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(Review)

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[Intervention Review]

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

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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 has been only limited evidence from randomised controlled trials, the previous guidelines of the American Heart Association/American College of Cardiology (AHA/ACC) and the European Society of Cardiology (ESC) strongly recommended the use of the IABP in patients with infarction-related cardiogenic shock on the basis of pathophysiological considerations, non-randomised trials and registry data. The recent guidelines downgraded the recommendation based on a meta-analysis which could only include non-randomised trials showing conflicting results. Up to now, there have been no guideline recommendations and no actual meta-analysis including the results of the large randomised multicentre IABP-SHOCK II Trial which showed no survival benefit with IABP support. This systematic review is an update of the review published in 2011.

Objectives

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 acute myocardial infarction complicated by cardiogenic shock.

Search methods

Searches of CENTRAL, MEDLINE (Ovid) and EMBASE (Ovid), LILACS, IndMed and KoreaMed, registers of ongoing trials and proceedings of conferences were updated in October 2013. 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 acute myocardial infarction complicated by cardiogenic shock.

Data collection and analysis

Data collection and analysis were performed according to the published protocol. Individual patient data were provided for six trials and merged with aggregate data. Summary statistics for the primary endpoints were hazard ratios (HRs) and odds ratios (ORs) with 95% confidence intervals (CIs).

Main results

Seven eligible studies were identified from a total of 2314 references. One new study with 600 patients was added to the original review. Four trials compared IABP to standard treatment and three to other percutaneous left assist devices (LVAD). Data from a total of 790 patients with acute myocardial infarction and cardiogenic shock were included in the updated meta-analysis: 406 patients were treated with IABP and 384 patients served as controls; 339 patients were treated without assisting devices and 45 patients with other LVAD. The HR for all-cause 30-day mortality of 0.95 (95% CI 0.76 to 1.19) provided no evidence for a survival benefit. Different non-fatal cardiovascular events were reported in five trials. During hospitalisation, 11 and 4 out of 364 patients from the intervention groups suffered from reinfarction or stroke, respectively. Altogether 5 out of 363 patients from the control group suffered from reinfarction or stroke. Reocclusion was treated with subsequent re-revascularization in 6 out of 352 patients from the intervention group and 13 out of 353 patients of the control group. The high incidence of complications such as moderate and severe bleeding or infection in the control groups has to be attributed to interventions with other LVAD. Possible reasons for bias were more frequent in small studies with high cross-over rates, early stopping and the inclusion of patients with IABP at randomisation.

Authors' conclusions

Available evidence suggests that IABP may have a beneficial effect on some haemodynamic parameters. However, this did not result in survival benefits so 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

Cardiogenic shock is a severe condition in which a suddenly weakened heart is not able to pump enough blood to meet the body's energy needs, so not enough oxygen will reach the body's organs. Cardiogenic shock is a life-threatening medical emergency and needs to be treated quickly to avoid organ damage or even death of the affected patient. Most often cardiogenic shock is caused by a severe heart attack and the induced damage to the heart muscle. Despite more than 50 years of effort, patients with cardiogenic shock still have a poor prognosis after primary revascularization procedures such as coronary artery bypass grafting or primary percutaneous coronary intervention. The main cause for the development of cardiogenic shock is the loss of myocardial function due to myocardial infarction leading to impaired left ventricular function with unstable haemodynamics and reduced systolic and mean arterial pressures. The reduced blood pressure leads to hypoperfusion and so reduced oxygen supply to vital organs and the corresponding clinical signs. These include cold and pale skin, reduced or a lack of urine output and signs of impaired cerebral function like dizziness or even unconsciousness.

On this basis, it was reasoned that the use of mechanical means of augmenting pressure and flow would prove effective. The very first mechanical means of assisting the circulation in such a manner was by a counter pulsation strategy using a device called the intra-aortic balloon pump (IABP). Through balloon inflations and deflations synchronized with the natural heartbeat the IABP increases diastolic aortic pressure, which enhances diastolic blood flow to the coronary arteries and vital organs, as well as reduces systolic aortic pressure, which reduces afterload and oxygen consumption of the myocardium and increases cardiac output. This support can be provided for a few hours and, in extreme cases, for several weeks. Evidence from earlier published studies suggested that certain patients with acute myocardial infarction complicated by cardiogenic shock and treated by thrombolysis may derive benefit from a period of support with the IABP. However, nowadays the most widely recommended and preferred revascularization procedure is primary percutaneous coronary intervention.

In contrast to the previous version of this review, this update now includes data from one large and six small randomised controlled trials. It allows more definitive conclusions about the potential beneficial or harmful clinical effects of IABP support beyond its immediate haemodynamic effects. Complications such as moderate and severe bleeding were more frequently observed in patients treated with more invasive devices than IABP. Small randomised trials suffered from inadequate power to address deaths and harmful effects of IABP and were biased by frequent cross-over to the more aggressive strategy, early stopping of the trial, or the inclusion of patients with IABP at randomisation. It is most noteworthy that a recently conducted and published large randomised trial showed no evidence for survival benefits of IABP support in patients with infarct-related cardiogenic shock treated by percutaneous coronary intervention (PCI). On the basis of these data, IABP support is no longer strongly recommended by the European Society of Cardiology (ESC) guidelines for treatment of patients with infarct-related cardiogenic shock. Rather, IABP use is based on the personal experience and decision of the physician and the particular circumstances of individual patients.

BACKGROUND

Description of the condition

Worldwide, cardiovascular disease is estimated to be the leading cause of death and loss of disability-adjusted life years (Gaziano 2010; Lozano 2012; Moran 2014; Mozaffarian 2014; Nieuwlaet 2013; The Global Burden Collaboration 2014). Each year approximately 920,000 people in the United States (US) experience acute myocardial infarction (AMI), with a prevalence of 5.1% of all males and 2.5% of all females over 20 years old and about 150,000 of them die. The estimated direct and indirect 2008 costs of coronary heart disease (ICD 10 codes I20 to I25) in the US was USD 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 the 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 ischaemia and reperfusion and the following inflammatory response. Clinically defined, cardiogenic shock is hypotension (a systolic blood pressure of < 90 mmHg for at least 30 minutes or the need for supportive measures to maintain a systolic blood pressure of ≥ 90 mmHg) and end-organ hypoperfusion (cool extremities or a urine output of < 30 mL per hour, altered mental status, or elevated serum lactate). Haemodynamic criteria that are sometimes used include cardiac index (< 1.8 L/min/m² or < 2.2 L/min/m² if inotropic drugs or vasopressors are used) and a pulmonary capillary wedge pressure of at least 15 mmHg (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 2005a; Thiele 2012; Werdan 2014). Fewer than 50% of 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 pump counterpulsation (IABP) support and early diagnostic angiography with primary percutaneous coronary revascularization (Ohman 2005a). Early mechanical revascularization, using either percutaneous coronary intervention (PCI) 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

IABP was introduced into clinical practice in 1968 (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, in registry trials, several

investigators have shown enhanced coronary, cerebral and renal perfusion (even microperfusion) with IABP, particularly among patients having PCI during cardiogenic shock. However, this impressive physiological profile has not been followed by equally important randomised clinical trial data (Ohman 2001; Werdan 2010).

During the last few years IABP insertion has become safer with the smaller diameters of the balloon catheters and the corresponding insertion sheaths. Nevertheless every additional arterial puncture, especially in the emergency situation, can lead to IABP-related complications such as bleeding, arterial ischaemia, venous thrombosis and also infections. Because bleeding complications, in particular, 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 the complication itself (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 ischaemia, aortic dissection, abdominal aorta perforation, bilateral limb ischaemia) in 8%, minor vascular complications (haematoma requiring operative revision, haemorrhage treated by IABP removal, limb ischaemia relieved by IABP removal, local infection and ischaemic skin loss) in 3%, and late vascular complications in 2% of patients (foot drop, pseudoaneurysm, limb ischaemia). Newer platelet inhibitors, such as prasugrel and ticagrelor, and anticoagulant drugs like the direct factor Xa- and thrombin-inhibitors are increasingly being used and may lead to increased bleeding risks with IABP support.

Why it is important to do this review

IABP has been the most commonly used mechanical assist device for patients with cardiogenic shock for more than four decades. Its use has been encouraged by a class I recommendation in the previous 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 Level C evidence in the ESC guidelines supporting this recommendation could 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 have been 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 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 morbidity, particularly among the patients with several high-risk features (Ishihara 1991; Ohman 1994). These studies were too small to address mortality but they favoured better outcomes with IABP treatment compared to standard therapy without IABP. Randomised trials of IABP in cardiogenic shock were 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 2005). The IABP SHOCK II Trial was the first large randomised controlled multicentre trial adequately powered to investigate the influence of IABP support on mortality, and enrolled 600 patients with infarct-related cardiogenic shock (Thiele 2012).

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; Mouloupoulos 1986b; Takano 1984; Weiss 1984). However, these studies are subject to selection bias and 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).

It seems probable that not all patients in cardiogenic shock benefit from IABP therapy (Hochman 2003), in particular in those where 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 Theologou 2011 suggests that preoperative IABP use may be beneficial on mortality and morbidity in specific high-risk patients groups undergoing coronary artery bypass surgery. However, they state many problems with the quality, validity and generalisability of the trials.

A systematic review by Sjaauw 2009 of IABP therapy in ST-elevation myocardial infarction (STEMI) performed two separate meta-analyses. The first meta-analysis included seven randomised trials in 1009 patients with STEMI restricted to patients without cardiogenic shock and the second used data from non-randomised trials of 10,529 STEMI patients with cardiogenic shock. A second systematic review by Cheng 2009 performed a meta-analysis of three studies comparing the safety and efficacy of IABP with percutaneous left ventricular assist devices (LVADs) and performed a meta-analysis of aggregate data for 30-day survival, haemodynamics (cardiac index (CI), mean arterial blood pressure (MAP) and pulmonary capillary wedge pressure (PCWP)) and adverse events (leg ischaemia, bleeding and sepsis).

Up to now no systematic review integrating the data of the IABP SHOCK II Trial has been performed and published. The results of this updated review will add more evidence and this review provides 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 the risk of complications and these potential risks

can only be justified by an acceptable (evidence-based) assessment of measurable beneficial clinical effects in IABP-treated patients. This will have implications for clinical practice. Three additional studies comparing IABP versus standard treatment without IABP (Arias 2005; Prondzinsky 2010; Thiele 2012) and subgroups of patients with myocardial infarction and cardiogenic shock from two other studies (Burkhoff 2006; Ohman 2005) were included. Extensive analyses of 30-day, 6-month and 12-month mortality distributions provide an important opportunity to examine the effects over a prolonged period of time. Analyses were adjusted for age, sex and diabetes as a comorbidity to see whether the observed effects were consistent across different types of patients.

As a consequence of the data from one systematic review (Sjaauw 2009) the corresponding guidelines of ACC/AHA and ESC, and also the German-Austrian guideline, for the treatment of infarct-related cardiogenic shock have been revised (O'Gara 2013; Steg 2012; Werdan 2012).

OBJECTIVES

The primary aim of this review was to evaluate, in terms of efficacy and safety, the effect of IABP versus non-IABP or other assist device 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 studies with cross-over of individual patients. Observational studies were excluded.

Types of participants

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

Types of interventions

IABP versus non-IABP or other assist device guideline compliant standard therapy. The term standard therapy describes guideline compliant therapies (PCI, CABG, 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, either to discharge, within 30 days, 6 months and 1 year)
- Non-fatal cardiovascular events (reinfarction, reocclusion and subsequent re-revascularization, stroke, recurrent ischaemia) (hierarchical lower ranked endpoint)

Secondary outcomes

- Haemodynamics (cardiac index (CI), mean arterial blood 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 October 2013. 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 pump counterpulsation) and the type of study design (randomised controlled trial). We used controlled vocabulary terms and text words and searched different sources. The search strategies used are documented in [Appendix 1](#) (2010) and [Appendix 2](#) (2013).

The following sources were searched. Health-related electronic bibliographic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (Issue 9, 2013), MEDLINE (Ovid) (1946 to September 2013, searched 2 October 2013), EMBASE (1947 to September 2013, searched 2 October 2013), PubMed (searched 2 October 2013), LILACS, IndMed and KoreaMed (unrestricted date to November 2013, searched 12 November 2013).

Searching other resources

The following sources were searched.

Registers of ongoing and completed trials:

- www.controlled-trials.com (searched 12 November 2013);
- www.centerwatch.com (searched 12 November 2013);
- Benchmark registry (www.datascope.com/ca/pdf/benchmark2_brochure.pdf); and
- National Research Register (www.controlled-trials.com/mrt/archived (2000 to 2007)).

Handsearching 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 2013).

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 the titles. In a second step, two authors (SU, RP or MM) independently screened abstracts and keywords. Full-text articles were taken into account for further assessment if the information given suggested 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 review author. 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 (Moher 2009).

