Counterpulsation Outcomes Registry. *Anaesthesia and Intensive Care* 2007;**35** (1):13–9.

**Lim 2003**
Lim N, Dubois MJ, de Backer D, Vincent JL. Do All Nonsurvivors of Cardiogenic Shock Die With a Low Cardiac Index?. *Chest* 2003;**124**:1885–91.

**McEnany 1978**
McEnany MT, Kay HR, Buckley MJ, Dagget WM, Erdmann AJ, Mundth ED, et al.Clinical experience with intraaortic balloon pump support in 728 patients. *Circulation* 1978;**58**:I124–32.

**Menon 2000**
Menon V, White H, LeJemtel T, Webb JG, Sleeper LA, Hochman JS. The clinical profile of patients with suspected cardiogenic shock due to predominant left ventricular failure: a report from the SHOCK Trial Registry. SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK?. *Journal of the American College of Cardiology* 2000;**36**(3 Suppl A):1071–6.

**Moher 2009**
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;**6**(7):1–6.

**Moulopoulos 1986b**
Moulopoulos S, Stametolopoulos S, Petrou P. Intraaortic balloon assistance in intractable cardiogenic shock. *European Heart Journal* 1986;**7**(5):396–403.

**Murray 1996**
Murray CJL, Lopez AD. Evidence-based health policy - lessons from the global burden of disease study. *Science* 1996;**274**:740–3.

**Ohman 2001**
Ohman EM, Hochmann JS. Aortic counterpulsation in acute myocardial infarction: physiologically important but does the patient benefit?. *American Heart Journal* 2001;**141**: 889–92.

**Ohman 2005b**
Ohman EM, Nanas J, Stomel RJ, Leesar MA, Nielsen DW, O'Dea D, et al.Thrombolysis and counterpulsation to improve survival in myocardial infarction complicated by hypotension and suspected cardiogenic shock or heart failure: results of the TACTICS trial. *Journal of Thrombosis and Thrombolysis* 2005;**19**(1):33–9.

**Pfeiffer 2005**
Pfeiffer S, Frisch P, Weyand M, Ensminger SM, Tandler R, Sirch J, et al.The use of preoperative intra-aortic balloon pump in open heart surgery. *Journal of Cardiovascular Surgery (Torino)* 2005;**46**(1):55–60.

**Piedbois 2004**
Piedbois P, Mondor H, Buyse M. Meta-analyses based on abstracted data: A step in the right direction, but only a first step. *Journal of Clinical Oncology* 2004;**22**(19):3839–41.

**Ramnarine 2005**
Ramnarine IR, Grayson AD, Dihmis WC, Mediratta NK, Fabri BM, Chalmers JA. Timing of intra-aortic balloon pump support and 1-year survival. *European Journal of Cardiothorac Surgery* 2005;**27**(5):887–92.

**Riaz 2008**
Riaz W, Shahbaz A, Sami W, Khan JS. Early vascular complications of intraaortic balloon counterpulsation in patients undergoing open heart surgery. *Journal of Ayub Medical College, Abbottabad* 2008;**20**(2):80–4.

**Riley 2007**
Riley RD, Simmonds MC, Look MP. Evidence combining individual patient data and aggregate data: a systematic review identified current practice and possible methods. *Journal of Clinical Epidemiology* 2007;**60**(5):431–9.

**Riley 2010**
Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data:rationale, conduct, and reporting. *BMJ* 2010;**340**(c221):521–5.

**Santa-Cruz 2006**
Santa-Cruz RA, Cohen MG, Ohman EM. Aortic counterpulsation: A review of the hemodynamic effects and indications for use. *Catheterization & Cardiovascular Interventions* 2006;**67**(1):68–77.

**Seely 2000**

Seely AJ, Christou NV. Multiple organ dysfunction syndrome: Exploring the paradigm of complex nonlinear systems. *Critical Care Medicine* 2000;**28**(7):2193–200.

**Sjauw 2009**

Sjauw KD, Engström AE, Vis MM, van der Schaaf RJ, Baan J, Koch KT, et al.A systematic review and meta-analysis of intra aortic balloon pump therapy in ST-elevation myocardial infarction: should we change the guidelines?. *European Heart Journal* 2009;**30**(4):459–68.

**Spencer 2001**

Spencer FA, Goldberg RJ, Frederick PD, Malmgren J, Becker RC, Gore JM. Age and the utilization of cardiac catheterization following uncomplicated first acute myocardial infarction treated with thrombolytic therapy (The Second National Registry of Myocardial Infarction [NRMI-2]). *The American Journal of Cardiology* 2001;**88** (2):107–11.

**Stone 2003**

Stone GW, Ohman EM, Miller MF, Joseph DL, Christenson JT, Cohen M, et al.Contemporary utilization and outcomes of intraaortic balloon counterpulsation in acute myocardial infarction: the benchmark registry. *Journal of the American College of Cardiology* 2003;**41**(11):1940–5.

**Takano 1984**

Takano T, Endo T, Saito H, Ida T, Tanaka K, Osaka S, et al.Clinical usefulness of intraaortic balloon pumping in acute myocardial infarction complicated with cardiogenic shock, ventricular septal perforation and mitral regurgitation. *Japanese Circulation Journal* 1984;**48**(7):678–89.

**Thiele 2001**

Thiele H, Lauer B, Hambrecht R, Boudriot E, Cohen HA, Schuler G. Reversal of cardiogenic shock by percutaneous left atrial-to-femoral arterial bypass assistance. *Circulation* 2001;**104**:2917-22.

**Thiele 2009**

Thiele H, Schuler G. Cardiogenic shock: to pump or not to pump?. *European Heart Journal* 2009;**30**(4):389–90.

**van de Werf 2008**

Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, et al.Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *European Heart Journal* 2008;**29**(23):2909–45.

**Weiss 1984**

Weiss AT, Engel S, Gotsman CJ, Shefer A, Hasin Y, Bitran D, et al.Regional and global left ventricular function during intra-aortic balloon counterpulsation in patients with acute myocardial infarction shock. *American Heart Journal* 1984; **108**(2):249–54.

**Werdan 2010a**

Werdan K, Ruß M, Buerke M. Procedures in ICU: IABP. In: Tubaro M, Danchin N, Filippatos G, Goldstein P, Vranckx P, Zahger D editor(s). *ESC textbook of intensive and acute cardiac care*. England: Oxford University Press (in press), 2010.

**Werdan 2010b**

Werdan K, Ruß M, Buerke M, Engelmann L, Ferrari M, Friedrich I, et al.Guideline "Infarct related cardiogenic shock - diagnosis, monitoring and therapy" [Leitlinie "Infarktbedingter kardiogener Schock – Diagnose, Monitoring und Therapie"]. AWMF (in evaluation) 2010.

**Whitehead 2002**

Whitehead N. *Meta-analysis of controlled clinical trials*. Chichester: John Wiley & Sons, 2002.

**Yusuf 2004**

Yusuf S, Hawken S, unpuu S, Dans T, Avezum A, Lanas F, et al.Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;**364**:937–52.

**Yusuf 2006**

Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, et al.Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *New England Journal of Medicine* 2006;**354**(14):1464–76.

* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Arias 2005**

| | |
|---|---|
| Methods | Parallel single-centre RCT of two groups (inotropics + IABP vs. inotropics)<br>Study duration: February 2001 to February 2003<br>Measurements: haemodynamic parameters (PCWP, CI) were measured using a pulmonary artery catheter (CI, PCWP). |
| Participants | group 1: +IABP (31)<br>group 2: -IABP (9)<br>group 2 crossover to Group 1: 11<br>criteria for cross-over: critical illness and absence of response to vasopressors<br>mean age: 65.5 ± 6.2 years<br>sex: 65% men<br>diabetes: 40%<br>previous infarction: 27.5%<br>dislipidemia: 30%<br>heart rate: 94 ± 12 /min<br>MAP: 68 ± 6.4 mm Hg (estimated from systolic and diastolic BP)<br>PCWP: 21.7 ± 2.45 mm Hg<br>cardiac index: 1.93 ± 0.22 L/min/$m^2$<br>No information about distribution between treatment groups. |
| Interventions | Myocardial revascularization: PCI+stenting.<br>Primary additional randomised intervention: Percutaneous guided insertion with fluoroscopy of Arrow AutoCAT 2 WAVE® IABP<br>Pharmacological support: inotropes (dopamine and dobutamine),vasopressor, analgetic and platelet inhibiting agents |
| Outcomes | In hospital mortality |
| Notes | Only in-hospital results from the coronary station. Analysis primary compares two cardiogenic shock groups (early and late CS). Translation from Spanish. Author was contacted and missing information were provided. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | random number table with stratified randomisation |
| Allocation concealment (selection bias) | Low risk | opaque sealed envelopes |
| Blinding (performance bias and detection bias)<br>mortality+haemodynamic | Unclear risk | no details available |

**Arias 2005** (*Continued*)

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) mortality | High risk | only in-hospital follow-up (10 to 15 days) |
| Incomplete outcome data (attrition bias) haemodynamics | High risk | only baseline data are reported |
| Selective reporting (reporting bias) | High risk | complications and course of haemodynamics missing |
| Other bias | High risk | 9 patients (27.5%) crossed over to IABP, we suppose results are from per protocol analysis |

**Burkhoff 2006**

| | |
|---|---|
| Methods | Parallel multicenter RCT of two groups (IABP vs. TandemHeart)<br>Study duration: April 2002 to April 2004<br>Measurements: Haemodynamic parameters (PCWP, CI) were measured using an indwelling right catheter. |
| Participants | 42 patients were included and 33 patients were randomised, 21 were diagnosed with acute myocardial infarction (AMI), 5 roll-in patients with AMI<br>group 1: +IABP (14) with AMI (10)<br>group 2: -IABP (19) with AMI (11)<br>group 1 cross-over to group 2: 4<br>group 2 cross-over to group 1: 0<br>median age: 66 (49-84) years (cardiogenic shock+AMI patients)<br>sex: 81% men (cardiogenic shock+AMI patients)<br>Haemodynamic values at baseline are influenced by IABP before randomisation. |
| Interventions | Myocardial revascularization: PCI, from 26 CS+AMI patients: PCI (85%), CABG (12%) , LVAD (4%).<br>Primary additional randomised intervention: IABP or TandemHeart pVAD System. Mean duration of support: 75 ± 95 hrs (group 1) vs. 61 ± 45 hrs (group 2).<br>Pharmacological support: Dose and choice of pressor, inotropic and pharmacologic agents based on physicians standard of care. |
| Outcomes | Haemodynamics, 30-day mortality, adverse events |
| Notes | Analysis of individual patient data. 42 patients were included in the study, 9 treated in the roll-in phase and 33 randomised. All patients had CS, 21 randomised patients were diagnosed with AMI. All mortality statistics bases on individual patient data of 21 AMI+CS patients, haemodynamic and description of complication base on data from 33 randomised patients. Autor was contacted, missing information and individual patient data were provided. |

**Burkhoff 2006** (*Continued*)

| *Risk of bias* | | |
|---|---|---|
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | random number table with blocked randomisation |
| Allocation concealment (selection bias) | Low risk | sealed opaque envelopes |
| Blinding (performance bias and detection bias)<br>mortality+haemodynamic | High risk | not possible |
| Incomplete outcome data (attrition bias)<br>mortality | Low risk | complete 30 day follow-up |
| Incomplete outcome data (attrition bias)<br>haemodynamics | Low risk | different numbers of patients for CI, MAP and PCWP measurements 16 hours of support, only aggregate data about differences to baseline available |
| Selective reporting (reporting bias) | Low risk | mortality, haemodynamic and adverse events were reported. |
| Other bias | High risk | early data depending stopping after enrolment of 33 randomised patients, most patients were enrolled after failure of IABP before enrolment and randomisation, 36% patients were bridged to another therapy. |

**Ohman 2005a**

| | |
|---|---|
| Methods | Parallel multicenter RCT of two groups (fibrinolysis+IABP vs. fibrinolysis)<br>Study duration: November 1996 to November 1999<br>Measurements: from the time of randomisation until hospital discharge or 30 days (whichever was earlier), patients were be monitored for the occurrence of death, stroke, reinfarction, new congestive heart failure, refractory ischemia, and rescue angioplasty (defined as thrombolytic failure to achieve TIMI grade 2 or 3 flow in the infarct-related artery) |
| Participants | 57 patients were included, 22 were diagnosed with Killip class IV and included in our analysis of patients with CS<br>group 1: +IABP (30) with CS (12)<br>group 2: -IABP (27) with CS (10)<br>group 2 crossover to IABP: 3 of 10 with CS<br>group 1 crossover to no IABP: 3 of 12 with CS<br>criteria for cross-over to IABP: emergency IABP (physicians discretion)<br>criteria for cross-over to no IABP: 2 deaths, 1 catheter could not be inserted |

**Ohman 2005a** (*Continued*)

| | |
|---|---|
| | median age: 69 (33-80) years (CS patients)<br>sex: 77% men (CS patients)<br>diabetes: 32% (CS patients)<br>previous infarction: 30%<br>MAP: 57 ± 12 mm Hg (estimated from systolic and diastolic BP, CS patients))<br>All values are equally distributed between groups. |
| Interventions | Myocardial revascularization: PCI (23%), Stent (14%), CABG (18%), lysis (100%) of CS patients<br>Primary additional randomised intervention: Femoral percutaneous insertion of an IABP up to three hours after starting fibrinolysis (standard or sheathless technique). Patients received IABP for 48 hours at a rate of 1:1 and were weaned gradually over 12 hours before pump removal. Stopping early because of complications or continuation because of ongoing ischemia or hypotension was possible. Mean duration of support: (45±32 hrs (group 1), information not available (group 2).<br>Pharmacological support: predefined doses of intravenous heparin to achieve an aPTT of 50-75 sec., use of other medications and procedures were left to the discretion of physicians. |
| Outcomes | 6-months and 30 day mortality (all-cause), in-hospital events (reinfarction, stroke, non-fatal reinfarction), composite in-hospital end point (death, reinfarction, or new congestive heart failure), safety events |
| Notes | Trial included patients with myocardial infarction complicated by hypotension and suspected cardiogenic shock or heart failure. Analysis of individual patient data was restricted to patients with suspected cardiogenic shock. The trial was stopped early because of missed enrolment goal (causes: bias among site investigators against randomisation in CS patients). |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | random number table with blocked randomisation |
| Allocation concealment (selection bias) | Low risk | central telephone allocation (North America) or sealed opaque envelopes |
| Blinding (performance bias and detection bias)<br>mortality+haemodynamic | High risk | Not possible |
| Incomplete outcome data (attrition bias)<br>mortality | Low risk | complete 6-months follow-up |
| Incomplete outcome data (attrition bias)<br>haemodynamics | High risk | no follow-up information |

**Ohman 2005a** (*Continued*)

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | all prespecified outcomes are reported |
| Other bias | High risk | If patients were deemed to be rapidly deteriorating, the treating physician was allowed to use IABP to save survival. crossover of 33% of patients from group 2. 10% of patients from groups 1 did not receive IABP, in 53% IABP was stopped early. |