Data extraction and management

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

- General information: title, authors, source, contact address, country, published or unpublished, language and year of publication, trial sponsor.
- Trial characteristics: including study design, timing and follow-up, quality assessment as specified above.
- Patients: inclusion and exclusion criteria, sample size, baseline characteristics, similarity of groups at baseline, withdrawals, cross-over, losses to follow-up.
- Interventions: type of standard therapy and comparison assist devices.
- 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, at 30 days, 6 months, 1 year), other clinical event outcomes (reinfarction, reocclusion, re-revascularization, stroke, recurrent ischaemia), haemodynamics (CI, MAP, PCWP), length of hospital and ICU stay, doses of catecholamines (dobutamine, norepinephrine, 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 a reliable and the most powerful method to calculate and compare times to death with adjustments for important co-variables (age, sex and diabetes) (Piedbois 2004).

Assessment of risk of bias in included studies

The review analyses the results of randomised controlled trials (RCTs). Two authors (SU, RP or 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 of patients, 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). Blinding of the investigated intervention was judged to be not possible. The description was based on the published study report, which was added to by a mixture of study reports, protocols, published comments on the study and contact with the investigators.

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 and length of hospital and ICU stay on the basis of individual patient or published aggregate data.

The HR and 95% CI for time to death as one of the primary outcome measures were calculated for seven studies with available IPD to describe the mortality distribution over 30 days and over the whole investigation period. For these trials, Kaplan-Meier curves and mortality rates at discharge from hospital and at 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 (WMDs) were calculated as effect measures for haemodynamics and length of hospital stay, and odds ratios (ORs) for IABP-related complications. All final effect measures were presented with their 95% CI.

Safety outcomes to describe IABP-related post-interventional complications were chosen a posteriori and included the following frequently reported possible device-related adverse events during support: bleeding, vascular injury, leg or limb ischaemia, embolism, infection and thrombocytopenia. The frequencies of these IABP-related complications and non-fatal cardiovascular events were presented in numbers and percentages with corresponding ORs.

Unit of analysis issues

Patients were individually randomised into two groups. Studies with cross-over of individual patients were included. These patients were investigated in their randomisation group according to the intention-to-treat (ITT) principle. A per protocol (PP) analysis was added in studies where the overall proportion of cross-over compared with the observed event risk might have had a

clinically relevant impact on the intervention effect, and available information on cross-over and all-cause mortality (Other potential sources of bias). 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) HRs and 95% CIs were not calculated because of missing information. The first author was contacted and provided some of the missing information. He was not able to provide any individual patient data and had no access to the database. ORs were used to describe the effect on in-hospital mortality in this trial. All other HRs were calculated from individual patient data.

Assessment of heterogeneity

Heterogeneity was classified by two independent review authors on methodological and clinical grounds. Inconsistency between studies was quantified by the I^2 statistic (Higgins 2002). In the case of substantial clinical, methodological or statistical heterogeneity ($I^2 > 50\%$) meta-analysis was restricted to subgroups. Independent of 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.

Data synthesis

The analysis was based on the intention-to-treat (ITT) principle. The IPD analysis contained data from all randomised patients with AMI and cardiogenic shock from six of the seven 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 HR (one-step approach). Based on the high heterogeneity between the 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-effects 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 the one-step meta-analyses to describe all-cause mortality distribution in the text and all additional analyses in Table 1. Data and analysis tables and forest plots display effect estimates and CIs for both individual studies and the two-step meta-analyses. IPD were not provided for one study. We reduced our available IPD describing in-hospital-mortality rates to aggregated data and combined the 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 5.2.

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 study data did not satisfy this assumption. 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 to execute the analysis as preplanned with the Cox proportional hazards model.

Subgroup analysis and investigation of heterogeneity

Stratified analyses were restricted to preplanned prognostic factors: age (< 75 versus ≥ 75 years), diabetes and sex to find differences in survival with IABP support.

Sensitivity analysis

Sensitivity analyses were performed to explore the influence of including or excluding certain types of studies. Due to the low 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

Results of the search

Having used the search strategies ([Appendix 1](#)) in January 2010, a total of 1410 potentially relevant references were identified (CENTRAL 5, MEDLINE 757, EMBASE 639 and other 9). The update in October 2013 identified 904 references (CENTRAL 126, MEDLINE 386, EMBASE 376, PubMed 15 and other 1) (search strategies in [Appendix 2](#)).

Forty-eight studies were thought to be of relevance and full papers were assessed against the inclusion and exclusion criteria. Of these only seven met our predefined inclusion criteria. The remaining studies are listed in [Characteristics of excluded studies](#). This update search process was recorded in PRISMA flow charts ([Figure 1](#)).

Figure 1. Flow diagram update January 2013.

Included studies

Seven eligible studies with a total of 790 patients with AMI and cardiogenic shock were identified for the comparison IABP versus no IABP (Arias 2005; Burkhoff 2006; Ohman 2005; Prondzinsky 2010; Seyfarth 2008; Thiele 2005; Thiele 2012). Four studies were conducted in Germany (Prondzinsky 2010; Seyfarth 2008; Thiele 2005; Thiele 2012), one study in the United States (Burkhoff 2006), one study in Mexico (Arias 2005) and one study in the United States, Australia and Europe (Ohman 2005). Most patients had Caucasian or Hispanic ethnicity.

Authors of all included studies provided additional information. Individual patient data (IPD) from six studies with 750 patients were collected in the database. Each study characteristic is presented briefly in tabulated form (please see [Characteristics of included studies](#) and Characteristics of ongoing studies). A more comprehensive assessment of the included studies is given below.

Ohman 2005 randomised between 1996 and 1999 57 patients in a multicentre open label trial into two groups, a control group (27) and an intervention group (30). Analysis and descriptions were 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 the 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. The 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 pre-specified, and use of other medications and procedures was left to the discretion of the physicians. During the first 30 days 6/12 patients (50%) died in the intervention group 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 0.66, 95% CI 0.22 to 1.99, log-rank $P = 0.42$) (Figure 2) slightly favoured the intervention with IABP but did not reach statistical significance. Adjustments for age, sex and diabetes showed little influence on these results; 2/12 patients (17%) suffered from stroke in the intervention group and no reinfarctions were documented as non-fatal cardiovascular events during hospital stay. There was only one related complication in the control group (limb ischaemia). Only clinical endpoints and no haemodynamic parameters or information about in-hospital stay and intensive care requirement were provided. The trial was stopped early because it did not achieve the enrolment goal.

Figure 2. All-cause mortality distribution of included studies on the basis of individual patient data

Thiele 2005 between 2000 and 2003 randomised 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 an 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% of patients). 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 HR of the all-cause 30-day mortality distribution (HR 1.09, 95% CI 0.44 to 2.79, log rank $P = 0.86$) (Figure 2) reflected 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 were documented with four non-fatal cardiovascular events during the in-hospital stay: one patient with reinfarction and one with recurrent ischaemia in the intervention group, and one patient with reocclusion and subsequent re-vascularization in the control group. The pre-implantation cardiac index (CI) was noted to fall in the intervention group (1.62 ± 0.37 to 1.19 ± 0.84 L/min/m² post-implantation, $P = 0.058$) and to rise in the control group (1.71 ± 0.38 to 2.32 ± 0.59 L/min/m² post-implantation, $P < 0.001$). Pre-implantation MAP was noted to rise in the intervention group (65 ± 14 to 72 ± 12 mmHg post-implantation, $P = 0.003$) as well as in the control group (62 ± 14 to 76 ± 13 mmHg post-implantation, $P < 0.001$). Pre-implantation PCWP was noted to fall in the intervention (25.1 ± 6.1 to 21.6 ± 5.8 mmHg post implantation, $P = 0.028$) as well as in the control group (20.8 ± 4.2 to 15.9 ± 3.8 mmHg 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. A total of 5/20 patients (25%) from the intervention group 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 ischaemia 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 patient from the intervention group suffered from embolism and one patient from the control group developed thrombocytopenia.

Arias 2005 between 2001 and 2003 randomised 40 patients into two groups in a single-centre open label trial. 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, an Arrow AutoCAT 2 WAVE® IABP. Myocardial revascularization was performed using PCI. Pharmacological support was given on the basis of inotropic (dopamine and dobutamine), vasopressor, 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 favoured intervention with IABP but did not reach statistical significance.

Burkhoff 2006 between 2002 and 2004 randomised 33 patients in a multicentre 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. The 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 vasopressor, inotropic and pharmacologic agents was based on the physician's standard of care. Mortality of cardiogenic shock and AMI patients during the first 30 days included 4/10 patients (40%) in the intervention group and 4/11 patients (36%) in the control group (OR 1.17, 95% CI 0.20 to 6.80). The resulting HR of the all-cause 30-day mortality distribution (HR 0.88, 95% CI 0.23 to 3.31, log rank $P = 0.85$) (Figure 2) reflected no significant difference between groups. Adjustments for age and sex showed no influence on these results. Predefined haemodynamic success criteria (no death during support or within 24 hours of device removal, CI ≥ 2.2 L/min/m², PCWP ≤ 24 mmHg and MAP ≥ 70 mmHg 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 to switch to TandemHeart. Therefore, pre-IABP haemodynamic information was not available and we decided not to include the 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 to treat a device-related adverse event (7.1%) and one device-related removal because of a 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 per patient (1.3 serious) in the control group. There were no specific adverse events related to the performance of the trans-septal puncture or insertion of the trans-septal 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 group and 4/19 patients (21%) from the control group developed leg ischaemia. No patient from the intervention group but 3/19 patients (16%) from the control group suffered from cannulation site infection; 3/14 patients (21%) from the intervention group and 3/19 patients (16%) from the control group suffered from thrombocytopenia. Proper discrimination between device-related and shock-induced symptoms was not performed according to the frequent occurrence of neurologic dysfunction.

Seyfarth 2008 between 2004 and 2007 randomised 26 patients in a two-centre 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 an 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. The 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 coronary artery bypass grafting (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 group and 6/13 patients (46%) in the control group (OR 1.00, 95% CI 0.21 to 4.67). During the hospital stay 5/13 patients (38%) in the intervention group and 7/13 patients (54%) in the control group 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 group 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 the all-cause 30-day mortality distribution (HR 0.99, 95% CI 0.31 to 3.15) and 6-month mortality distribution (HR 0.73, 95% CI 0.25 to 2.11, log-rank $P = 0.55$) (Figure 2) reflected no significant differences between groups. Adjustments for age, sex and diabetes showed little influence on these results. During the 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 CI 30 minutes after implantation. Pre-implantation CI remained stable in the intervention group (1.73 ± 0.59 to 1.84 ± 0.71 L/min/m² 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/m² post-implantation, $P = 0.003$). Pre-implantation MAP remained stable in the intervention group (72 ± 17 to 71 ± 22 mmHg post-implantation, $P = 0.79$) and was noted to rise in the control group (78 ± 16 to 87 ± 18 mmHg post-implantation, $P = 0.039$). Pre-implantation PCWP tended to decrease in the intervention group (21.9 ± 6.6 to 20.2 ± 5.5 mmHg post-implantation, $P = 0.08$) as well as in the control group (22.1 ± 8.1 to 19.3 ± 4.7 mmHg 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, and one patient with bleeding and one patient with acute limb ischaemia requiring surgery after device explantation in the control group. No complication could be directly attributed to the use of the devices.

Prondzinsky 2010 between 2003 and 2004 randomised 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 ≥ 48 hr; and for one patient no post-randomisation data were available for technical reasons). Among the 22 patients randomised to the 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 or IIIa receptor-blocker, heparin according to standard intensive care guidelines. Mortality during the first 30 days included 6/19 patients (32%) in the intervention group and 5/21 patients in the control group (24%) (OR 1.48, 95% CI 0.37 to 5.96). During the hospital stay 7/19 patients (37%) died in the intervention group 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 group and six patients (33%) in the control group had died (OR 2.57, 95% CI 0.64 to 10.34). The HRs of the all-cause 30-day mortality distribution (HR 1.55, 95% CI 0.47 to 5.08) and 12-month mortality distribution (HR 1.71, 95% CI 0.63 to 4.63, log-rank $P = 0.28$) (Figure 2) reflected no significant difference between groups. Adjustments for age, sex and diabetes showed little influence on these results. Eleven patients (28%) with 22 non-fatal cardiovascular events were documented during the in-hospital stay: in the intervention group one patient had reinfarction and recurrent ischaemia and two patients (11%) had reocclusion and subsequent re-vascularization; eight patients (38%) had reocclusion and subsequent re-vascularization in the control group. Mean CI was noted to stay nearly constant in the intervention group with a high variability of post-interventional values (2.32 ± 0.57 to 2.93 ± 1.42 L/min/m² post-intervention, $P = 0.93$) as well as in the control group (1.73 ± 0.37 to 2.44 ± 0.67 L/min/m² post-intervention, $P = 0.23$). Mean MAP showed comparable small changes and high variability in the intervention group (81 ± 11 to 76 ± 16 mmHg post-intervention, $P = 0.64$) as well as in the control group (83 ± 17 to 80 ± 16 mmHg 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 mmHg post-intervention, $P = 0.96$), and on a lower level in the control group (14.9 ± 5.6 to 16.2 ± 5.1 mmHg post-intervention, $P = 0.78$). Length of in-hospital stay was 18 ± 14 days in the intervention group and 29 ± 29 days in the control group. The length of intensive care requirement was 8 ± 7 days in the intervention group and 14 ± 12 days in the control group ($P = 0.06$). There was only one possibly related complication (leg ischaemia) in the intervention group. No patient developed other complications such as bleeding, vascular injury, embolism, infection or thrombocytopenia that could be attributed to IABP use.

Thiele 2012 between 2009 and 2012 randomised 600 patients in a multicentre, open label trial into two groups, a control group (299) and an intervention group (301). Both groups received early revascularization and optimum medical therapy; the intervention group got IABP, the control group no IABP. One patient assigned to IABP was lost to follow-up before 30 days and one patient in the control group withdrew consent. Three additional patients (one from the IABP group and two from the control group) were lost to follow-up before six months. The intervention group got IABP via the femoral artery, and a sheathless insertion was recommended. Mean duration of support was 3.0 days (Interquartile range (IQR) 2.0 to 4.0 days, range 1 to 16 days). Myocardial revascularization was performed using PCI (95.8% of patients) or CABG (3.5% of patients). No revascularization was performed in 3.2% of patients. Pharmacological support was given by haemodynamic monitoring for optimal adjustment of fluid administration and inotropic drugs. All additional treatments were performed according to the standards of the German-Austrian S3-Guidelines (Werdan 2012). During the hospital stay 107/301 patients (36%) in the intervention group and 116/299 patients (39%) in the control group died (OR 0.87, 95% CI 0.62 to 1.21). Mortality during the first 30 days included 119/300 patients (40%) in the intervention group and 123/298 patients (41%) in the control group (OR 0.94, 95% CI 0.67 to 1.30). Six months after randomisation a total of 146/299 patients (49%) in the intervention group and 146/296 patients (49%) in the control group had died (OR 0.98, 95% CI 0.71 to 1.35). One year after randomisation a total of 155/299 patients (52%) in the intervention

and 152/296 patients (51%) in the control group had died (OR 1.02, 95% CI 0.74 to 1.41). The resulting HR of the all-cause 30-day mortality distribution (HR 0.93, 95% CI 0.72 to 1.19) and over 12 months (HR 1.01, 95% CI 0.81 to 1.25, log-rank $P = 0.94$) (Figure 2) reflected no significant difference between groups. Adjustments for age, sex and diabetes showed little influence on these results. In the intervention group, nine patients (3.0%) suffered from reinfarction, four patients (1.3%) had stent thrombosis and two patients (0.7%) suffered from stroke during the in-hospital stay; four patients (1.3%) suffered from reinfarction, three patients (1.0%) had stent thrombosis and five patients (1.7%) suffered from stroke in the control group during the in-hospital stay. Median MAP showed comparable changes and high variability in the intervention group (69 mmHg (IQR 59 to 80) to 73 mmHg (IQR 63 to 87) post-revascularization) and control group (68 mmHg (IQR 59 to 80) to 73 mmHg (IQR 63 to 84) post-revascularization). The length of intensive care unit treatment was 6.0 days (IQR 3 to 13) in both groups. Rates of potential IABP-related complications showed no difference between groups. In the intervention group, 13 patients (4.3%) had peripheral complications requiring intervention, 10 patients (3.3%) suffered from life-threatening or severe bleeding and 52 patients (17.3%) from moderate bleeding. In the control group, 10 patients (3.4%) suffered from peripheral complications requiring intervention and 13 and 49 patients (4.4% and 16.4%) had life-threatening or severe bleeding, or moderate bleeding respectively.

Participants

The age of the patients in the study population of all trials ranged from 28 to 89 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 22.1% and 58%. The distribution of other baseline characteristics and haemodynamic parameters of patients included in the RCTs are presented in [Characteristics of included studies](#).

Patients were included in eligible RCTs between 1996 and 2012. Between 2 and 274 patients were included per year. [Burkhoff 2006](#) randomised 33 patients with cardiogenic shock due to AMI 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 AMI (10 IABP patients and 11 TandemHeart patients). In the study by [Ohman 2005](#) patients with myocardial infarction complicated by hypotension, suspected cardiogenic shock or heart failure were included for randomisation. At the time of randomisation, 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, 790 patients were included for meta-analysis, of whom 406 patients were treated with IABP and 384 were treated without IABP.

Interventions

Four studies which included 702 patients with AMI and cardiogenic shock compared the intervention IABP versus standard treatment without IABP ([Arias 2005](#); [Ohman 2005](#); [Prondzinsky 2010](#); [Thiele 2012](#)) and three studies with 88 randomised patients compared the intervention IABP with percutaneous left ventricular assist devices (LVAD). 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 included all treatment groups with patients randomised to get IABP and the control group included all treatment groups without IABP.

Combining the results of four trials with available data ([Ohman 2005](#); [Prondzinsky 2010](#); [Seyfarth 2008](#); [Thiele 2005](#)), the mean duration of support with IABP was 59 ± 57 hours in the IABP group. Myocardial revascularization was performed using PCI in all studies. In total, 95% of patients were revascularized with PCI. Only few patients (5%) underwent thrombolysis as the primary reperfusion strategy, in the trial by [Ohman 2005](#).

Outcomes

Primary data were 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 ischaemia, embolism, infection and thrombocytopenia. Complications in the single trials were described in [Included studies](#). Quality of life was described on the basis of data from one study ([Thiele 2012](#)). Time of follow-up varied between time in coronary unit and 10 to 15 days ([Arias 2005](#)), 30 days ([Burkhoff 2006](#); [Thiele 2005](#)), six months ([Ohman 2005](#); [Seyfarth 2008](#)) and one year ([Prondzinsky 2010](#); [Thiele 2012](#)).

Excluded studies

Fifteen of the investigated trials did not use a randomised allocation ([Anderson 1997](#); [Barron 2001](#); [Bengtson 1992](#); [Gu 2010](#); [Kovack 1997a](#); [Moulopoulos 1986a](#); [Sanborn 2000](#); [Stomel 1994](#); [Stub 2011](#); [Taguchi 2000](#); [Vis 2007a](#); [Vis 2007b](#); [Waksman 1993](#); [Zeymer 2011](#); [Zeymer 2013](#)).

Most RCTs on IABP excluded patients with cardiogenic shock ([Christenson 1997a](#); [Christenson 1997b](#); [Christenson 1997c](#); [Christenson 1999](#); [Christenson 2003](#); [Flaherty 1985](#); [Gu 2011](#); [Kono 1996](#); [Ohman 1994](#); [Onorati 2005](#); [Perera 2009](#); [Stone 1997](#); [Vijayalakshmi 2007](#)) or pre-specified cross-over to IABP in the case of cardiogenic shock ([Van 't Hof 1999](#)). One trial excluded patients with AMI ([O'Neill 2012](#)) and in two trials the patients had no cardiogenic shock at the time of randomisation ([Li 2007](#); [Marra 2002](#)). In one trial ([O'Rourke 1981](#)) only four patients suffered from cardiogenic shock. Finally, one trial ([RECOVER II Trial](#)) included only one patient due to protocol challenges caused by insertion, no cross-over option, consent issues and ethical concerns. The reasons 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. Six trials acknowledged the support of either Datascope ([Ohman 2005](#); [Prondzinsky 2010](#)), Cardiac Assist ([Burkhoff 2006](#); [Thiele](#)

2005), Abiomed Europe GmbH (Seyfarth 2008) or Maquet Cardiopulmonary and Teleflex Medical (Thiele 2012). Datascope, Maquet Cardiopulmonary and Teleflex Medical are manufacturers of the IABP; 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 600. Four trials

compared IABP to percutaneous LVAD, three trials to standard treatment without IABP. In five trials the analysis was done by ITT (Burkhoff 2006; Ohman 2005; Prondzinsky 2010; Seyfarth 2008; Thiele 2005; Thiele 2012). Figure 3 and Figure 4 present the risk of bias in the seven eligible studies and summarize risk of bias.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): mortality+haemodynamic	Incomplete outcome data (attrition bias): mortality	Incomplete outcome data (attrition bias): haemodynamics	Selective reporting (reporting bias)	Other bias
Arias 2005	+	+	?	-	-	-	-
Burkhoff 2006	+	+	-	+	+	+	-
Ohman 2005	+	+	-	+	-	+	-
Prondzinsky 2010	+	+	-	+	+	+	+
Seyfarth 2008	+	+	-	+	+	+	+
Thiele 2005	+	+	-	+	+	+	+
Thiele 2012	+	+	+	+	+	+	+

Figure 4. 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 sequence generation was provided by the author. All trials used random tables. One trial used random number tables without further restriction (Thiele 2005), two trials used a stratified randomisation (Arias 2005; Thiele 2012) and four trials used a blocked randomisation technique (Burkhoff 2006; Ohman 2005; 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. Adequate 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 2005).

Blinding

Only one trial described blinding in the study without further detailed information (Arias 2005). Blinding of the intervention to study personnel was not possible introducing the risk of differential behaviour of healthcare providers in all trials. Unblinding of outcome assessment of 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. In Thiele 2012 two patients (0.3%) were lost to the 30-day follow-up. Six-month follow-up data for the all-cause mortality distribution were available in four trials (Ohman 2005; Prondzinsky 2010; Seyfarth 2008; Thiele 2012) with missing follow-up data for 10/683 (1.4%) patients. Only two of these studies (Prondzinsky 2010; Thiele 2012) reported 12-month survival status with missing follow-up data for 13/640 (2.0%) patients.

Haemodynamic post-interventional data were reported in four trials (Prondzinsky 2010; Seyfarth 2008; Thiele 2005; Thiele 2012) with follow-up times ranging from post-revascularization (Thiele 2012) to 28 days (Prondzinsky 2010). IPD of three trials (Prondzinsky

2010; Seyfarth 2008; Thiele 2005) were included in the analysis. Follow-up information was lost for 11/106 patients (10.4%, CI), 5/106 (4.7%, MAP) and 16/106 (15.1%, PCWP).

Selective reporting

Key outcomes of mortality, haemodynamic parameters and adverse events were reported in six of seven trials. Any information on haemodynamics after randomisation was missed in Arias 2005.

Other potential sources of bias

In three studies (Arias 2005; Burkhoff 2006; Ohman 2005) important deviations from the study plan, which were 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 analysis with cross-over of 11/20 patients to the intervention group. Only results of the per protocol analysis were available. These results were restricted to the analysis of in-hospital mortality rates. In Ohman 2005 3/10 patients (33%) from the control group crossed over to the intervention group, and 3/12 (25%) from the intervention group to the control group. The results of the ITT and per protocol (PP) analysis did 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 ORs were 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 was too low to have a clinically relevant impact on the intervention effect estimate for mortality. Most patients (66%) in Burkhoff 2006 were enrolled after failure of IABP before enrolment and randomisation, but all patients still met the haemodynamic criteria for cardiogenic shock. The trial was stopped early on the recommendation of the Data Safety Monitoring Board. Haemodynamic effects were superior in the TandemHeart group compared with the IABP group and it was deemed unlikely to enrol a sufficient number of patients in a reasonable time frame to achieve a more definitive answer concerning mortality. Being aware of these methodological restrictions, we nevertheless decided to include all studies with

randomisation of patients with the predefined 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](#).

The funnel plot ([Figure 5](#)) was nearly symmetrical for the 30-day mortality distribution with no evidence of publication bias.

Figure 5. Funnel plot of comparison: IABP versus control, outcome: all-cause 30-day mortality distribution.

Effects of interventions

Primary outcome measures

(a) All-cause mortality

Thirty-day all-cause mortality

Across all trials, 6 trials with 750 patients ([Burkhoff 2006](#); [Ohman 2005](#); [Prondzinsky 2010](#); [Seyfarth 2008](#); [Thiele 2005](#);

[Thiele 2012](#)) reported 150/374 (40.1%) deaths in the intervention group compared with 153/374 (40.9%) deaths in the control group ([Analysis 1.4](#)). The HR indicated no difference in mortality distribution between groups (HR 0.95, 95% CI 0.76 to 1.19, [Figure 6](#)). This result was consistent whether a one- or a two-step approach was used. Adjustments for age, sex and diabetes did not change the result ([Table 1](#)). There was only small 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 six studies (Arias 2005; Burkhoff 2006; Prondzinsky 2010; Seyfarth 2008; Thiele 2005; Thiele 2012) were revascularized by PCI, and in Ohman 2005 patients were revascularized with thrombolytic therapy. An additional sensitivity analysis comparing the influence of the control group intervention (standard without IABP or other LVAD) showed no influence on the results.