**Prondzinsky 2010**

| | |
|---|---|
| Methods | Parallel single-centre RCT of two groups (Standard+IABP vs. Standard) undergoing percutaneous coronary intervention (PCI)<br>Study duration: March 2003-June 2004<br>Measurements: invasive monitoring<br>Cardiac output data were obtained using the thermodilution method and was indexed to body surface area using standard formulas. The initial data point for cardiac index was taken immediately after cath/PCI when the thermodilution catheter was placed. Frequent blood sampling was done to determine laboratory markers. |
| Participants | group 1: +IABP (23)<br>group 2: -IABP (22)<br>group 2 crossover to IABP: 1<br>criteria for cross-over: no preplanned cross-over<br>5 patients excluded from analysis<br>median age: 64.2 (38-82) years<br>sex: 78% men<br>diabetes: 50%<br>previous infarction: 22.5%<br>hypertension: 45%<br>smoker: 38%<br>dyslipidemia: 7.5%<br>heart rate: 92 ± 30 /min<br>Apache II- Score: 22 ± 10<br>MAP: 78 ± 14 mm Hg<br>lactate: 4.3 ± 3.6 mmol/L<br>pH:7.38 ± 0.14<br>cardiac index: 2.0 ± 0.1 L/min/$m^2$<br>PCWP:17.6 ± 1.0 mm Hg<br>All high risk factors (beside PCWP) are distributed equally between groups. |
| Interventions | Myocardial revascularization: PCI (90%) , CABG (0%)<br>Primary additional randomised intervention: A 40mL IABP (IABP System 97, Datascope; Fairfield, NJ) was inserted via the femoral artery using an 8-French sheath immediately after PCI. Aortic counterpulsation was continued for a minimum of 48 hrs. Mean duration of support: 45 ± 34 hrs (group 1), 184 hrs (1 patient in group 2).<br>Pharmacological support: inotropic and vasopressor agents, aspirin, glycoprotein-IIb-/IIIa-receptor-blocker, heparin, as required, ventilatory support |

**Prondzinsky 2010** (*Continued*)

| | |
|---|---|
| Outcomes | in-hospital-mortality, change in APACHE II scores over 4 days from enrolment, cardiac index, plasma brain natriuretic peptide, interleukin-6 |
| Notes | Analysis of individual patient data. The authors (SU, RP, MB, KW and JH) were included in this study. |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | random number table with block randomisation |
| Allocation concealment (selection bias) | Low risk | sealed opaque envelopes |
| Blinding (performance bias and detection bias)<br>mortality+haemodynamic | High risk | not possible |
| Incomplete outcome data (attrition bias) mortality | Low risk | complete in-hospital and 30 days follow-up, missing information in long-term follow up (12.5%) in 6 months-follow up, 15% in 1 year-follow up) |
| Incomplete outcome data (attrition bias) haemodynamics | Low risk | in-hospital data (intensive care unit) up to 28 days |
| Selective reporting (reporting bias) | Low risk | all prespecified outcomes are reported |
| Other bias | Low risk | 5 patients were excluded from analysis (4 not fulfilled inclusion criteria, 1 no post randomisation data), 1 cross-over to IABP, sensitivity analyses were calculated |

**Seyfarth 2008**

| | |
|---|---|
| Methods | Parallel two-centre RCT of two groups (IABP vs. Impella LP2.5 (Abiomed Europe GmbH, Aachen, Germany)<br>Study duration: September 2004 to January 2007<br>Measurements: Haemodynamic parameters were measured using a Swan-Ganz catheter. |
| Participants | group 1: +IABP (13)<br>group 2: -IABP (13)<br>1 death in group 2 before implantation<br>median age: 66 (33-87) years<br>Sex: 76% men<br>diabetes: 31% |

**Seyfarth 2008** (*Continued*)

| | |
|---|---|
| | previous infarction: 58%<br>hypertension: 61%<br>smoker: 58%<br>hypercholesterolaemia: 58%<br>cardiac output: 3.3 ± 1.2 L/min<br>MAP: 75 ± 16 mm Hg<br>lactate: 6.4 ± 4.2 mmol/L<br>pH: 7.27 ± 0.16<br>cardiac index: 1.72 ± 0.52 L/min/$m^2$<br>PCWP: 22.0 ± 7.2 mm Hg<br>All high risk factors (beside gender distribution: 3 men more in group 1 gives a difference of 23%) are distributed equally between groups. |
| Interventions | Myocardial revascularization: PCI (92%) , CABG (4%)<br>Primary additional randomised intervention: The assigned device was implanted after revascularization therapy via the access site. The time required to implant the device was longer in group 2 (Impella: 22 ± 9 min; IABP: 14±8 min). As long as the assigned device was implanted, heparin was given intravenously adjusted to a partial thromboplastin time of 60 to 80 sec. Mean duration of support: (26 ± 19 hrs (group 1), 27 ± 16 hrs (group 2).<br>Pharmacological support: positive inotropic drugs as needed, vasopressors remain unchanged over 30 min during implantation of devices, no further regulations by protocol. |
| Outcomes | change in cardiac index, haemodynamic and metabolic parameters; 30-day mortality (all cause), device-related complications, multiple-organ dysfunction scores at 30 days (MODS and SOFA) criteria |
| Notes | Analysis of individual patient data. |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | random number table with blocked randomisation |
| Allocation concealment (selection bias) | Low risk | opaque sealed and numbered envelopes |
| Blinding (performance bias and detection bias)<br>mortality+haemodynamic | High risk | not possible |
| Incomplete outcome data (attrition bias)<br>mortality | Low risk | complete 6 months follow-up |
| Incomplete outcome data (attrition bias)<br>haemodynamics | Low risk | 30 min, 22 hrs (CPI), 72h (serum-lactate, haemoglobin) |

**Seyfarth 2008** (*Continued*)

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | haemodynamic effects, mortality and device-related complications were reported. |
| Other bias | Low risk | small number of patients, early time point for primary end point assessment (30 min after implantation) |

**Thiele 2005**

| | |
|---|---|
| Methods | Parallel single-centre RCT of two groups (IABP vs. TandemHeart) undergoing percutaneous coronary intervention (PCI) as first line treatment option<br>Study duration: August 2000 to December 2003<br>Measurements: Haemodynamic parameters were acquired in the cath lab before and after device implantation. At the ICU, measurements were obtained every 8 hrs on subsequent days. Metabolic parameters such as standard base excess, serum lactate, and pH were determined. |
| Participants | group 1: +IABP (20)<br>group 2: -IABP (21)<br>1 patient with rapid haemodynamic improvement not received VAD (Group 2)<br>median age: 64 (40-78) years<br>sex: 76% men<br>diabetes: 54%<br>previous infarction: 54%<br>hypertension: 83%<br>smoker: 37%<br>hypercholesterolaemia: 49%<br>cardiac output: 3.4 ± 0.9 L/min<br>MAP: 63 ± 14 mm Hg<br>lactate: 5.7 ± 3.8 mmol/L<br>pH: 7.31 ± 0.10<br>cardiac index: 1.68 ± 0.38 L/min/$m^2$<br>PCWP: 22.6 ± 5.4 mm Hg (group 1: 25.1 ± 6.1 vs. group 2: 20.8 ± 4.1)<br>All high risk factors (beside PCWP) are distributed equally between groups. |
| Interventions | Myocardial revascularization: PCI (95%) , CABG (5%)<br>Primary additional randomised intervention: In patients randomised to Group 1, an IABP (Datascope Corporation, Fairfield, NJ, USA) was inserted percutaneously according to standard procedures. All patients were initially on a pumping ratio of 1:1 with 100% balloon inflation. In patients randomised to Group 2 (TandemHeart, Cardiac Assist, Pittsburgh, PA, USA), after transseptal puncture a venous inflow cannula is inserted into the left atrium. Oxygenated blood is drawn from there and returned via a centrifugal pump and via an arterial cannula in the femoral artery (17 or 12 French) to the lower abdominal aorta. Mean duration of support: (84 ± 54 hrs (group 1), 77 ± 47 hrs (group 2).<br>Pharmacological support: continuously heparin administration through the device lubrication system, activated clotting time was maintained at 180-200 s, iv administration of dopamine and dobutamine (in case of high systemic vascular resistance), diuretics and |