A preplanned subgroup analysis investigated the influence of the prognostic factors age and sex on all-cause mortality on the basis of IPD. Combining results across all trials, 97/252 (38.5%) men and 53/123 (43.1%) women died in the intervention group and 107/264 (40.5%) men and 49/111 women (44.1%) in the control group. In total, 86/251 (34.3%) of patients < 75 years and 64/124 (51.6%) of patients ≥ 75 years died in the intervention group, and 108/281 (38.4%) and 48/94 (51.1%) in the control group, respectively (Table 1).

In-hospital all-cause mortality

The meta-analysis was conducted on 5 trials with 747 patients to describe in-hospital mortality rates (Arias 2005; Prondzinsky 2010; Seyfarth 2008; Thiele 2005; Thiele 2012). Across trials, 139/384 patients (36.2%) died in the intervention group and 143/363 patients (39.4%) in the control group (OR 0.87, 95% CI 0.65 to 1.18) (Analysis 1.3) with no heterogeneity between trials.

Six-month and 12-month all-cause mortality

The meta-analysis on six-month mortality was conducted on four trials with 678 patients to describe all-cause six month mortality (Ohman 2005; Prondzinsky 2010; Seyfarth 2008; Thiele 2012). Across trials, 166/341 patients (48.7%) died in the intervention group and 167/337 patients (49.6%) in the control group (Analysis 1.5).

One-year mortality information was available from 627 patients of two trials (Prondzinsky 2010; Thiele 2012). In total, 164/315 patients (52.1%) died in the intervention group and 158/312 patients (50.6%) in the control group.

The HR of 1.02 (95% CI 0.84 to 1.25) indicated no difference in mortality distribution 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 analyses.

A preplanned analysis according to the types of revascularization also showed no differences between groups. Most patients in Prondzinsky 2010 Seyfarth 2008 and Thiele 2012 were revascularized by PCI, and in Ohman 2005 patients were revascularized with thrombolytic therapy. An additional sensitivity analysis comparing standard care without IABP or other LVAD did not influence the results.

(b) Non-fatal cardiovascular events

Data were available in 5 trials with 727 patients (Ohman 2005; Prondzinsky 2010; Seyfarth 2008; Thiele 2005; Thiele 2012). Reported results were combined across trials. During hospitalisation, 11/364 patients (3.0%) from the intervention group and 5/363 patient (1.4%) from the control group suffered from reinfarction; 4/364 patients (1.1%) from the intervention group and 5/363 (1.4%) patients from the control group had a stroke. Reocclusion and subsequent re-revascularization were reported in 4 trials with 705 patients (Prondzinsky 2010; Seyfarth 2008; Thiele 2005; Thiele 2012). Altogether, 6/352 patients (1.7%) from the intervention group and 13/353 patients (3.7%) from the control group had re-occlusion with subsequent re-revascularization. Recurrent ischaemia was reported in 2 trials with 81 patients (Prondzinsky 2010; Thiele 2005). Overall, 2/39 patients (5.1%) from the intervention group and 0/42 patients from the control group had recurrent ischaemia (Table 2).

Secondary outcome measures

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

Cardiac index (CI)

The CI measured after device implantation was available for 95 patients from 3 eligible studies (Prondzinsky 2010; Seyfarth 2008; Thiele 2005), with substantial heterogeneity ($I^2 = 85\%$) between trials. To explore the heterogeneity, a subgroup analysis according to the comparison group was conducted and showed relevant differences according to comparison group (non-IABP versus other LVAD) on the results. In Prondzinsky 2010, patients randomised to IABP ($n = 16$) had a higher mean CI compared to control group patients ($n = 14$) without any assist devices (mean difference (MD) 0.49 L/min/m², 95% CI -0.29 to 1.27). In contrast, combining the results of 2 trials, patients randomised to IABP ($n = 32$) had lower mean CI compared to control group patients ($n = 32$) with LVAD (MD -0.75 L/min/m², 95% CI -1.51 to 0.00).

Mean arterial pressure (MAP)

The MAP after device implantation was available on 101 patients from 3 eligible studies. Combining across trials, patients in the intervention group ($n = 50$) showed lower mean MAP values post-implantation compared to control group patients ($n = 51$) with high variation between patients (MD -5.1 mmHg, 95% CI -10.9 to 0.66) and low heterogeneity between trials.

These differences were not stated in Thiele 2012. Median MAP showed comparable changes and high variability in both groups. In the intervention group, MAP increased from median 69 mmHg (IQR 59 to 80) to 73 mmHg (IQR 63 to 87) post-revascularization, and patients in the control group showed comparable changes from median 68 mmHg (IQR 59 to 80) to 73 mmHg (IQR 63 to 84) post-revascularization.

Pulmonary capillary wedge pressure (PCWP)

The PCWP after device implantation was available for 90 patients from 3 eligible studies. Combining across 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 mmHg, 95% CI 1.1 to 6.7), with moderate heterogeneity between trials ($I^2 = 44\%$). To explore the heterogeneity a subgroup analysis according to the comparison group (non-IABP or other LVAD) was conducted but a difference according to comparison group was not found.

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

Information about length of hospital stay was available from 4 trials with 677 patients (Prondzinsky 2010; Seyfarth 2008; Thiele 2005; Thiele 2012) and information about ICU requirements was available from 640 patients in 2 trials (Prondzinsky 2010; Thiele 2012). Combining trials, no difference in length of in-hospital stay was shown between the two treatment groups (MD -1.1 days, 95% CI -4.9 to 2.7) with low heterogeneity between trials ($I^2 = 24\%$). Prondzinsky 2010 showed a benefit in the ICU requirement with a shorter mean time in the intervention group ($n = 19$) compared to patients in the control group ($n = 21$) (MD -6.2 days, 95% CI -12.3 to -0.07), but this difference was not seen by Thiele 2012 with a median of 6 days of ICU treatment in both groups.

(c) Quality of life

Information on quality of life was available on 1-year survivors of one trial with 600 patients (Thiele 2012). They reported information on health-related quality of life and assessed symptoms of heart failure according to the New York Heart Association (NYHA) and angina according to the Canadian Cardiovascular society (CCS) classification. Health-related quality of life was described by the EQ-5D-3L index value in 5 dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) and was assessed for 274/286 (95%) of the 1-year survivors. Less than 10% of patients described severe problems, especially in usual activities, self-care and anxiety or depression, with no differences between treatment groups. NYHA and CCS class were recorded in 253 and 252 (both 88%) of the 286 1-year survivors. Of these patients 115/127 (91%) from the intervention group and 118/126 (94%) from the control group were in NYHA class I or II. In total, 125/127 (98%) in the intervention group and 124/125 (99%) in the control group were in CCS class I or II.

(d) All IABP-related post-interventional complications

Possible IABP-related complications were described heterogeneously in the trials. Analyses displayed frequencies of possibly related complication such as moderate or severe bleeding, vascular injury, leg or limb ischaemia, embolism, infection and thrombocytopenia. In detail, a high incidence of complications in the control groups had to be attributed to interventions with other LVAD. As a consequence, the frequency in the intervention group versus control groups with LVAD and without LVAD were analysed separately (Table 3). Reported results were combined across trials. Six trials (Burkhoff 2006; Ohman 2005; Prondzinsky 2010; Seyfarth 2008; Thiele 2005; Thiele 2012) reported the frequency of post-interventional complications.

In total, 27/378 patients (7.1%) from the intervention group and 21/329 (6.4%) patients in the control group without LVAD, but 27/53 patients (51%) from the control group with LVAD, suffered from moderate or severe bleeding. None of the 33 patients in the intervention group and 21 patients in the control group without LVAD, but 2/19 patients (10%) from the control group with LVAD, suffered from vascular injury. Three of 78 patients (3.8%) from the intervention and 1/31 patient (3.2%) from the control group without LVAD, but 12/53 patients (23%) from control groups with LVAD, had leg or limb ischaemia. Embolism was reported in 2 trials, 1/40 patient (2.5%) from the intervention group but no patient from control groups suffered from embolism. Fifteen of 66 patients (23%) from the intervention group and none of 21 patients 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. Three of 53 patients (5.7%) from the intervention group and none of 21 patients from the control group without LVAD, but 4/40 patients (10%) from the control group with LVAD, suffered from thrombocytopenia. Peripheral ischaemic complications requiring intervention were reported in 1 trial, where 12/300 (4.3%) from the intervention group and 10/298 (3.4%) patients from the control group without LVAD suffered from a peripheral ischaemic complication.

DISCUSSION

Summary of main results

Data from seven eligible studies with a total of 790 patients with AMI and cardiogenic shock that compared IABP versus no IABP could not show convincing evidence for either benefit or harm to support the use of intra-aortic balloon pump counterpulsation (IABP). Six of these analysed studies were too small to be sufficiently powered to investigate the beneficial or harmful effects of IABP support beyond initial haemodynamic improvements. One trial ([Thiele 2012](#)) was powered to discover a 12% absolute difference in the 30-day survival rates reported in registries and meta-analyses. This study and even the aggregated study population of all included trials did not show a significant reduction of mortality in patients with AMI and cardiogenic shock.

Four trials compared IABP to standard treatment and three to other percutaneous LVAD. Combining the result of all six trials, in the intervention and control arms 40% and 41% of patients died during the first 30 days and 49% and 50% of patients died during the 6 months after randomisation, respectively. Hazard ratios (HRs) of the all-cause mortality distribution provide no evidence for a survival benefit. Adjustments for age, sex and diabetes in subgroups (IABP versus non-IABP and IABP versus other LVAD) confirmed these results. While differences in survival were comparable in patients treated with IABP, compared to with and without LVAD, haemodynamic results from three small studies showed heterogeneous results. Post-implantation, patients randomised to IABP had a higher mean CI than patients without assist devices, and lower mean CI than patients with LVAD. Patients in the IABP group showed lower MAP values and higher mean PCWP. Differences in MAP were not stated in the larger trial, whereas CI and PCWP were not reported.

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. Results on quality of life are in line with former published follow-up data of the SHOCK Trial ([Sleeper 2005](#)), where survivors of infarct-related cardiogenic shock showed a surprisingly good quality of life. Although one-year mortality after emergency revascularization was still high (54%), most survivors had good functional status.

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 most trials, the heterogeneity of included patients at baseline, and the fact that IABP has been compared to no-IABP and to other LVADs.

a) While the patient numbers in previous results have been too small to address mortality, this review now includes individual patient data (IPD) of the latest and also largest RCT on this topic ([Thiele 2012](#)). For this reason, this updated review comprises the latest available evidence from RCTs to evaluate the therapeutic effects on mortality of IABP support in infarct-related cardiogenic shock. Additionally, it can be looked upon as a positive aspect that all included trials have been performed by different investigators at different institutions, so that bias due to repeated single-centre experiences can be excluded.

b) All these analysed trials have been conducted properly under the conditions of prospective RCTs, so that this meta-analysis can

contribute valuable data to estimate the effects of the IABP support in infarct-related cardiogenic shock, although six of these seven trials were not powered to detect differences in mortality. The evidence which could have been derived by former meta-analyses had been hampered by small patient numbers being included in the trials. This methodological gap now can be closed by the IABP-SHOCK II Trial, which was adequately powered to detect mortality differences under IABP support. More specifically, there are points of concern within most of the included and analysed studies.

There was frequent cross-over in several trials.

[Ohman 2005](#): in total, 33% of patients from the control group with cardiogenic shock crossed over to emergency IABP and 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](#): altogether 27.5% of patients assigned to the control group crossed over to IABP and were analysed in this group.

[Burkhoff 2006](#): this multicentre trial with a small sample size stopped recruitment earlier than initially intended. Furthermore, different therapeutic strategies were performed in the included patients. Moreover, there was 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 stent placement, 1 patient to mitral valve repair).

[Prondzinsky 2010](#): one patient in the control group was treated with IABP.

[Seyfarth 2008](#): one patient assigned to the control group died before implantation and did not receive the LVAD.

c) With the limited number of included trials, there was one trial ([Ohman 2005](#)) which included patients with acute decompensated heart failure and haemodynamically instable patients at the same time. In this case only IPD eligible according to the criteria of cardiogenic shock could be extracted and evaluated.

d) Another limitation is given by the fact that only four RCTs compared IABP support versus a control without any device giving haemodynamic support. Three trials compared the IABP support to other assist devices such as the Tandem-Heart or the Impella system.

e) For the limited number of four trials comparing IABP to no IABP, IPD of only three of the four trials were available. One trial included patients being revascularized by thrombolysis and the others by PCI. Indeed, in this meta-analysis there were only 640 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 a favourable trend in haemodynamics for IABP support compared to standard treatment without IABP, it could be shown that systemic inflammation and also multi-organ failure seem to have a higher impact on prognosis in infarct-related cardiogenic shock than haemodynamic parameters ([Lim 2003](#); [Prondzinsky 2010](#)). Based on this background the issue of IABP timing becomes of scientific interest.

While the effect of IABP timing in the field of cardiac surgery has been discussed during the last few years (Ramnarine 2005) this discussion currently has been continued in the field of cardiogenic shock (Abdel-Wahab 2010; Cheng 2013). As shown in Lim 2003 the haemodynamic parameters in critically ill cardiogenic shock patients are less predictive than expected. These surprising findings might be explained in particular by the effect of timing (early or late initiation of IABP support). Haemodynamic stabilization under the terms of cardiogenic shock has to be achieved as soon as possible, following the principle of early goal directed therapy, to prevent the prognostically relevant multi-organ dysfunction syndrome (MODS) or multi-organ failure (MOF).

g) Another methodological limitation is the heterogeneity of the investigated patient groups themselves. While patients with acute NSTEMI or STEMI can be described very well regarding their baseline conditions, haemodynamically unstable patients with infarct-related cardiogenic shock show a broader variation of physiological parameters at baseline. Especially so are the markers of MOF and systemic inflammation (SIRS), which have had the greatest impact on prognosis in infarct-related cardiogenic shock (Prondzinsky 2010), and they are often not measured at baseline.

h) Here we refer to section b), where major concerns regarding the issue of cross-over designs were explained.

i) The duration of IABP support differed in the intervention groups in 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 well as IABP weaning.

j) As shown by the OASIS-5 trial (Yusuf 2006), the 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, in particular bleeding, were performed in a comparable way in all analysed trials i.e. by the TIMI-bleeding definition. Therefore, the bleeding-related impact on outcomes could not be determined. It cannot be excluded that bleeding counteracts the trend 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 cardiogenic shock patients in whom the IABP support had been initiated prior to primary PCI. Indeed, the issue of timing of 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 an impact on outcome, due to earlier increased macro-circulation with improved consecutive microcirculatory disturbances preventing multi-organ dysfunction or failure. However, other trials did not show a benefit with earlier IABP timing (Cheng 2013).

For many years there has been a strong recommendation by the ACC/AHA and also ESC for the use of intra-aortic counterpulsation under the conditions of cardiogenic shock. Instead of these strong recommendations the utilization rate of adjunctive IABP support in STEMI complicated by cardiogenic shock remained low (20% to 39%). This gap of a 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 should now be resolved in the light of the revised guidelines of the ACC/AHA, ESC and also the corresponding German-Austrian Guideline (Steg 2012; O'Gara 2013; Werdan 2012). The impact of the IABP-SHOCK II Trial and this current meta-analysis on guideline recommendations needs to be elucidated in the future.

Additionally, our findings showed an increased rate of bleeding with the use of intra-aortic counterpulsation. Mortality in acute coronary syndrome (ACS) is predominantly driven by bleeding, especially major bleeding, showing a strong relationship to poor outcome in ACS patients. Based on this background the findings of our review might explain why the majority of clinicians, being afraid of significant bleeding, avoided IABP support in cardiogenic shock.

Agreements and disagreements with other studies or reviews

Other randomised studies and reviews

During the last decades several prospective RCTs (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 have recently been investigated and analysed in different meta-analyses (Cassese 2012; Cheng 2009; Sjaauw 2009). The first published systematic review (Sjaauw 2009) included seven RCTs with 1009 patients after STEMI with and without cardiogenic shock. IABP neither showed a 30-day survival benefit nor improved left ventricular function, while IABP support was associated with higher stroke and bleeding rates. Another systematic review compared the results of RCTs comparing percutaneous LVAD with IABP, on the basis of three available trials on patients with cardiogenic shock (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 ischaemia and device-related bleeding. This result was stated by Cassese 2012 looking at 1054 patients with AMI without CS from six randomised trials.

The present review adds evidence from three additional studies (Arias 2005; Prondzinsky 2010; Thiele 2012) and subgroups of patients with myocardial infarction and cardiogenic shock from two other studies (Burkhoff 2006; Ohman 2005), and represents a formal assessment of mortality distribution.

Other non-randomised studies and reviews

Recent reviews on randomised and non-randomised trials (Bahekar 2012; Romeo 2013; Sjaauw 2009; Zhang 2013) came to different conclusions.

Sjaauw 2009 conducted a second meta-analysis in 9 cohort studies with 10,529 patients with STEMI and cardiogenic shock. In this meta-analysis, the subgroup treated with thrombolysis showed an 18% (95% CI 16 to 20) decrease in 30-day mortality with 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 cardiogenic shock had a relevant impact on outcomes. Additionally, there was a bias towards younger age in the IABP group. For this reason the reported beneficial effects of IABP

support in AMI patients after thrombolysis have to be interpreted carefully. On the other hand, in patients treated with PCI, IABP was associated with an increased mortality rate of 6% (95% CI 3 to 10) with IABP support.

Bahekar 2012 conducted a meta-analysis in 6 cohort studies with 24,541 patients with AMI complicated by cardiogenic shock and stated a significant reduction in mortality, by 28% (95% CI 14 to 40), with IABP. Another systematic review (Zhang 2013) analysed 13 RCTs with 1958 patients following AMI. The authors summarized that IABP therapy is effective in reducing earlier mortality post-AMI, particularly for patients with cardiac shock, and reduced 30-day mortality by 35% (95% CI 3 to 56). Unfortunately only the abstract is published in English, while the paper has been published in Chinese so that a broad discussion in the scientific community may be hampered.

In contrast to this result, Romeo 2013 concluded on the basis of 17 cohort studies involving 7407 patients with AMI and cardiogenic shock that IABP support is only effective in patients with thrombolytic therapy (reduction by 23%, 95% CI 13 to 32), but is associated with a significant increase in in-hospital mortality, by 18% (95% CI 4 to 34), in patients revascularized by primary PCI. This review included three RCTs with randomisation of IABP (Ohman 2005; Prondzinsky 2010; Thiele 2012) and 14 observational studies.

In contrast to these beneficial findings, data from the National Registry for Acute Myocardial Infarction (Spencer 2001), the Euro Heart Survey on PCI (Zeymer 2011) and the German ALKK-PCI registry (Zeymer 2013) showed no hint of beneficial effects with IABP support in patients with infarct-related cardiogenic shock who were revascularized by PCI.

AUTHORS' CONCLUSIONS

Implications for practice

In contrast to the previous version, this review includes data from 790 patients and allows more definite conclusions on the potential beneficial or harmful clinical effects of IABP support beyond the initial haemodynamic improvements. IABP support should no longer be 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 2012).

Implications for research

According to the recently reported data (Prondzinsky 2010) systemic inflammation substantially contributes to the 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 use of inotropes and vasopressors (Debrunner 2008; Geppert 2002; Geppert 2006; Hochman 2003; Kohsaka 2006; Seely 2000).

As a consequence, subgroups of patients and the phases of cardiogenic shock regarding systemic inflammation and multi-organ failure clearly have to be defined to allow a better discrimination of patient groups, regardless of which assist device will be investigated. 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 outcomes in different subgroups.

Future trials investigating haemodynamic support by other active left ventricular assist devices (LVAD) will have to examine whether significant haemodynamic improvements without increased bleeding rates can be provided.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Arias 2005

Study characteristics

Methods	Parallel single-centre RCT of two groups (inotropics + IABP versus inotropics) Study duration: February 2001 to February 2003 Measurements: haemodynamic parameters (PCWP, CI) were measured using a pulmonary artery catheter (CI, PCWP)
Participants	Group 1: + IABP (31) Group 2: - IABP (9) Group 2 cross-over to Group 1:11 Criteria for cross-over: critical illness and absence of response to vasopressors Mean age: 65.5 ± 6.2 years Sex: 65% men Diabetes: 40% Previous infarction: 27.5% Dislipidaemia: 30% Heart rate: 94 ± 12 /min MAP: 68 ± 6.4 mmHg (estimated from systolic and diastolic BP) PCWP: 21.7 ± 2.45 mmHg Cardiac index: 1.93 ± 0.22 L/min/m ² No information about distribution between treatment groups
Interventions	Myocardial revascularization: PCI + stenting Primary additional randomised intervention: percutaneous guided insertion with fluoroscopy of Arrow AutoCAT 2 WAVE® IABP Pharmacological support: inotropes (dopamine and dobutamine), vasopressor, analgesic and platelet inhibiting agents
Outcomes	In-hospital mortality
Inclusion/exclusion criteria	Inclusion: ≥ 18 years or older, AMI (ST-segment elevation > 1 mV in 2 or more derivations, PCI complicated by cardiogenic shock Exclusion: acute coronary syndrome without ST elevation and no other ischaemic causes of cardiogenic shock
CS definition	Hypotension (systolic blood pressure < 90 mmHg for > 1 hr consistent with administration of fluids), haemodynamic criteria: pulmonary capillary wedge pressure > 18 mmHg and cardiac index ≤ 2.2 L/min/m ²
Sponsor	No sponsor
Notes	Only in-hospital results from the coronary station. Primary analysis 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)	Unclear risk	no details available

Arias 2005 (Continued)

mortality+haemodynamic

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
Study characteristics

Methods	Parallel multicentre RCT of two groups (IABP versus TandemHeart) Study duration: April 2002 to April 2004 Measurements: haemodynamic parameters (PCWP, CI) were measured using an indwelling right catheter
Participants	A total of 42 patients were included and 33 patients were randomised, 21 were diagnosed with acute myocardial infarction (AMI), 5/9 patients in the non-randomised pilot phase with AMI Group 1: + IABP (14) with AMI (10) Group 2: - IABP (19) with AMI (11) Group 1 cross-over to group 2: 4 Group 2 cross-over to group 1: 0 Median age: 66 (49 to 84) years (cardiogenic shock + AMI patients) Sex: 81% men (cardiogenic shock + AMI patients) 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%) Primary additional randomised intervention: IABP or TandemHeart pVAD System. Mean duration of support: 75 ± 95 hr (group 1) versus 61 ± 45 hr (group 2) Pharmacological support: dose and choice of pressor, inotropic and pharmacologic agents based on physicians standard of care
Outcomes	Haemodynamics, 30-day mortality, adverse events
Inclusion/exclusion criteria	Inclusion: ≥ 18 years or older, CS within 24 hr, required to have an indwelling right catheter for measurement of PCWP and cardiac index, patients already having an IABP were eligible if they still met haemodynamic criteria for CS Exclusion: isolated right sided heart failure, coagulopathy, sepsis, severe peripheral vascular disease, stroke within 6 months, 2+ or greater aortic regurgitation, ventricular septal rupture
CS definition	Cardiac index ≤ 2.2 L/min/m ² , MAP ≤ 70 mmHg, PCWP ≥ 15 mmHg, evidence of end-organ hypoperfusion (as decreased urine output, altered mental status) or the need for administration of high-dose pressor or inotropic support to maintain the patient out of CS

Burkhoff 2006 (Continued)

Sponsor	Supported by Cardiac Assist, Inc, Pittsburgh, PA, USA
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 based on individual patient data of 21 AMI + CS patients, haemodynamic and description of complications based on data from 33 randomised patients. Author was contacted, missing information and individual patient data were provided. The principal investigator (DB) is co-author of this review

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) mortality+haemodynamic	High risk	not possible
Incomplete outcome data (attrition bias) mortality	Low risk	complete 30-day follow-up
Incomplete outcome data (attrition bias) haemodynamics	Low risk	different numbers of patients for CI, MAP and PCWP measurements, 16 hours of support, only aggregate data on differences from baseline available
Selective reporting (reporting bias)	Low risk	mortality, haemodynamic and adverse events were reported
Other bias	High risk	early data caused 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 2005

Study characteristics

Methods	Parallel multicentre RCT of two groups (fibrinolysis + IABP versus fibrinolysis) Study duration: November 1996 to November 1999 Measurements: from the time of randomisation until hospital discharge or 30 days (whichever was earlier), patients were monitored for the occurrence of death, stroke, reinfarction, new congestive heart failure, refractory ischaemia, and rescue angioplasty (defined as thrombolytic failure to achieve TIMI grade 2 or 3 flow in the infarct-related artery)
Participants	A total of 57 patients were included, 22 were diagnosed with Killip class IV and included in our analysis of patients with CS Group 1: + IABP (30) with CS (12) Group 2: - IABP (27) with CS (10) Group 2 cross-over to IABP: 3 of 10 with CS Group 1 cross-over to no IABP: 3 of 12 with CS Criteria for cross-over to IABP: emergency IABP (physician's discretion)

Ohman 2005 (Continued)

Criteria for cross-over to no IABP: 2 deaths, 1 catheter could not be inserted
Median age: 69 (33 to 80) years (CS patients)
Sex: 77% men (CS patients)
Diabetes: 32% (CS patients)
Previous infarction: 30%
MAP: 57 ± 12 mmHg (estimated from systolic and diastolic BP, CS patients)
All values are equally distributed between groups