**Thiele 2005** (*Continued*)

| | |
|---|---|
| | fluids (base of the estimated optimal filling pressures) according to standard intensive care guidelines. Patients with PCI were started with aspirin 500 mg and clopidogrel 300 mg, continuation for a minimum of 4 weeks with clopidogrel at 75 mg and aspirin indefinitely at 100 mg. |
| Outcomes | Cardiac power index, change in haemodynamic and metabolic parameters, 30-day mortality, device related complications |
| Notes | Analysis of individual patient data. |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | table of random numbers |
| Allocation concealment (selection bias) | Low risk | sealed opaque envelopes |
| Blinding (performance bias and detection bias)<br>mortality+haemodynamic | High risk | not possible |
| Incomplete outcome data (attrition bias) mortality | Low risk | complete 30 days follow-up |
| Incomplete outcome data (attrition bias) haemodynamics | Low risk | not all patients included in the analysis as a consequence of death, measurements up to 72hrs after implantation |
| Selective reporting (reporting bias) | Low risk | haemodynamic and metabolic parameters, mortality and complications are reported. |
| Other bias | Low risk | exclusion criteria eliminated >50% of all patients with CS (no generalization to the entire CS population possible) |

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Anderson 1997 | no randomised trial |
| Barron 2001 | no randomised trial |

(*Continued*)

| | |
|---|---|
| Bengtson 1992 | no randomised trial |
| Christenson 1997a | no inclusion of patients with preoperatively AMI+CS |
| Christenson 1997b | no inclusion of patients with preoperatively AMI+CS |
| Christenson 1997c | no inclusion of patients with preoperatively AMI+CS |
| Christenson 1999 | no inclusion of patients with preoperatively AMI+CS |
| Christenson 2003 | no inclusion of patients with preoperatively AMI+CS |
| Flaherty 1985 | exclusion of patients with CS |
| Kono 1996 | exclusion of patients with CS |
| Kovack 1997a | no randomised trial |
| Li 2007 | no CS at time of randomisation |
| Marra 2002 | no CS patients |
| Moulopoulos 1986a | no randomised trial |
| O'Rourke 1981 | 4 of 30 patients had CS (1 IABP patient) |
| Ohman 1994 | exclusion of patients with CS |
| Perera 2009 | exclusion of patients with CS |
| Sanborn 2000 | no randomised trial |
| Stomel 1994 | no randomised trial |
| Stone 1997 | exclusion of patients with CS |
| Van 't Hof 1999 | for patients with CS crossover to balloon pumping was pre-specified |
| Vijayalakshmi 2007 | patients with CS were excluded |
| Vis 2007a | no randomised trial |
| Vis 2007b | no randomised trial |
| Waksman 1993 | no randomised trial. IABP was available in unit A (used in 20 patients) and not available in unit B (21 patients) |

## Characteristics of ongoing studies *[ordered by study ID]*

**IABP Shock II**

| | |
|---|---|
| Trial name or title | Intraaortic Balloon Pump in Cardiogenic Shock II |
| Methods | Parallel multicenter RCT of two groups (Standard+IABP vs. Standard) undergoing percutaneous coronary intervention (PCI) |
| Participants | n = 600 |
| Interventions | Comparison of PCI + intensive care treatment+ IABP vs. PCI+intensive care treatment without IABP. Intensive care treatment is performed according to standard care including haemodynamic monitoring using a pulmonary artery catheter for optimal volume status adaption and inotropic drug administration. |
| Outcomes | 30-day mortality, 6month and 1-year mortality, inflammatory and haemodynamic parameters, catecholamines, serum lactate, creatinine clearance, requirement of haemofiltration or dialysis, length of ICU stay, mechanical ventilation, active assist device implementation, SAPS-II Score, quality of life |
| Starting date | June 2009 |
| Contact information | Holger Thiele, MD (thielh@medizin.uni-leipzig.de) |
| Notes | The principal investigator (HT) is coauthor of this review. |

**RECOVER II Trial**

| | |
|---|---|
| Trial name or title | RECOVER II Trial: A prospective randomised trial investigating the use of the IMPELLA RECOVER LP 2.5 system in patients with acute myocardial infarction induced haemodynamic instability |
| Methods | Parallel multicenter RCT of two groups (Impella LP 2.5 vs. IABP) |
| Participants | n = 384 |
| Interventions | Device: Impella LP2.5 vs. device: Intra-Aortic Balloon Pump |
| Outcomes | composite rate of major adverse events within 30 days or hospital discharge (primary outcome), maximum CPO increase from baseline |
| Starting date | July 2008 |
| Contact information | Karim Benali, MD (kbenali@abiomed.com) |
| Notes | Study stopped due to slow recruitment |

## DATA AND ANALYSES

### Comparison 1. IABP versus Control

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 All-cause 30-day mortality distribution | 5 | 150 | Hazard Ratio (Random, 95% CI) | 1.04 [0.62, 1.74] |
| 1.1 IABP versus non-IABP | 2 | 62 | Hazard Ratio (Random, 95% CI) | 1.09 [0.46, 2.58] |
| 1.2 IABP versus other LVAD | 3 | 88 | Hazard Ratio (Random, 95% CI) | 1.02 [0.54, 1.93] |
| 2 All-cause 6-month mortality distribution | 3 | 83 | Hazard Ratio (Random, 95% CI) | 0.93 [0.49, 1.77] |
| 2.1 IABP versus non-IABP | 2 | 57 | Hazard Ratio (Random, 95% CI) | 1.05 [0.40, 2.76] |
| 2.2 IABP versus other LVAD | 1 | 26 | Hazard Ratio (Random, 95% CI) | 0.72 [0.24, 2.13] |
| 3 All-cause 30-day mortality rates | 5 | 150 | Odds Ratio (M-H, Random, 95% CI) | 1.08 [0.55, 2.09] |
| 3.1 IABP versus non-IABP | 2 | 62 | Odds Ratio (M-H, Random, 95% CI) | 1.07 [0.36, 3.15] |
| 3.2 IABP versus other LVAD | 3 | 88 | Odds Ratio (M-H, Random, 95% CI) | 1.08 [0.46, 2.51] |
| 4 All-cause in-hospital mortality rates | 4 | 147 | Odds Ratio (M-H, Random, 95% CI) | 0.88 [0.44, 1.76] |
| 4.1 IABP versus non-IABP | 2 | 80 | Odds Ratio (M-H, Random, 95% CI) | 0.78 [0.21, 2.91] |
| 4.2 IABP versus other LVAD | 2 | 67 | Odds Ratio (M-H, Random, 95% CI) | 0.94 [0.36, 2.47] |
| 5 All-cause 6-month mortality rates | 3 | 83 | Odds Ratio (M-H, Random, 95% CI) | 0.84 [0.34, 2.05] |
| 5.1 IABP versus non-IABP | 2 | 57 | Odds Ratio (M-H, Random, 95% CI) | 0.98 [0.25, 3.87] |
| 5.2 IABP versus other LVAD | 1 | 26 | Odds Ratio (M-H, Random, 95% CI) | 0.54 [0.11, 2.55] |
| 6 Haemodynamics (CI) post intervention | 3 | 95 | Mean Difference (IV, Random, 95% CI) | -0.38 [-1.23, 0.47] |
| 6.1 IABP versus non-IABP | 1 | 30 | Mean Difference (IV, Random, 95% CI) | 0.49 [-0.29, 1.27] |
| 6.2 IABP versus other LVAD | 2 | 65 | Mean Difference (IV, Random, 95% CI) | -0.75 [-1.51, -2.96] |
| 7 Haemodynamics (MAP) post intervention | 3 | 101 | Mean Difference (IV, Random, 95% CI) | -5.10 [-10.86, 0.66] |
| 7.1 IABP versus non-IABP | 1 | 36 | Mean Difference (IV, Random, 95% CI) | -3.27 [-13.47, 6.93] |
| 7.2 IABP versus other LVAD | 2 | 65 | Mean Difference (IV, Random, 95% CI) | -7.55 [-18.59, 3.50] |
| 8 Haemodynamics (PCWP) post intervention | 3 | 90 | Mean Difference (IV, Random, 95% CI) | 3.89 [1.10, 6.68] |
| 8.1 IABP versus non-IABP | 1 | 28 | Mean Difference (IV, Random, 95% CI) | 4.71 [1.12, 8.30] |
| 8.2 IABP versus other LVAD | 2 | 62 | Mean Difference (IV, Random, 95% CI) | 3.37 [-1.35, 8.09] |
| 9 Length of hospital stay | 3 | 77 | Mean Difference (IV, Random, 95% CI) | -4.67 [-10.85, 1.51] |
| 9.1 IABP versus non-IABP | 1 | 40 | Mean Difference (IV, Random, 95% CI) | -11.10 [-24.96, 2.76] |
| 9.2 IABP versus other LVAD | 2 | 37 | Mean Difference (IV, Random, 95% CI) | -3.08 [-9.98, 3.83] |