Interventions	Myocardial revascularization: PCI (23%), stent (14%), CABG (18%), lysis (100%) of CS patients 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 ischaemia or hypotension was possible. Mean duration of support: (45 ± 32 hrs (group 1), information not available (group 2) Pharmacological support: predefined doses of intravenous heparin to achieve an aPTT of 50 to 75 sec, use of other medications and procedures were left to the discretion of physicians
Outcomes	Six-month and 30-day mortality (all-cause), in-hospital events (reinfarction, stroke, non-fatal reinfarction), composite in-hospital endpoint (death, reinfarction, or new congestive heart failure), safety events
Inclusion/exclusion criteria	Inclusion criteria: eligibility for fibrinolytic therapy, MI or reinfarction, indicated by acute ischaemic symptoms of ≥ 20 min in < 12 hr before randomisation; ST-segment elevation > 1 mm in two precordial or limb leads or left bundle-branch block, or ST-segment depression ≥ 2 mm indicative of posterior MI; and cardiogenic shock Exclusion criteria: absolute contraindication to fibrinolytic, heparin, or aspirin therapy; known internal bleeding < 1 month before enrolment; planned primary angioplasty for acute MI; inability to insert IABP < 3 hours after starting fibrinolysis; other known serious, advanced illnesses likely to alter short-term prognosis; haemodynamically significant aortic insufficiency or stenosis; mitral regurgitation from rupture of mitral valve; ventricular septal defect; severe peripheral vascular disease, including aortic aneurysm, severe calcific aortoiliac disease, absent bilateral femoral pulses, or bilateral iliofemoral bypass; haematocrit $< 30\%$, $< 100,000$ platelets/mm ³ ; inability to give informed consent or previous study participation
CS definition	(1) Anterior MI complicated by hypotension (SBP ≤ 90 mmHg for ≥ 30 min) or (2) any MI complicated by hypotension (SBP ≤ 110 mmHg for ≥ 30 min, heart rate ≥ 100 beats/min), severe heart failure (frank pulmonary edema, Killip class III) or acute heart failure with hypotension (SBP ≤ 110 mmHg for ≥ 30 min, unresponsive to fluid replacement alone, believed secondary to cardiac dysfunction, and associated with either signs of hypoperfusion: cool, clammy skin, oliguria, or altered sensorium (Killip class IV) or a cardiac index ≤ 2.2 L/min/m ² (2.5 L/min/m ² if receiving inotropic drugs)
Sponsor	Funded by a grant from Datascope Corporation, Montvale, NJ, USA
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). Analysis of individual patient data. The principal investigator (EMO) is co-author of this review

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

Ohman 2005 (Continued)

Blinding (performance bias and detection bias) mortality+haemodynamic	High risk	not possible
Incomplete outcome data (attrition bias) mortality	Low risk	complete 6-month follow-up
Incomplete outcome data (attrition bias) haemodynamics	High risk	no follow-up information
Selective reporting (reporting bias)	Low risk	all pre-specified outcomes are reported
Other bias	High risk	if patients were deemed to be rapidly deteriorating, the treating physician was allowed to use IABP for survival; cross-over 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

Study characteristics

Methods	<p>Parallel single-centre RCT of two groups (standard + IABP versus standard) undergoing percutaneous coronary intervention (PCI)</p> <p>Study duration: March 2003 to June 2004</p> <p>Measurements: invasive monitoring</p> <p>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 catheterization and PCI when the thermodilution catheter was placed. Frequent blood sampling was done to determine laboratory markers</p>
Participants	<p>Group 1: + IABP (23)</p> <p>Group 2: - IABP (22)</p> <p>Group 2 cross-over to IABP: 1</p> <p>Criteria for cross-over: no pre-planned cross-over</p> <p>Five patients excluded from analysis</p> <p>Median age: 64.2 (38 to 82) years</p> <p>Sex: 78% men</p> <p>Diabetes: 50%</p> <p>Previous infarction: 22.5%</p> <p>Hypertension: 45%</p> <p>Smoker: 38%</p> <p>Dyslipidaemia: 7.5%</p> <p>Heart rate: 92 ± 30 /min</p> <p>Apache II Score: 22 ± 10</p> <p>MAP: 78 ± 14 mmHg</p> <p>Lactate: 4.3 ± 3.6 mmol/L</p> <p>Blood pH: 7.38 ± 0.14</p> <p>Cardiac index: 2.0 ± 0.1 L/min/m²</p> <p>PCWP: 17.6 ± 1.0 mmHg</p> <p>All high risk factors (besides PCWP) are distributed equally between groups</p>
Interventions	<p>Myocardial revascularization: PCI (90%), CABG (0%)</p> <p>Primary additional randomised intervention: a 40 mL IABP (IABP System 97, Datascope; Fairfield, NJ) was inserted via the femoral artery using an 8-French sheath immediately after PCI. Aortic counterpul-</p>

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

Prondzinsky 2010 (Continued)

sation was continued for a minimum of 48 hr. Mean duration of support: 45 ± 34 hr (group 1), 184 hr (1 patient in group 2)
Pharmacological support: inotropic and vasopressor agents, aspirin, glycoprotein-IIb or IIIa receptor-blocker, heparin, as required, ventilatory support

Outcomes	In-hospital-mortality, change in APACHE II scores over 4 days from enrolment, cardiac index, plasma brain natriuretic peptide, interleukin-6
Inclusion/exclusion criteria	<p>Inclusion criteria: patients treated with primary PCI for CS secondary to AMI who required inotropic or vasopressor support despite appropriate volume filling</p> <p>AMI definition: symptoms present for 30 min within the preceding 48 hr and one of the following: electrocardiogram ST-segment elevation in two or more contiguous leads (requiring ≥ 2 mm in the precordial leads or ≥ 1 mm in limb leads), new left bundle branch block (LBBB), new pathologic Q waves, non-specific electrocardiogram changes, an acute coronary syndrome associated with a serum creatinine kinase activity increase to ≥ 2.85 $\mu\text{mol/L}^*$s or elevation in troponin I to > 1.5 ng/mL, or radiographic evidence of acute coronary artery occlusion on coronary angiography</p> <p>Exclusion criteria: absent lower limb pulses (precluding IABP placement) or any mechanical complications of AMI such as acute, severe mitral valve insufficiency, an ischaemic ventricular septal defect, or haemodynamically relevant aortic valve insufficiency</p>
CS definition	Symptoms and signs of organ hypoperfusion (e.g., cool peripheries, oliguria) plus one of the following: systolic blood pressure ≤ 90 mmHg for ≥ 30 min or hypotension requiring inotropic or vasopressor therapy at a heart rate $\geq 60/\text{min}$ or a cardiac index ≤ 2.2 L/min/m ² on invasive monitoring
Sponsor	Supported by Datascope, USA
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) mortality+haemodynamic	High risk	not possible
Incomplete outcome data (attrition bias) mortality	Low risk	complete in-hospital and 30-day follow-up, missing information in long-term follow-up: 12.5% in 6-month 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 pre-specified outcomes are reported
Other bias	Low risk	5 patients were excluded from analysis (4 had not fulfilled inclusion criteria, 1 no post-randomisation data), 1 cross-over to IABP, sensitivity analyses were performed

Seyfarth 2008

Study characteristics

Methods	<p>Parallel two-centre RCT of two groups (IABP versus Impella LP2.5 (Abiomed Europe GmbH, Aachen, Germany))</p> <p>Study duration: September 2004 to January 2007</p> <p>Measurements: haemodynamic parameters were measured using a Swan-Ganz catheter</p>
Participants	<p>Group 1: + IABP (13)</p> <p>Group 2: - IABP (13)</p> <p>One death in group 2 before implantation</p> <p>Median age: 66 (33 to 87) years</p> <p>Sex: 76% men</p> <p>Diabetes: 31%</p> <p>Previous infarction: 58%</p> <p>Hypertension: 61%</p> <p>Smoker: 58%</p> <p>Hypercholesterolaemia: 58%</p> <p>Cardiac output: 3.3 ± 1.2 L/min</p> <p>MAP: 75 ± 16 mmHg</p> <p>Lactate: 6.4 ± 4.2 mmol/L</p> <p>Blood pH: 7.27 ± 0.16</p> <p>Cardiac index: 1.72 ± 0.52 L/min/m²</p> <p>PCWP: 22.0 ± 7.2 mmHg</p> <p>All high-risk factors (beside gender distribution: 3 men more in group 1 gives a difference of 23%) are distributed equally between groups</p>
Interventions	<p>Myocardial revascularization: PCI (92%), CABG (4%)</p> <p>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 hr (group 1), 27 ± 16 hr (group 2)</p> <p>Pharmacological support: positive inotropic drugs as needed, vasopressors remained unchanged over 30 min during implantation of devices, no further regulations by protocol</p>
Outcomes	<p>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)</p>
Inclusion/exclusion criteria	<p>Inclusion criteria: 1) acute myocardial infarction < 48 hrs, confirmed by ischaemic symptoms for at least 30 min with elevated cardiac markers or ST-segment elevation or left bundle-branch block. An AMI was suspected when patients were resuscitated and cardiac markers or electrocardiographic changes met criteria for AMI or acute coronary syndrome; 2) cardiogenic shock (CS) within 24 hr</p> <p>Exclusion criteria: age < 18 years, prolonged resuscitation (> 30 min); hypertrophic obstructive cardiomyopathy; definite thrombus in left ventricle; treatment with IABP; severe valvular disease or mechanical heart valve; CS caused by mechanical complications of AMI such as ventricular septal defect, acute mitral regurgitation greater > II, or rupture of the ventricle; predominant right ventricular failure or the need for a right ventricular assist device; sepsis; known cerebral disease; bleeding with a need for surgical intervention; pulmonary embolism; allergy to heparin, or any known coagulopathy; aortic regurgitation > II; pregnancy; inclusion in another study or trial</p>
CS definition	<p>According to the SHOCK trial, clinical criteria: hypotension (systolic blood pressure < 90 mmHg) and a heart rate > 90 beats/min or the need for positive inotropic drugs to maintain a systolic blood pressure > 90 mmHg and end-organ hypoperfusion (cool extremities or a urine output of < 30 mL/hr) or pulmonary edema. Haemodynamic criteria: cardiac index ≤ 2.2 L/min/m² and a pulmonary capillary</p>

Seyfarth 2008 (Continued)

wedge pressure > 15 mmHg or an angiographically measured left ventricular ejection fraction < 30% and left ventricular end-diastolic pressure > 20 mmHg

Sponsor	Supported by Abiomed Europe GmbH, Germany
Notes	Analysis of individual patient data. The principal investigator (MS) is co-author of this review

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) mortality+haemodynamic	High risk	not possible
Incomplete outcome data (attrition bias) mortality	Low risk	complete 6-month follow-up
Incomplete outcome data (attrition bias) haemodynamics	Low risk	30 min, 22 hr (CPI), 72 hr (serum lactate, haemoglobin)
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 endpoint assessment (30 min after implantation)

Thiele 2005

Study characteristics

Methods	Parallel single-centre RCT of two groups (IABP versus TandemHeart) undergoing percutaneous coronary intervention (PCI) as first line treatment option Study duration: August 2000 to December 2003 Measurements: haemodynamic parameters were acquired in the catheter laboratory before and after device implantation. In the ICU, measurements were obtained every 8 hr on subsequent days. Metabolic parameters such as standard base excess, serum lactate and pH were determined
Participants	Group 1: + IABP (20) Group 2: - IABP (21) One patient with rapid haemodynamic improvement not received ventricular assist device (VAD) (Group 2) Median age: 64 (40 to 78) years Sex: 76% men Diabetes: 54% Previous infarction: 54% Hypertension: 83% Smoker: 37% Hypercholesterolaemia: 49%

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

Thiele 2005 (Continued)

Cardiac output: 3.4 ± 0.9 L/min
MAP: 63 ± 14 mmHg
Lactate: 5.7 ± 3.8 mmol/L
Blood pH: 7.31 ± 0.10
Cardiac index: 1.68 ± 0.38 L/min/m²
PCWP: 22.6 ± 5.4 mmHg (group 1: 25.1 ± 6.1 versus group 2: 20.8 ± 4.1)
All high-risk factors (besides PCWP) are distributed equally between groups

Interventions	Myocardial revascularization: PCI (95%), CABG (5%) 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 trans-septal puncture a venous in-flow 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 hr (group 1), 77 ± 47 hr (group 2) Pharmacological support: continuously heparin administration through the device lubrication system, activated clotting time was maintained at 180 to 200 sec, intravenous administration of dopamine and dobutamine (in case of high systemic vascular resistance), diuretics and 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
Inclusion/exclusion criteria	Inclusion criteria: ≥ 18 years or older, cardiogenic shock + AMI and the intention to revascularize the infarcted artery by PCI as first line treatment option Exclusion criteria: age > 75 years, mechanical complications of AMI, duration of CS > 12 hr, right heart failure, sepsis, significant aortic regurgitation, severe cerebral damage, resuscitation > 30 min, severe peripheral vascular disease, and other diseases with reduced life expectancy
CS definition	(1) Persistent systolic blood pressure < 90 mmHg or vasopressors required to maintain blood pressure > 90 mmHg; (2) evidence of end-organ failure (e.g. urine output < 30 mL/hr, cold skin and extremities, and serum lactate > 2 mmol/L); (3) evidence of elevated left ventricular filling pressures (pulmonary congestion or pulmonary capillary wedge pressure) > 15 mmHg; and (4) cardiac index < 2.1 L/min/m ²
Sponsor	Supported by a research grant from Cardiac Assist, Pittsburgh, PA, USA
Notes	Analysis of individual patient data. The principal investigator (HT) is co-author of this review

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) mortality+haemodynamic	High risk	not possible
Incomplete outcome data (attrition bias) mortality	Low risk	complete 30-day follow-up

Thiele 2005 (Continued)

Incomplete outcome data (attrition bias) haemodynamics	Low risk	not all patients included in the analysis as a consequence of death, measurements up to 72 hr 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 generalisation to the entire CS population possible)

Thiele 2012
Study characteristics

Methods	<p>Parallel multicentre RCT of two groups (standard + IABP versus standard) undergoing early revascularization (PCI or CABG) and optimum medical therapy</p> <p>Study duration: June 2009 to March 2012</p>
Participants	<p>Total n = 600</p> <p>Group 1: + IABP (301)</p> <p>Group 2: - IABP (299)</p> <p>Median age: 70 (interquartile range (IQR) 28 to 78) years</p> <p>Sex: 69% men</p> <p>Diabetes: 33%</p> <p>Previous infarction: 22%</p> <p>Hypertension: 69%</p> <p>Smoker: 34%</p> <p>Hypercholesterolaemia: 38%</p> <p>MAP: 69 (IQR 59 to 80) and 68 (IQR 59 to 80) mmHg</p> <p>Lactate: 3.6 (IQR 2.1 to 7.2) and 4.7 (IQR 2.3 to 8.2) mmol/L</p> <p>Heart rate: 92 (IQR 72 to 110) beats/min</p> <p>Baseline characteristics were distributed equally between groups</p>
Interventions	<p>Comparison of PCI + intensive care treatment + IABP versus 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</p> <p>Myocardial revascularization: primary PCI 575 (95.8%), primary CABG 6 (1.0%), no revascularization 19 (3.5%)</p> <p>Primary additional randomised intervention: in patients randomised to Group 1, an IABP (Maquet Cardiopulmonary AG, Hirrlingen, Germany and Teleflex Medical, Everett, MA) was inserted via the femoral artery. Sheathless insertion was recommended. IABP support was instituted using 1:1 electrocardiographic triggering until sustained haemodynamic stabilisation. Weaning is performed by reduction of the electrocardiographic triggering from 1:1 to 1:2 to 1:3 trigger ratio</p> <p>Pharmacological support: by haemodynamic monitoring for optimal adjustment of fluid administration and inotropes. All additional treatments were performed according to the standards of the German/Austrian S3-Guidelines (Werdan 2012)</p>
Outcomes	<p>Efficacy: 30-day all-cause mortality, haemodynamic parameters (systolic, diastolic, MAP, heart rate pre- and post-IABP plus revascularization), time to haemodynamic stabilization, catecholamine dose and duration of catecholamine therapy, inflammatory markers, serum lactate, creatinine level and creati-</p>

Thiele 2012 (Continued)

nine clearance, requirement for renal replacement therapy, length of ICU stay, requirement and length of mechanical ventilation, SAPS II score, requirement for active LVAD implantation or heart transplantation, quality of life, 6-month and 1-year mortality, reinfarction, additional revascularization by either PCI or CABG and the need for implantable cardioverter defibrillator implantation

Safety: bleeding until hospital discharge, peripheral ischaemic vascular complications requiring surgical or interventional therapy, sepsis with clinical signs of infection and elevated pro-calcitonin (≥ 2 ng/mL), stroke with any new neurologic symptoms in conjunction with signs of ischaemia or bleeding

Inclusion/exclusion criteria	<p>Inclusion criteria: ≥ 18 years or older, AMI (STEMI or NSTEMI) + CS and planned revascularization (PCI or alternatively CABG)</p> <p>Exclusion criteria: typical contraindications for inclusion in CS trials and those for the use of IABP: ≥ 90 years or older, patients without informed consent, resuscitation > 30 minutes, no intrinsic heart action, cerebral deficit with fixed dilated pupils (not drug-induced), mechanical causes of CS (ventricular septal defect or acute mitral regurgitation, onset of shock > 12 hours; massive pulmonary embolism, severe peripheral artery disease precluding IABP insertion, aortic regurgitation $> II$, shock because of other cause (sepsis or hypovolaemia), other severe concomitant disease with limited life expectancy < 6 months</p>
CS definition	Standard definition of CS as used in previous large-scale trials (Hochman 1999): (1) systolic blood pressure < 90 mmHg for > 30 minutes or catecholamines required to maintain pressure > 90 mmHg during systole plus clinical signs of pulmonary congestion; (2) signs of impaired organ perfusion with at least one of the following criteria: (a) altered mental status; (b) cold, clammy skin and extremities; (c) oliguria with urine output < 30 mL/h; and (d) serum lactate > 2.0 mmol/L
Sponsor	Investor-initiated trial, supported by the German Research Foundation, the German Heart Research Foundation, the German Cardiac Society, the Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausärzte, the University of Leipzig—Heart Center and unrestricted grants from Maquet Cardiopulmonary AG, Hirrlingen, Germany, and Teleflex Medical, Everett, MA
Notes	Analysis of individual patient data. The principal investigator (HT) is co-author of this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	internet-based randomisation program
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) mortality+haemodynamic	Low risk	all clinical and safety endpoints were adjudicated by a Clinical End Points Committee blinded to the patients' assigned treatment
Incomplete outcome data (attrition bias) mortality	Low risk	1 patient (IABP group) was lost to follow-up and 1 patient (control group) withdrew consent before 30 days, 3 additional patients (1 from the IABP and 2 from the control group) were lost to follow-up before 6 months
Incomplete outcome data (attrition bias) haemodynamics	Low risk	
Selective reporting (reporting bias)	Low risk	haemodynamic parameters, mortality and complications are reported

Thiele 2012 (Continued)

Other bias	Low risk	30 (10.0%) cross-over to IABP (26 were protocol violations), 13 (4.3%) cross-over from IABP to non-IABP
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Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Anderson 1997	Not randomised trial
Barron 2001	Not randomised trial
Bengtson 1992	Not randomised trial
Christenson 1997a	No inclusion of patients with preoperative AMI + CS
Christenson 1997b	No inclusion of patients with preoperative AMI + CS
Christenson 1997c	No inclusion of patients with preoperative AMI + CS
Christenson 1999	No inclusion of patients with preoperative AMI + CS
Christenson 2003	No inclusion of patients with preoperative AMI + CS
Flaherty 1985	Exclusion of patients with CS
Gu 2010	Not randomised trial
Gu 2011	Exclusion of patients with CS
Kono 1996	Exclusion of patients with CS
Kovack 1997a	Not randomised trial
Li 2007	No CS at time of randomisation
Marra 2002	No CS patients
Moulopoulos 1986a	Not randomised trial
O'Neill 2012	Exclusion of patients with AMI
O'Rourke 1981	Four of 30 patients had CS (1 IABP patient)
Ohman 1994	Exclusion of patients with CS
Onorati 2005	No CS patients
Perera 2009	Exclusion of patients with CS
RECOVER II Trial	Inclusion of one patient due to protocol challenges on insertion, no cross-over option, consent issues and ethical concerns
Sanborn 2000	Not randomised trial

Study	Reason for exclusion
Stomel 1994	Not randomised trial
Stone 1997	Exclusion of patients with CS
Stub 2011	Not randomised trial
Taguchi 2000	Not randomised trial
Van 't Hof 1999	For patients with CS cross-over to balloon pumping was pre-specified
Vijayalakshmi 2007	Patients with CS were excluded
Vis 2007a	Not randomised trial
Vis 2007b	Not randomised trial
Waksman 1993	Not randomised trial. IABP was available in unit A (used in 20 patients) and not available in unit B (21 patients)
Zeymer 2011	Not randomised trial
Zeymer 2013	Not randomised trial

DATA AND ANALYSES

Comparison 1. IABP versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause 30-day mortality distribution	6	750	Hazard Ratio (IV, Random, 95% CI)	0.95 [0.76, 1.19]
1.1.1 IABP versus non-IABP	3	662	Hazard Ratio (IV, Random, 95% CI)	0.94 [0.74, 1.20]
1.1.2 IABP versus other LVAD	3	88	Hazard Ratio (IV, Random, 95% CI)	1.02 [0.54, 1.93]
1.2 All-cause mortality distribution	4	683	Hazard Ratio (IV, Random, 95% CI)	1.00 [0.82, 1.23]
1.2.1 IABP versus non-IABP	3	657	Hazard Ratio (IV, Random, 95% CI)	1.02 [0.83, 1.25]
1.2.2 IABP versus other LVAD	1	26	Hazard Ratio (IV, Random, 95% CI)	0.73 [0.25, 2.11]
1.3 All-cause in-hospital mortality rates	5	747	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.65, 1.18]
1.3.1 IABP versus non-IABP	3	680	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.63, 1.18]
1.3.2 IABP versus other LVAD	2	67	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.36, 2.47]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 All-cause 30-day mortality rates	6	748	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.72, 1.29]
1.4.1 IABP versus non-IABP	3	660	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.69, 1.29]
1.4.2 IABP versus other LVAD	3	88	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.46, 2.51]
1.5 All-cause 6-month mortality rates	4	678	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.71, 1.30]
1.5.1 IABP versus non-IABP	3	652	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.72, 1.34]
1.5.2 IABP versus other LVAD	1	26	Odds Ratio (M-H, Random, 95% CI)	0.54 [0.11, 2.55]
1.6 All-cause 12-month mortality rates	2	627	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.77, 1.47]
1.7 Haemodynamics (CI) post intervention	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.7.1 IABP versus non-IABP	1	30	Mean Difference (IV, Random, 95% CI)	0.49 [-0.29, 1.27]
1.7.2 IABP versus other LVAD	2	65	Mean Difference (IV, Random, 95% CI)	-0.75 [-1.51, -0.00]
1.8 Haemodynamics (MAP) post intervention	3	101	Mean Difference (IV, Random, 95% CI)	-5.10 [-10.86, 0.66]
1.8.1 IABP versus non-IABP	1	36	Mean Difference (IV, Random, 95% CI)	-3.27 [-13.47, 6.93]
1.8.2 IABP versus other LVAD	2	65	Mean Difference (IV, Random, 95% CI)	-7.55 [-18.59, 3.50]
1.9 Haemodynamics (PCWP) post intervention	3	90	Mean Difference (IV, Random, 95% CI)	3.89 [1.10, 6.68]
1.9.1 IABP versus non-IABP	1	28	Mean Difference (IV, Random, 95% CI)	4.71 [1.12, 8.30]
1.9.2 IABP versus other LVAD	2	62	Mean Difference (IV, Random, 95% CI)	3.37 [-1.35, 8.09]
1.10 Length of hospital stay	4	677	Mean Difference (IV, Random, 95% CI)	-1.12 [-4.93, 2.69]
1.10.1 IABP versus non-IABP	2	640	Mean Difference (IV, Random, 95% CI)	-3.14 [-13.84, 7.55]
1.10.2 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

Analysis 1.2. Comparison 1: IABP versus control, Outcome 2: All-cause mortality distribution

Analysis 1.3. Comparison 1: IABP versus control, Outcome 3: All-cause in-hospital mortality rates

Analysis 1.4. Comparison 1: IABP versus control, Outcome 4: All-cause 30-day mortality rates

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

Analysis 1.6. Comparison 1: IABP versus control, Outcome 6: All-cause 12-month mortality rates

Analysis 1.7. Comparison 1: IABP versus control, Outcome 7: Haemodynamics (CI) post intervention

Analysis 1.8. Comparison 1: IABP versus control, Outcome 8: Haemodynamics (MAP) post intervention

Analysis 1.9. Comparison 1: IABP versus control, Outcome 9: Haemodynamics (PCWP) post intervention **Analysis 1.10. Comparison 1: IABP versus control, Outcome 10: Length of hospital stay** **ADDITIONAL TABLES****Table 1. Mortality distribution - additional information**

Lengths of follow up	adjustment fac- tors	model	Subgroup analy- sis	HR, 95% CI
All-cause 30-day mortality	no	one-step meta-analysis	no	0.95, 95% CI 0.76-1.19
All-cause 30-day mortality	no	two-step meta-analysis	no	0.95, 95% CI 0.76-1.19
All-cause 30-day mortality	age, sex	one-step meta-analysis	no	0.95, 95% CI 0.76-1.19