### Analysis 1.1. Comparison 1 IABP versus Control, Outcome 1 All-cause 30-day mortality distribution.

Review: Intra-aortic balloon pump counterpulsation (IABP) for myocardial infarction complicated by cardiogenic shock

Comparison: 1 IABP versus Control

Outcome: 1 All-cause 30-day mortality distribution

| Study or subgroup | IABP N | Control N | log [Hazard Ratio] (SE) | Hazard Ratio IV,Random,95% CI | Weight | Hazard Ratio IV,Random,95% CI |
|---|---|---|---|---|---|---|
| 1 IABP versus non-IABP | | | | | | |
| Ohman 2005a | 12 | 10 | -0.28835 (0.63385) | | 17.1 % | 0.75 [ 0.22, 2.60 ] |
| Prondzinsky 2010 | 19 | 21 | 0.43586 (0.60641) | | 18.6 % | 1.55 [ 0.47, 5.08 ] |
| **Subtotal (95% CI)** | | | | | **35.7 %** | **1.09 [ 0.46, 2.58 ]** |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.68$, df = 1 (P = 0.41); $I^2 = 0.0\%$ | | | | | | |
| Test for overall effect: Z = 0.20 (P = 0.84) | | | | | | |
| 2 IABP versus other LVAD | | | | | | |
| Thiele 2005 | 20 | 21 | 0.08595 (0.47965) | | 29.8 % | 1.09 [ 0.43, 2.79 ] |
| Burkhoff 2006 | 10 | 11 | -0.12869 (0.67585) | | 15.0 % | 0.88 [ 0.23, 3.31 ] |
| Seyfarth 2008 | 13 | 13 | 0.01788 (0.59305) | | 19.5 % | 1.02 [ 0.32, 3.26 ] |
| **Subtotal (95% CI)** | | | | | **64.3 %** | **1.02 [ 0.54, 1.93 ]** |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.07$, df = 2 (P = 0.97); $I^2 = 0.0\%$ | | | | | | |
| Test for overall effect: Z = 0.05 (P = 0.96) | | | | | | |
| **Total (95% CI)** | | | | | **100.0 %** | **1.04 [ 0.62, 1.74 ]** |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.77$, df = 4 (P = 0.94); $I^2 = 0.0\%$ | | | | | | |
| Test for overall effect: Z = 0.16 (P = 0.87) | | | | | | |
| Test for subgroup differences: $Chi^2 = 0.02$, df = 1 (P = 0.89), $I^2 = 0.0\%$ | | | | | | |

### Analysis 1.2. Comparison 1 IABP versus Control, Outcome 2 All-cause 6-month mortality distribution.

Review: Intra-aortic balloon pump counterpulsation (IABP) for myocardial infarction complicated by cardiogenic shock

Comparison: 1 IABP versus Control

Outcome: 2 All-cause 6-month mortality distribution

| Study or subgroup | IABP N | Control N | log [Hazard Ratio] (SE) | Hazard Ratio IV,Random,95% CI | Weight | Hazard Ratio IV,Random,95% CI |
|---|---|---|---|---|---|---|
| 1 IABP versus non-IABP | | | | | | |
| Ohman 2005a | 12 | 10 | -0.48162 (0.6049) | | 29.0 % | 0.62 [ 0.19, 2.02 ] |
| Prondzinsky 2010 | 17 | 18 | 0.50627 (0.54105) | | 36.2 % | 1.66 [ 0.57, 4.79 ] |
| **Subtotal (95% CI)** | | | | | **65.2 %** | **1.05 [ 0.40, 2.76 ]** |
| Heterogeneity: $Tau^2$ = 0.16; $Chi^2$ = 1.48, df = 1 (P = 0.22); $I^2$ =33% | | | | | | |
| Test for overall effect: Z = 0.10 (P = 0.92) | | | | | | |
| 2 IABP versus other LVAD | | | | | | |
| Seyfarth 2008 | 13 | 13 | -0.3253 (0.55253) | | 34.8 % | 0.72 [ 0.24, 2.13 ] |
| **Subtotal (95% CI)** | | | | | **34.8 %** | **0.72 [ 0.24, 2.13 ]** |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: Z = 0.59 (P = 0.56) | | | | | | |
| **Total (95% CI)** | | | | | **100.0 %** | **0.93 [ 0.49, 1.77 ]** |
| Heterogeneity: $Tau^2$ = 0.0; $Chi^2$ = 1.81, df = 2 (P = 0.40); $I^2$ =0.0% | | | | | | |
| Test for overall effect: Z = 0.21 (P = 0.83) | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.26, df = 1 (P = 0.61), $I^2$ =0.0% | | | | | | |

### Analysis 1.3. Comparison 1 IABP versus Control, Outcome 3 All-cause 30-day mortality rates.

Review: Intra-aortic balloon pump counterpulsation (IABP) for myocardial infarction complicated by cardiogenic shock

Comparison: 1 IABP versus Control

Outcome: 3 All-cause 30-day mortality rates

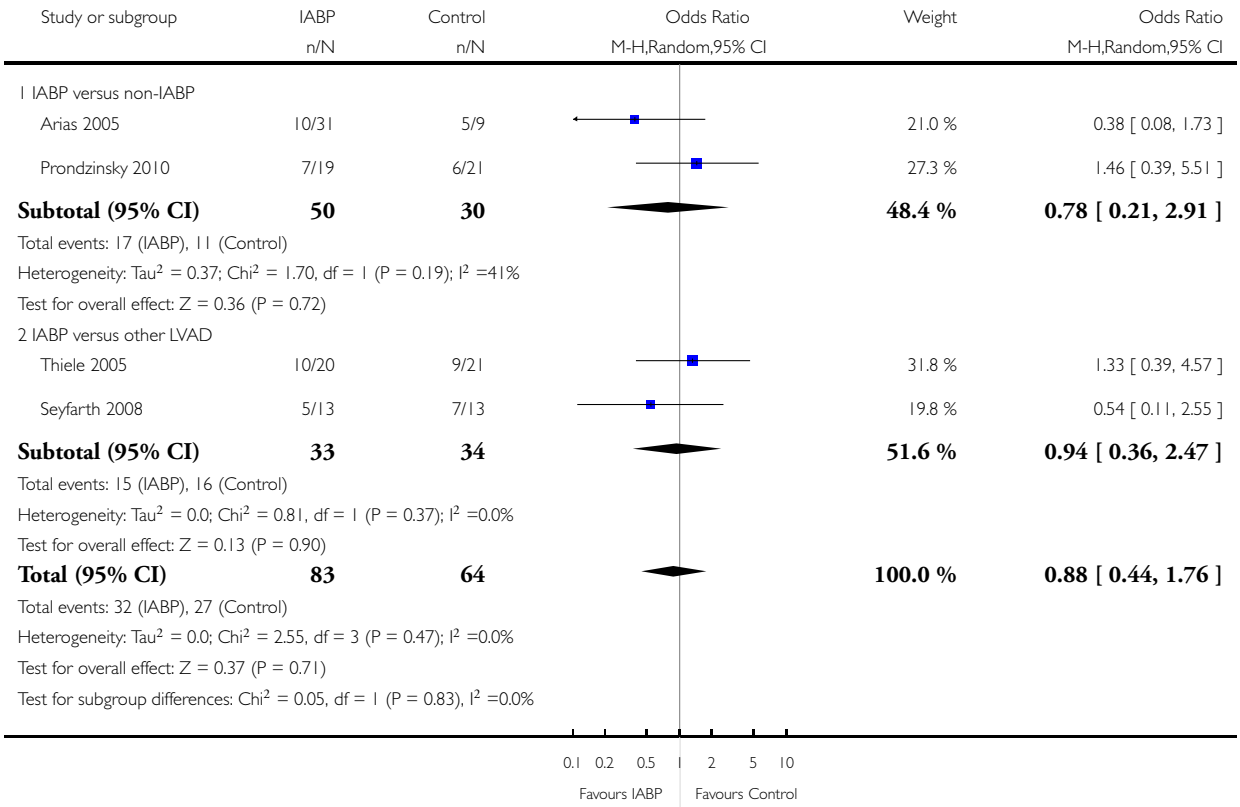
| Study or subgroup | IABP n/N | Control n/N | Odds Ratio M-H,Random,95% CI | Weight | Odds Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 IABP versus non-IABP | | | | | |
| Ohman 2005a | 6/12 | 6/10 | | 15.4 % | 0.67 [ 0.12, 3.64 ] |
| Prondzinsky 2010 | 6/19 | 5/21 | | 22.8 % | 1.48 [ 0.37, 5.96 ] |
| **Subtotal (95% CI)** | **31** | **31** | | **38.1 %** | **1.07 [ 0.36, 3.15 ]** |
| Total events: 12 (IABP), 11 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.50$, df = 1 (P = 0.48); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 0.13 (P = 0.90) | | | | | |
| 2 IABP versus other LVAD | | | | | |
| Thiele 2005 | 9/20 | 9/21 | | 29.1 % | 1.09 [ 0.32, 3.75 ] |
| Burkhoff 2006 | 4/10 | 4/11 | | 14.2 % | 1.17 [ 0.20, 6.80 ] |
| Seyfarth 2008 | 6/13 | 6/13 | | 18.6 % | 1.00 [ 0.21, 4.67 ] |
| **Subtotal (95% CI)** | **43** | **45** | | **61.9 %** | **1.08 [ 0.46, 2.51 ]** |
| Total events: 19 (IABP), 19 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.02$, df = 2 (P = 0.99); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 0.18 (P = 0.86) | | | | | |
| **Total (95% CI)** | **74** | **76** | | **100.0 %** | **1.08 [ 0.55, 2.09 ]** |
| Total events: 31 (IABP), 30 (Control) | | | | | |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.52$, df = 4 (P = 0.97); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: Z = 0.22 (P = 0.83) | | | | | |
| Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.99), $I^2 = 0.0\%$ | | | | | |

### Analysis 1.4. Comparison 1 IABP versus Control, Outcome 4 All-cause in-hospital mortality rates.

Review: Intra-aortic balloon pump counterpulsation (IABP) for myocardial infarction complicated by cardiogenic shock

Comparison: 1 IABP versus Control

Outcome: 4 All-cause in-hospital mortality rates

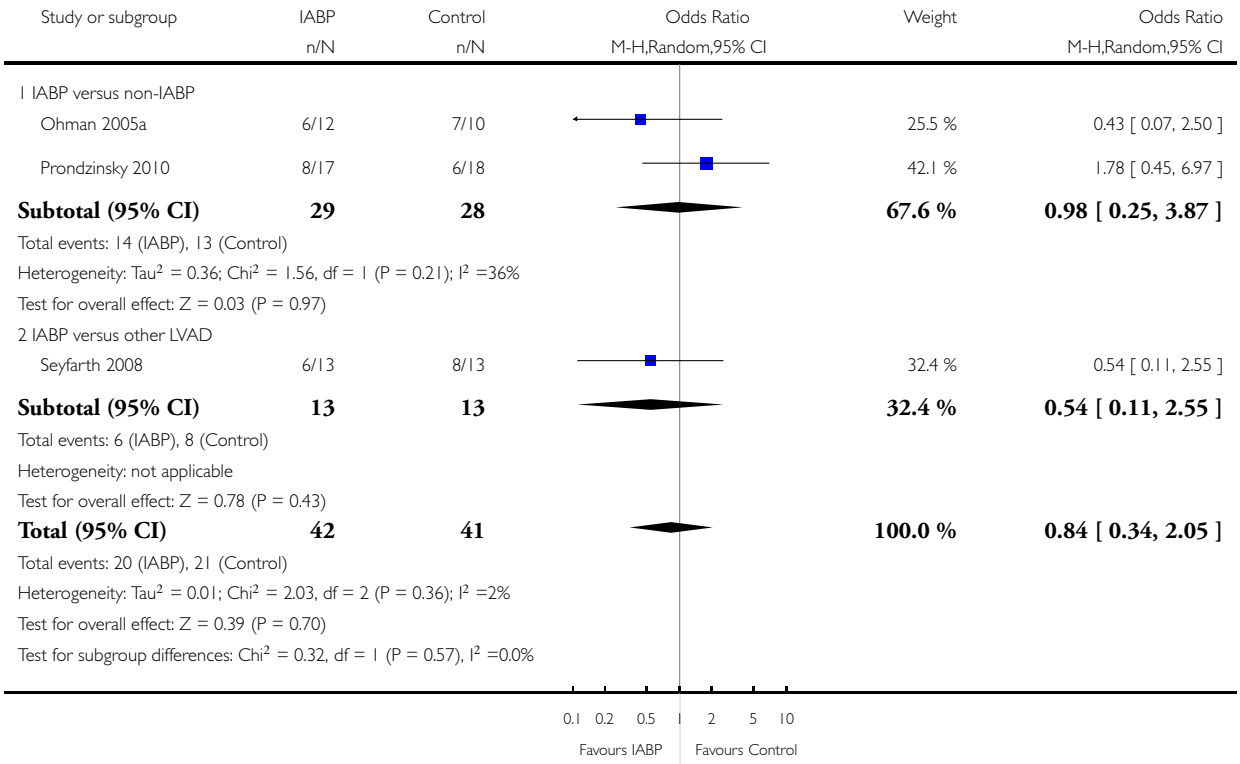


### Analysis 1.5. Comparison 1 IABP versus Control, Outcome 5 All-cause 6-month mortality rates.

Review: Intra-aortic balloon pump counterpulsation (IABP) for myocardial infarction complicated by cardiogenic shock

Comparison: 1 IABP versus Control

Outcome: 5 All-cause 6-month mortality rates



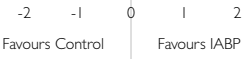
### Analysis 1.6. Comparison 1 IABP versus Control, Outcome 6 Haemodynamics (CI) post intervention.

Review: Intra-aortic balloon pump counterpulsation (IABP) for myocardial infarction complicated by cardiogenic shock

Comparison: 1 IABP versus Control

Outcome: 6 Haemodynamics (CI) post intervention

| Study or subgroup | IABP N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| 1 IABP versus non-IABP | | | | | | | |
| Prondzinsky 2010 | 16 | 2.93 (1.43) | 14 | 2.44 (0.67) | | 29.8 % | 0.49 [ -0.29, 1.27 ] |
| **Subtotal (95% CI)** | **16** | | **14** | | | **29.8 %** | **0.49 [ -0.29, 1.27 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 1.23 (P = 0.22) | | | | | | | |
| 2 IABP versus other LVAD | | | | | | | |
| Thiele 2005 | 19 | 1.19 (0.85) | 20 | 2.32 (0.59) | | 35.6 % | -1.13 [ -1.59, -0.67 ] |
| Seyfarth 2008 | 13 | 1.84 (0.71) | 13 | 2.2 (0.64) | | 34.6 % | -0.36 [ -0.88, 0.16 ] |
| **Subtotal (95% CI)** | **32** | | **33** | | | **70.2 %** | **-0.75 [ -1.51, 0.00 ]** |
| Heterogeneity: $Tau^2$ = 0.23; $Chi^2$ = 4.72, df = 1 (P = 0.03); $I^2$ =79% | | | | | | | |
| Test for overall effect: Z = 1.96 (P = 0.050) | | | | | | | |
| **Total (95% CI)** | **48** | | **47** | | | **100.0 %** | **-0.38 [ -1.23, 0.47 ]** |
| Heterogeneity: $Tau^2$ = 0.47; $Chi^2$ = 13.31, df = 2 (P = 0.001); $I^2$ =85% | | | | | | | |
| Test for overall effect: Z = 0.88 (P = 0.38) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 5.03, df = 1 (P = 0.02), $I^2$ =80% | | | | | | | |



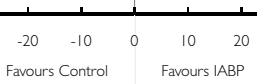
### Analysis 1.7. Comparison 1 IABP versus Control, Outcome 7 Haemodynamics (MAP) post intervention.

Review: Intra-aortic balloon pump counterpulsation (IABP) for myocardial infarction complicated by cardiogenic shock

Comparison: 1 IABP versus Control

Outcome: 7 Haemodynamics (MAP) post intervention

| Study or subgroup | IABP N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| 1 IABP versus non-IABP | | | | | | | |
| Prondzinsky 2010 | 18 | 76.26 (15.59) | 18 | 79.53 (15.65) | | 31.9 % | -3.27 [ -13.47, 6.93 ] |
| **Subtotal (95% CI)** | **18** | | **18** | | | **31.9 %** | **-3.27 [ -13.47, 6.93 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 0.63 (P = 0.53) | | | | | | | |
| 2 IABP versus other LVAD | | | | | | | |
| Thiele 2005 | 19 | 72.11 (12.07) | 20 | 75.65 (12.83) | | 54.3 % | -3.54 [ -11.35, 4.27 ] |
| Seyfarth 2008 | 13 | 71.15 (21.97) | 13 | 86.62 (18.2) | | 13.8 % | -15.47 [ -30.98, 0.04 ] |
| **Subtotal (95% CI)** | **32** | | **33** | | | **68.1 %** | **-7.55 [ -18.59, 3.50 ]** |
| Heterogeneity: $Tau^2$ = 31.91; $Chi^2$ = 1.81, df = 1 (P = 0.18); $I^2$ =45% | | | | | | | |
| Test for overall effect: Z = 1.34 (P = 0.18) | | | | | | | |
| **Total (95% CI)** | **50** | | **51** | | | **100.0 %** | **-5.10 [ -10.86, 0.66 ]** |
| Heterogeneity: $Tau^2$ = 0.0; $Chi^2$ = 1.99, df = 2 (P = 0.37); $I^2$ =0.0% | | | | | | | |
| Test for overall effect: Z = 1.74 (P = 0.083) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.31, df = 1 (P = 0.58), $I^2$ =0.0% | | | | | | | |



### Analysis 1.8. Comparison 1 IABP versus Control, Outcome 8 Haemodynamics (PCWP) post intervention.

Review: Intra-aortic balloon pump counterpulsation (IABP) for myocardial infarction complicated by cardiogenic shock

Comparison: 1 IABP versus Control

Outcome: 8 Haemodynamics (PCWP) post intervention

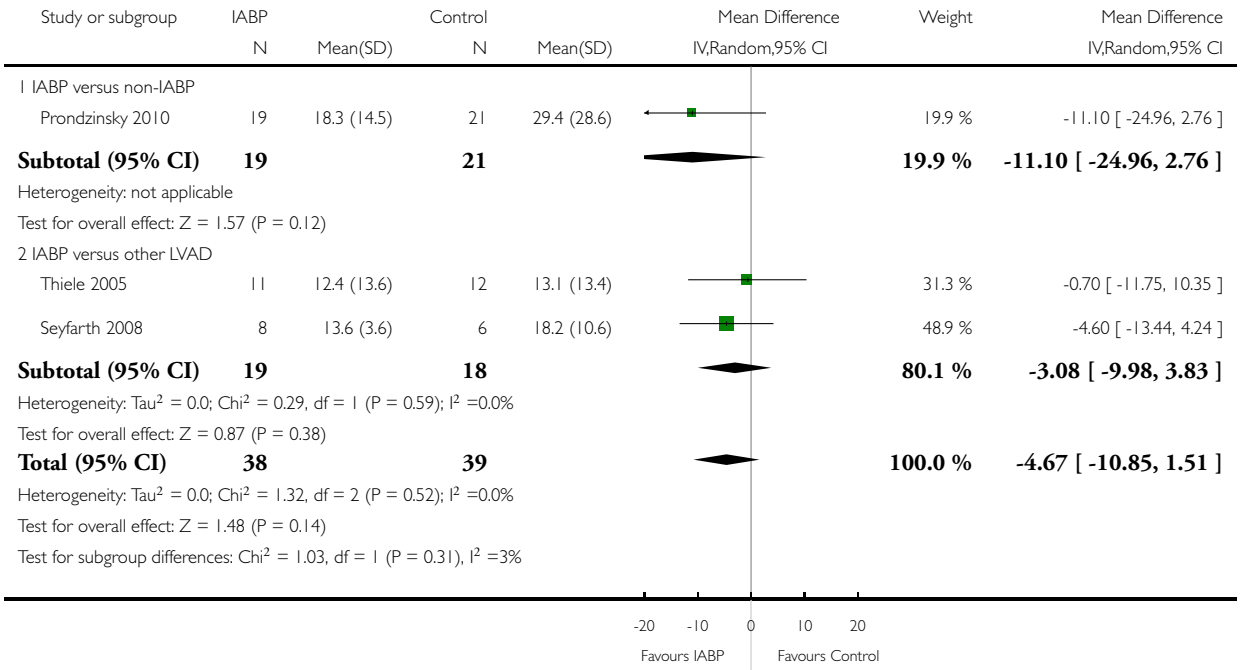
| Study or subgroup | IABP N | Mean(SD) | Control N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| 1 IABP versus non-IABP | | | | | | | |
| Prondzinsky 2010 | 16 | 20.88 (4.36) | 12 | 16.17 (5.1) | | 33.4 % | 4.71 [ 1.12, 8.30 ] |
| **Subtotal (95% CI)** | **16** | | **12** | | | **33.4 %** | **4.71 [ 1.12, 8.30 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 2.57 (P = 0.010) | | | | | | | |
| 2 IABP versus other LVAD | | | | | | | |
| Thiele 2005 | 16 | 21.56 (5.82) | 20 | 15.9 (3.82) | | 36.5 % | 5.66 [ 2.35, 8.97 ] |
| Seyfarth 2008 | 13 | 20.15 (5.51) | 13 | 19.31 (4.68) | | 30.1 % | 0.84 [ -3.09, 4.77 ] |
| **Subtotal (95% CI)** | **29** | | **33** | | | **66.6 %** | **3.37 [ -1.35, 8.09 ]** |
| Heterogeneity: $Tau^2$ = 8.18; $Chi^2$ = 3.38, df = 1 (P = 0.07); $I^2$ =70% | | | | | | | |
| Test for overall effect: Z = 1.40 (P = 0.16) | | | | | | | |
| **Total (95% CI)** | **45** | | **45** | | | **100.0 %** | **3.89 [ 1.10, 6.68 ]** |
| Heterogeneity: $Tau^2$ = 2.70; $Chi^2$ = 3.60, df = 2 (P = 0.17); $I^2$ =44% | | | | | | | |
| Test for overall effect: Z = 2.74 (P = 0.0062) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.20, df = 1 (P = 0.66), $I^2$ =0.0% | | | | | | | |

**Analysis 1.9. Comparison 1 IABP versus Control, Outcome 9 Length of hospital stay.**

Review: Intra-aortic balloon pump counterpulsation (IABP) for myocardial infarction complicated by cardiogenic shock

Comparison: 1 IABP versus Control

Outcome: 9 Length of hospital stay




# APPENDICES

## Appendix 1. Search strategies

### CENTRAL on The Cochrane Library, *Issue 1, 2010*

#1 MeSH descriptor Intra-Aortic Balloon Pumping explode all trees
#2 assisted next circulation in All Text
#3 (aort* in All Text near/6 balloon* in All Text)
#4 IABP in All Text
#5 (intra-aort* in All Text near/6 balloon in All Text)
#6 (intraaort* in All Text near/6 balloon in All Text)
#7 counterpulsation in All Text
#8 (#1 or #2 or #3 or #4 or #5 or #6 or #7)
#9 MeSH descriptor myocardial infarction explode all trees
#10 heart next infarction in All Text

#11 myocardial next infarction in All Text
#12 shock in All Text
#13 ami in All Text
#14 (#9 or #10 or #11 or #12 or #13)
#15 (#8 and #14)

**Medline (on Ovid) 1966 to January 2010**

1 Intra-Aortic Balloon Pumping/
2 intra-aortic balloon.tw.
3 intraaortic balloon.tw.
4 iabp.tw.
5 assisted circulation.tw.
6 aort$ balloon.tw.
7 intraaort$ counterpulsation.tw.
8 intra aort$ counterpulsation.tw.
9 or/1-8
10 exp Myocardial Infarction/
11 myocardial infarction.tw.
12 heart infarction.tw.
13 ami.tw.
14 cardiogenic shock.tw.
15 or/10-14
16 9 and 15
17 randomized controlled trial.pt.
18 controlled clinical trial.pt.
19 Randomized controlled trials/
20 random allocation/
21 double blind method/
22 single-blind method/
23 or/17-22
24 exp animal/ not humans/
25 23 not 24
26 clinical trial.pt.
27 exp Clinical Trials as Topic/
28 (clin$ adj25 trial$).ti,ab.
29 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab.
30 placebos/
31 placebo$.ti,ab.
32 random$.ti,ab.
33 research design/
34 or/26-33
35 34 not 24
36 35 not 25
37 comparative study.pt.
38 exp evaluation studies/
39 follow up studies/
40 prospective studies/
41 (control$ or prospectiv$ or volunteer$).ti,ab.
42 or/37-41
43 42 not 24
44 43 not (25 or 36)
45 25 or 36 or 44

46 16 and 45

**Embase (on Ovid) 1980 to 2010, week 2**

1 exp Aorta Balloon/
2 intra-aortic balloon.af.
3 intraaortic balloon.af.
4 iabp.af.
5 assisted circulation.af.
6 aort$ balloon.af.
7 intraaort$ counterpulsat$.af.
8 intra-aort$ counterpulsat$.af.
9 6 or 3 or 7 or 2 or 8 or 1 or 4 or 5
10 exp Heart Infarction/
11 myocardial infarction.af.
12 heart infarction.af.
13 ami.af.
14 cardiogenic shock.af.
15 11 or 13 or 10 or 12 or 14
16 9 and 15
17 Randomized Controlled Trial/
18 exp controlled clinical trial/
19 Randomized Controlled Trial/
20 random allocation.af.
21 double blind method$.pt,af.
22 single-blind method$.af.
23 22 or 21 or 18 or 19 or 17 or 20
24 exp ANIMAL/
25 "not human$".af.
26 25 or 24
27 23 not 26
28 clinical trial$.pt,af.
29 clinical trial$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
30 (clin$ adj25 trial$).ti,ot,ab.
31 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,pt,ot,ab.
32 placebo$.af.
33 random$.pt,af.
34 research design$.af.
35 33 or 32 or 34 or 28 or 30 or 31 or 29
36 35 not 26
37 36 not 27
38 comparative stud$.af.
39 evaluat$ stud$.af.
40 follow up stud$.af.
41 prospective stud$.pt,af.
42 (control$ or prospectiv$ or volunteer$).ti,ot,ab.
43 42 or 38 or 39 or 40 or 41
44 43 not 26
45 44 not (27 or 37)
46 27 or 37 or 45
47 46 and 16

**Individual search terms used for LILACS, IndMED and KoreaMed to January 2010**

IABP, Intra-Aortic Balloon Pumping, intraaortic, assisted circulation, cardiogenic shock, counterpulsation

## HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 7, 2011

## CONTRIBUTIONS OF AUTHORS

Susanne Unverzagt (SU): Protocol development, eligibility and quality assessment, data extraction and analysis, drafting of final review.

Maria-Theresia Machemer (MM): Assessment of eligibility and quality, data extraction, drafting of final review

Alexander Solms: Statistician (AS); statistician, drafting of final review

Holger Thiele (HT): Clinical and scientific advice, assessment of eligibility and quality, drafting of final review

Daniel Burkhoff (DB): Clinical and scientific advice, drafting of final review

Melchior Seyfarth (MS): Clinical and scientific advice, drafting of final review

Antoinette de Waha (AW): Data management, scientific advice, drafting of final review

Michael Buerke (MB): Clinical and scientific advice, drafting of final review

Johannes Haerting (JH): Statistical and scientific advice, drafting of final review

Karl Werdan (KW): Clinical and scientific advice, drafting of final review

Erik Ohman (EO): Clinical and scientific advice, drafting of final review

Roland Prondzinsky (RP): Clinical and scientific advice, assessment of eligibility and quality, drafting of final review.

## DECLARATIONS OF INTEREST

The authors (SU, RP, MB, KW, JH) were involved in the IABP Shock Trial (2003 to 2004) (Prondzinsky 2010). Melchior Seyfarth and Antoinette de Waha in Seyfarth 2008, Holger Thiele in Thiele 2005, Daniel Burkhoff in Burkhoff 2006 and Erik Ohman in Ohman 2005a. Holger Thiele, Roland Prondzinsky, Michael Buerke and Karl Werdan are involved in one ongoing trial (IABP Shock II). Judgements of inclusion criteria and risk of bias for these studies and interpretation of results were appraised by SU and RP, in case of Prondzinsky 2010 by HT.

## SOURCES OF SUPPORT

### Internal sources

- Wilhelm-Roux-Programme, University Halle-Wittenberg, Germany.
financial support

### External sources

- Ministery for Education and Research (grant number: 01KG0811), Germany.
financial support

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In five of six included studies patients were revascularised by PCI as first line treatment option. Only 22 eligible patients in one study were revascularised with thrombolytic therapy. Therefore, a preplanned separate analysis for different types of revascularization to the primary outcome were included.

We added subgroup analyses to investigate the influence of different therapies in the control group (standard without IABP or other assist devices) on all investigated outcomes. Due to the small number of studies and very heterogenous sources of bias, we did not perform sensitivity analyses on other preplanned influencing factors as pharmacological support, characteristics of IABP intervention, influence of cross-over or and risk of bias in studies.

Stratified analyses were planned for the prognostic factors age, sex and degree of cardiogenic shock according to Menon 2000 to find differences on benefit and harms under IABP support. Because of missing information we restricted our investigation on the influence of age and sex and will try to analyse subgroups of cardiogenic shock regarding systemic inflammation and multiorgan failure on the basis of data form the ongoing IABP Shock II trial.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Intra-Aortic Balloon Pumping [*methods]; Myocardial Infarction [*complications]; Randomized Controlled Trials as Topic; Shock, Cardiogenic [etiology; *therapy]

### MeSH check words

Humans