Table 1. Mortality distribution - additional information *(Continued)*

All-cause 30-day mortality	age, sex, diabetes	one-step meta-analysis	no	0.93, 95% CI 0.74-1.17
All-cause 30-day mortality	no	one-step meta-analysis	male	0.92, 95% CI 0.70-1.21
All-cause 30-day mortality	no	one-step meta-analysis	female	0.99, 95% CI 0.67-1.46
All-cause 30-day mortality	no	one-step meta-analysis	<75 years	0.86, 95% CI 0.64-1.14
All-cause 30-day mortality	no	one-step meta-analysis	≥75 years	1.04, 95% CI 0.72-1.52
All-cause 30-day mortality	no	one-step meta-analysis	no diabetes	0.90, 95% CI 0.68-1.21
All-cause 30-day mortality	no	one-step meta-analysis	diabetes	0.97, 95% CI 0.67-1.41
All-cause mortality	no	one-step meta-analysis	no	1.02, 95% CI 0.84-1.25
All-cause mortality	no	two-step meta-analysis	no	1.00, 95% CI 0.82-1.23
All-cause mortality	age, sex	one-step meta-analysis	no	1.03, 95% CI 0.85-1.26
All-cause mortality	age, sex, diabetes	one-step meta-analysis	no	1.02, 95% CI 0.83-1.25

Table 2. Frequency of non-fatal events

study	event	Control group	IABP		Control		Odds Ratio (95% CI)
			Events	Total	Events	Total	
Ohman 2005	reinfarction (in-hospital)	non-IABP	0 (0.0%)	12	0 (0.0%)	10	not estimable
Thiele 2005	reinfarction (in-hospital)	other LVAD	1 (5.0%)	20	0 (0.0%)	21	3.31(0.01-86.06)
Seyfarth 2008	reinfarction (in-hospital)	other LVAD	0 (0.0%)	13	1 (7.7%)	13	0.31 (0.01-8.30)
Prondzinsky 2010	reinfarction (in-hospital)	non-IABP	1 (5.3%)	19	0 (0.0%)	21	3.49 (0.13-90.86)
Thiele 2012	reinfarction (in-hospital)	non-IABP	9 (3.0%)	300	4 (1.3%)	298	2.27 (0.69-7.46)
Total events	reinfarction (in-hospital)		11(3.0%)	364	5 (1.4%)	363	not estimated
Thiele 2012	reinfarction (1-year survivors)	non-IABP	13 (9.0%)	144	5 (3.5%)	144	2.76 (0.95-6.04)
Ohman 2005	stroke (in-hospital)	non-IABP	2 (16.7%)	12	0 (0.0%)	10	5.00 (0.21-117.21)
Prondzinsky 2010	stroke (in-hospital)	non-IABP	0 (0.0%)	19	0 (0.0%)	21	not estimable
Thiele 2005	stroke (in-hospital)	other LVAD	0 (0.0%)	20	0 (0.0%)	21	not estimable
Seyfarth 2008	stroke (in-hospital)	other LVAD	0 (0.0%)	13	0 (0.0%)	13	not estimable
Thiele 2012	stroke (in-hospital)	non-IABP	2 (0.7%)	300	5 (1.7%)	298	0.39 (0.08-2.04)
Total events	stroke (in hospital)		4 (3.1%)	364	5 (0.0%)	363	not estimated
Thiele 2012	stroke (1-year survivor)	non-IABP	3 (2.0%)	144	2 (1.4%)	144	1.51 (0.25-9.18)
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)

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

Thiele 2012	stent thrombosis (in hospital)	non-IABP	4 (1.3%)	300	3 (1.0%)	298	1.33 (0.29-5.99)
Total events	reocclusion (in hospital)		6 (1.7%)	352	13 (3.7%)	353	not estimated
Thiele 2012	re-revascularization (1-year survivor)	non-IABP	29 (20%)	144	32 (22%)	144	0.88 (0.50-1.55)
Prondzinsky 2010	recurrent ischaemia	non-IABP	1 (5.3%)	19	0 (0.0%)	21	3.49 (0.13-90.86)
Thiele 2005	recurrent ischaemia	other LVAD	1 (5.0%)	20	0 (0.0%)	21	3.31 (0.13-86.06)
Total events	recurrent ischaemia		2 (5.1%)	39	0 (0.0%)	42	not estimated

Table 3. Frequency of IABP-related complications

sStudy	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
Thiele 2012	life-threatening or severe bleeding	non-IABP	10 (3.3%)	300	13 (4.3%)	298	0.76 (0.33-1.75)
Thiele 2012	moderate bleeding	non-IABP	52 (17.3%)	300	49 (16.4%)	298	1.07 (0.69-1.63)
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)
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)

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

Ohman 2005	leg or limb ischaemia	non-IABP	0 (0.0%)	12	1 (10.0%)	10	0.28 (0.01-7.57)
Prondzinsky 2010	leg or limb ischaemia	non-IABP	1 (5.3%)	19	0 (0.0%)	21	3.49 (0.13-90.86)
Total events	leg or limb ischaemia	non-IABP	1 (3.2%)	31	1 (3.2%)	31	not estimated
Burkhoff 2006	leg or limb ischaemia	other LVAD	2 (14.3%)	14	4 (21.1%)	19	0.63 (0.10-4.01)
Seyfarth 2008	leg or limb ischaemia	other LVAD	0 (0.0%)	13	1 (7.7%)	13	0.31 (0.01-8.30)
Thiele 2005	leg or limb ischaemia	other LVAD	0 (0.0%)	20	7 (33.3%)	21	0.05 (0.00-0.89)
Total events	leg or limb ischaemia	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)
Thiele 2005	thrombocytopenia	other LVAD	0 (0.0%)	20	1 (4.8%)	21	0.33 (0.01-8.67)
Total events	thrombocytopenia	other LVAD	3 (8.8%)	34	4 (10.0%)	40	not estimated
Thiele 2012	peripheral ischaemic complication requiring intervention	non-IABP	13 (4.3%)	300	10 (3.4%)	298	1.30 (0.62-2.89)

APPENDICES

Appendix 1. Search strategies January 2010

CENTRAL in The Cochrane Library 2010, Issue 1

#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 20 January 2010

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

Appendix 2. Search strategies October 2013

CENTRAL

#1MeSH descriptor: [Intra-Aortic Balloon Pumping] explode all trees
 #2assisted next circulation
 #3(aort* near/6 balloon*)
 #4IABP
 #5(intra-aort* near/6 balloon)
 #6(intraaort* near/6 balloon)
 #7counterpulsation
 #8#1 or #2 or #3 or #4 or #5 or #6 or #7
 #9MeSH descriptor: [Myocardial Infarction] explode all trees
 #10heart next infarct*
 #11myocardial next infarct*
 #12cardiac next infarct*
 #13shock
 #14ami
 #15"coronary occlusion*"
 #16#9 or #10 or #11 or #12 or #13 or #14 or #15
 #17#8 and #16

MEDLINE Ovid

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. (myocard* adj2 infarct*).tw.
 12. (heart adj2 infarct*).tw.
 13. (cardiac adj2 infarct*).tw.
 14. ami.tw.
 15. (coronary adj3 occlusion*).tw.
 16. cardiogenic shock.tw.
 17. or/10-16
 18. 9 and 17
 19. randomized controlled trial.pt.
 20. controlled clinical trial.pt.
 21. randomized.ab.
 22. placebo.ab.
 23. drug therapy.fs.
 24. randomly.ab.
 25. trial.ab.
 26. groups.ab.
 27. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
 28. exp animals/ not humans.sh.
 29. 27 not 28
 30. 18 and 29

EMBASE OVID

1. exp aorta balloon/
 2. intra-aortic balloon.tw.
 3. intraaortic balloon.tw.
 4. iabp.tw.
 5. assisted circulation.tw.
 6. aort\$ balloon.tw.
 7. intraaort\$ counterpulsat\$.tw.

8. intra-aort\$ counterpulsat\$.tw.
9. or/1-8
10. exp Heart Infarction/
11. (myocard* adj2 infarct*).tw.
12. (heart adj2 infarct*).tw.
13. (cardiac adj2 infarct*).tw.
14. ami.tw.
15. (coronary adj3 occlusion*).tw.
16. cardiogenic shock.tw.
17. or/10-16
18. 9 and 17
19. random\$.tw.
20. factorial\$.tw.
21. crossover\$.tw.
22. cross over\$.tw.
23. cross-over\$.tw.
24. placebo\$.tw.
25. (doubl\$ adj blind\$).tw.
26. (singl\$ adj blind\$).tw.
27. assign\$.tw.
28. allocat\$.tw.
29. volunteer\$.tw.
30. crossover procedure/
31. double blind procedure/
32. randomized controlled trial/
33. single blind procedure/
34. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. (animal/ or nonhuman/) not human/
36. 34 not 35
37. 18 and 36

PubMed

((((((((((("Intra-Aortic Balloon Pumping"[Mesh]) OR assisted next circulation) OR (aort* near/6 balloon*)) OR IABP) OR (intra-aort* near/6 balloon)) OR (intraaort* near/6 balloon)) OR counterpulsation)) AND (((((((("Myocardial Infarction"[Mesh]) OR heart next infarct*) OR myocardial next infarct*) OR cardiac next infarct*) OR shock) OR ami) OR "coronary occlusion*")))) AND (((((((((((randomized controlled trial[Publication Type]) OR controlled clinical trial[Publication Type]) OR randomized[Title/Abstract]) OR placebo[Title/Abstract]) AND drug therapy[MeSH Subheading]) OR randomly[Title/Abstract]) OR trial[Title/Abstract]) OR groups[Title/Abstract])) NOT ((animals[MeSH Terms]) NOT humans[MeSH Terms])) NOT medline[SB]

LILACS

1. IABP
2. Intra-Aortic Balloon Pumping
3. intraaortic and shock
4. assisted circulation AND shock
5. cardiogenic shock AND Intra-Aortic
6. counterpulsation AND shock

IndMed

1. IABP
2. Intra-Aortic Balloon Pumping
3. intraaortic
4. assisted circulation
5. cardiogenic shock
6. counterpulsation

KoreaMed

1. IABP AND Shock
2. Intra-Aortic Balloon Pumping
3. intraaortic AND shock
4. assisted circulation AND shock

5. cardiogenic shock AND Intra-Aortic
6. counterpulsation

WHAT'S NEW

Date	Event	Description
21 September 2021	Review declared as stable	This review is not a priority for the current scope of the Heart Group.

HISTORY

Protocol first published: Issue 4, 2008
Review first published: Issue 7, 2011

Date	Event	Description
17 September 2014	New citation required but conclusions have not changed	Search updated from 2010 to October 2013 with one new large eligible study identified and strengthened conclusions due to increasing evidence.
1 April 2014	New search has been performed	Complete update with additional studies, revised analysis, risk of bias assessment, and revised conclusions.

CONTRIBUTIONS OF AUTHORS

SU developed the original protocol.

SU, RP conducted the data extraction and analysis.

SU, HT, RP assessed eligibility and quality of studies.

DP, JH provided statistical support.

AW assisted with data management.

AW provided scientific advice.

HT, MB, MS, KW, GS, UZ, RP provided clinical and scientific advice.

All authors were involved in drafting the final version of the review.

DECLARATIONS OF INTEREST

Roland Prondzinsky (principal investigator), Michael Buerke (study site), Karl Werdan (study site), Susanne Unverzagt (statistician) and Johannes Haerting (co-investigator) were involved in the IABP SHOCK Trial (2003 to 2004) ([Prondzinsky 2010](#))

Melchior Seyfarth (principal investigator) and Antoinette de Waha in [Seyfarth 2008](#)

Holger Thiele (principal investigator) in [Thiele 2005](#)

Holger Thiele (principal investigator and chair, steering committee, clinical endpoints committee, study site), Gerhard Schuler (steering committee, study site), Karl Werdan (steering committee, study site), Uwe Zeymer (steering committee, clinical endpoints committee, study site), Johannes Haerting (data safety and monitoring board), Antoinette de Waha (study site), Melchior Seyfarth (study site), Michael Buerke (study site), Roland Prondzinsky (study site) were involved in [Thiele 2012](#)

Judgements of inclusion criteria and risk of bias for these studies and interpretation of results were appraised by SU and RP, and in the case of [Prondzinsky 2010](#) by HT.

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

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In six of seven included studies patients were revascularised by PCI as the first line treatment option. Only 22 eligible patients in one study were revascularised with thrombolytic therapy. Therefore, a preplanned separate analysis for the influence of the different types of revascularization on the primary outcome was 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 heterogenous sources of bias, we did not perform sensitivity analyses on other preplanned influencing factors such as pharmacological support, characteristics of IABP intervention, influence of cross-over 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 in benefit and harms under IABP support. Because of missing information we restricted our investigation to the influence of age and sex.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans