Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial

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Summary

Background In current international guidelines the recommendation for intra-aortic balloon pump (IABP) use has been downgraded in cardiogenic shock complicating acute myocardial infarction on the basis of registry data. In the largest randomised trial (IABP-SHOCK II), IABP support did not reduce 30 day mortality compared with control. However, previous trials in cardiogenic shock showed a mortality benefit only at extended follow-up. The present analysis therefore reports 6 and 12 month results.

Methods The IABP-SHOCK II trial was a randomised, open-label, multicentre trial. Patients with cardiogenic shock complicating acute myocardial infarction who were undergoing early revascularisation and optimum medical therapy were randomly assigned (1:1) to IABP versus control via a central web-based system. The primary efficacy endpoint was 30 day all-cause mortality, but 6 and 12 month follow-up was done in addition to quality-of-life assessment for all survivors with the Euroqol-5D questionnaire. A masked central committee adjudicated clinical outcomes. Patients and investigators were not masked to treatment allocation. Analysis was by intention to treat. This trial is registered at ClinicalTrials.gov, NCT00491036.

Findings Between June 16, 2009, and March 3, 2012, 600 patients were assigned to IABP (n=301) or control (n=299). Of 595 patients completing 12 month follow-up, 155 (52%) of 299 patients in the IABP group and 152 (51%) of 296 patients in the control group had died (relative risk [RR] 1·01, 95% CI 0·86–1·18, p=0·91). There were no significant differences in reinfarction (RR 2·60, 95% CI 0·95–7·10, p=0·05), recurrent revascularisation (0·91, 0·58–1·41, p=0·77), or stroke (1·50, 0·25–8·84, p=1·00). For survivors, quality-of-life measures including mobility, self-care, usual activities, pain or discomfort, and anxiety or depression did not differ significantly between study groups.

Interpretation In patients undergoing early revascularisation for myocardial infarction complicated by cardiogenic shock, IABP did not reduce 12 month all-cause mortality.

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Introduction

Despite advances in treatment, mainly by early revascularisation, mortality in acute myocardial infarction complicated by cardiogenic shock remains high.[1–4] Intra-aortic balloon pump (IABP) counterpulsation has been the most widely used mechanical haemodynamic support device for nearly five decades.[5] It improves diastolic blood pressure, thereby improving coronary perfusion, and by its afterload reduction properties myocardial oxygen consumption is reduced leading to an increase in cardiac output.[6] However, on the basis of insufficient and conflicting evidence derived only from registry data,[7] American and European guidelines recently downgraded IABP use for cardiogenic shock from a class I to a class IIa and IIb recommendation.[8–10]

Currently, only one sufficiently large randomised trial of intra-aortic counterpulsation in cardiogenic shock secondary to myocardial infarction (IABP-SHOCK II trial) has been done. Short-term follow-up data at 30 days from this trial showed no survival benefit with IABP support by comparison with control.[11] However, long-term follow-up is necessary, especially since a previous trial in cardiogenic shock examining early revascularisation with no difference after 30 days showed a significant mortality benefit at extended follow-up.[3,12,13] Therefore, the IABP-SHOCK II trial had prespecified intermediate 6 and 12 month follow-up for clinical outcome and quality of life.

Methods

Study design

The trial design of the prospective, randomised, open-label, controlled IABP-SHOCK II trial at 37 German centres, and the 30 day results including the primary endpoint, have been previously published.[11,14] The study was investigator-initiated and coordinated by

the University of Leipzig—Heart Centre, Leipzig, Germany, and the Institut für Herzinfarktforschung, Ludwigshafen, Germany, acted as the clinical research organisation.

In brief, the main inclusion criterion was cardiogenic shock with planned early revascularisation preferably by percutaneous coronary intervention (PCI). Cardiogenic shock was defined by the presence of systemic hypotension, pulmonary congestion, and signs of impaired organ perfusion. Exclusion criteria were no intrinsic heart action, resuscitation for longer than 30 min, severe cerebral deficit, mechanical causes of cardiogenic shock, onset of shock longer than 12 h, severe peripheral artery disease precluding IABP insertion, aortic regurgitation greater than grade II in severity, age greater than 90 years, shock of other cause, and other severe concomitant disease with life expectancy less than 6 months. Patients with cardiogenic shock who were not eligible for randomisation were entered into a registry to define the number of screened and excluded patients.

The study was approved by national regulatory authorities and ethics committees of the participating centres. Patients or their legally authorised representatives provided written informed consent using a previously validated and dedicated informed consent process.[14] An independent data safety monitoring board reviewed unmasked data every year and a steering committee was responsible for the conduct of the trial.

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See **Online** for appendix

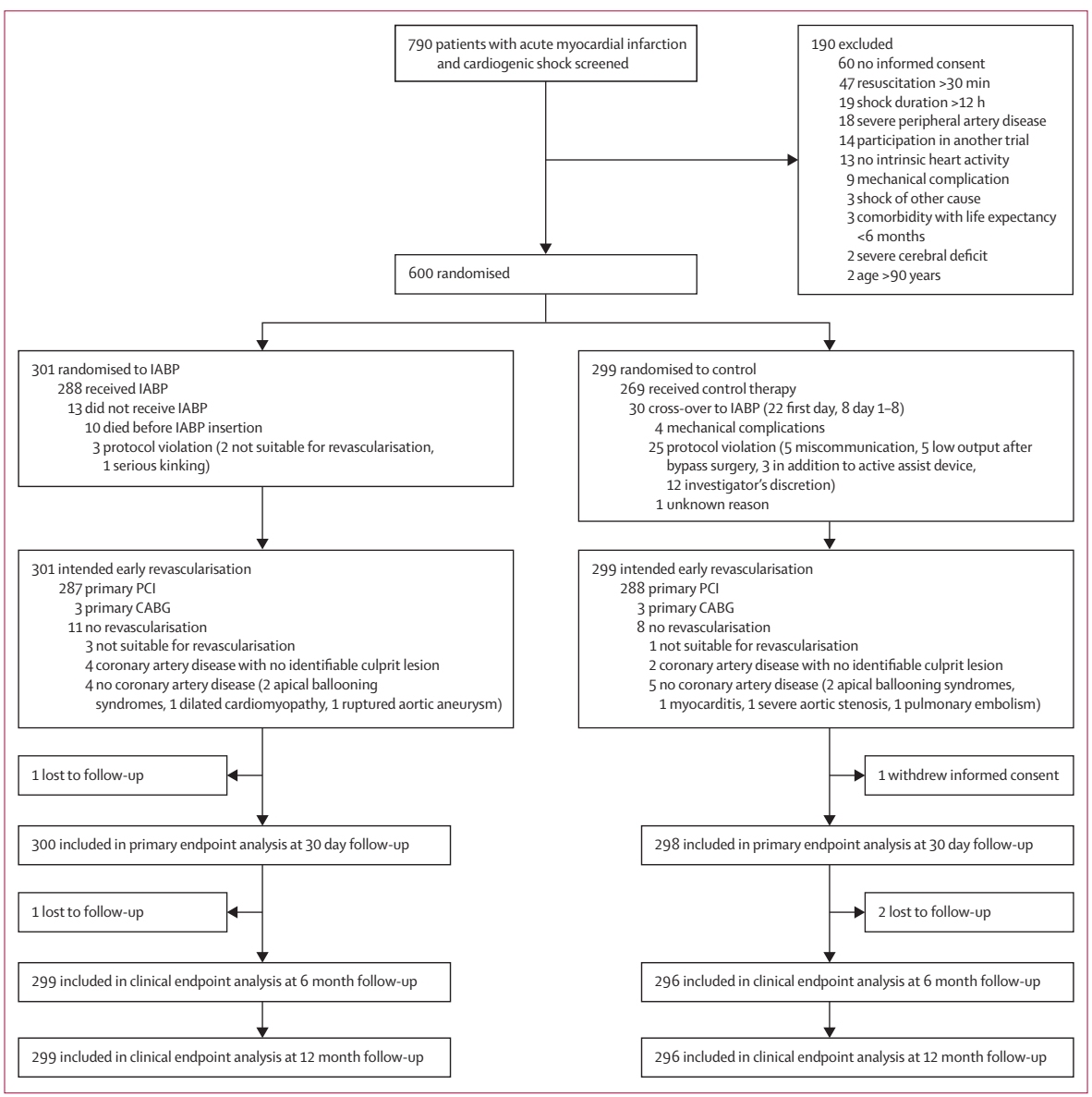

Figure 1: **Trial profile**
IABP=intra-aortic balloon pump. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting.

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Randomisation

Randomisation to IABP or control was done centrally, with a 1:1 ratio, via an internet-based program and stratification according to centre with blocks of six patients per centre. Additionally, there was the option to randomly assign patients by telephone with pregenerated randomisation lists, which was used in less than 3% of cases. Patients and investigators were not masked to treatment allocation. IABP support was recommended until sustained haemodynamic stabilisation, which was defined as systolic blood pressure greater than 90 mm Hg for longer than 30 min without any inotropic medical support.[14] By protocol, crossover to IABP in the control group was only allowed for patients developing a mechanical complication—eg, ventricular septal defect or papillary muscle rupture. All other treatment was done according to specific recommendations of the German/Austrian S3-Guideline on cardiogenic shock including early revascularisation plus optimum medical treatment; therefore, the only difference in treatment between groups was IABP support.[15] Follow-up at 6 and 12 months including quality of life was done by a structured telephone interview with interviewers masked to the treatment allocation. Any clinical event was verified by hospital or general practitioner records.[14]

Procedures

In addition to the primary study endpoint, 30 day all-cause mortality,[11,14] mortality at 6 and 12 months was assessed by protocol.[11,14] Furthermore, reinfarction using the universal definition of myocardial infarction,[16] revascularisation by either PCI or coronary artery bypass grafting (CABG), stroke, and implantable cardioverter defibrillator implantation were assessed. A clinical event committee masked to the treatment group adjudicated the clinical outcome measures using detailed outcome definitions published previously.[14]

At 6 and 12 month follow-up, symptoms of heart failure according to the New York Heart Association (NYHA) classification and angina according to the Canadian Cardiovascular Society (CCS) classification were assessed in survivors in addition to quality of life with the EuroQol EQ-5D-3L questionnaire. This questionnaire is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression), each of which can have one of three responses: no problems, some or moderate problems, and extreme problems. Additionally, the EQ visual analogue scale (EQ VAS) was obtained. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale on which the endpoints are labelled "Best imaginable health state" and "Worst imaginable health state".[17] Results were displayed as EQ-5D-3L index value with 1 indicating best quality of life and the EQ VAS with 100 indicating the best subjective health status.[18]

The secondary endpoints of serial serum lactate assessments, creatinine clearance, C-reactive protein, the Simplified Acute Physiology Score II, and the process-of-care outcomes were only assessed during the initial hospital phase and have been reported previously.[11] Safety with respect to the measures of bleeding, stroke, sepsis, and peripheral ischaemic vascular complication was only assessed for the initial hospital phase up to 30 days. Further safety analyses were not done.[11]

	IABP (n=299)	Control (n=296)	Relative risk (95% CI)	p value
All-cause mortality	155/299 (52%)	152/296 (51%)	1·01 (0·86–1·18)	0·91
Cardiac mortality	150/299 (50%)	148/296 (50%)	1·00 (0·85–1·18)	0·97
Non-cardiac mortality	5/299 (2%)	4/296 (1%)	1·23 (0·34–4·56)	1·00
Events in 1-year survivors				
Reinfarction	13/144 (9%)	5/144 (3%)	2·60 (0·95–7·10)	0·05
Stroke	3/144 (2%)	2/144 (1%)	1·50 (0·25–8·84)	1·00
Recurrent revascularisation	29/144 (20%)	32/144 (22%)	0·91 (0·58–1·41)	0·77
Repeat PCI	22/144 (15%)	25/144 (17%)	0·88 (0·52–1·49)	0·63
Additional CABG	7/144 (5%)	7/144 (5%)	1·00 (0·36–2·78)	1·00
ICD implantation	14/144 (10%)	14/144 (10%)	1·00 (0·49–2·02)	1·00

Data are n/N (%), relative risk (95% CI), or p value. IABP=intra-aortic balloon pump. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. ICD=implantable cardioverter defibrillator.

Table 1: **Clinical outcomes at 12 months**

Statistical analysis

The study was powered to detect a 12% absolute difference for the primary endpoint, 30 day mortality, on the assumption of a mortality rate of 56% in the control group. To account for two interim analyses, a putative centre effect, and a 2% dropout rate, 600 patients were recruited.[11,14] All data were analysed by intention to treat, with additional sensitivity analysis done per protocol and for the as-treated population for evaluation of data robustness.

Survival times were calculated as the time from randomisation to the time of death or last known follow-up. The log-rank test was used to analyse continuous survival times and the χ^2 test was used to compare mortality rates. Other endpoints were assessed by Fisher's or χ^2 test for binary and Mann-Whitney *U* test for quantitative secondary endpoints to compare both treatment groups. Cox proportional hazards regression modelling was used to identify independent clinical and laboratory risk factors at admission associated with mortality. All baseline variables related to mortality in the univariable analysis (defined by $p<0{\cdot}10$) were further analysed in a stepwise multivariable model. Predefined subgroup analyses were done for sex, age (groups <50 years, 50–75 years, >75 years), diabetes, arterial hypertension, ST-elevation versus non-ST-elevation myocardial infarction, anterior versus non-anterior myocardial infarction, and previous myocardial infarction. Post-hoc subgroups evaluated were hypothermia versus no hypothermia and baseline blood pressure lower than 80 mm Hg versus 80 mm Hg or higher. The Breslow-Day test was used to analyse the interaction of treatment

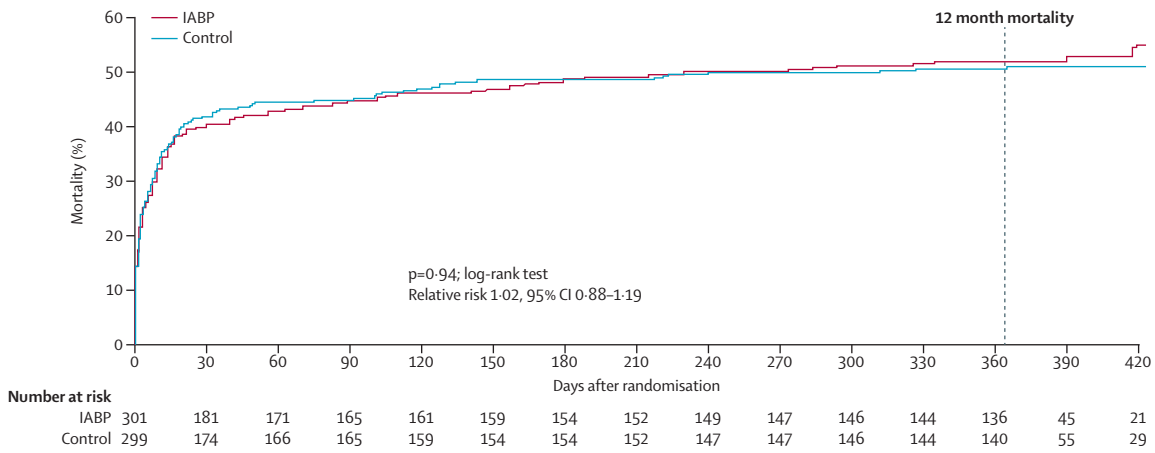

Figure 2: **Time-to-event curves for all-cause mortality up to 12 months**
Event rates represent Kaplan-Meier estimates. Two patients in the IABP group died at days 388 and 419 postrandomisation, which is represented in the Kaplan-Meier curves. IABP=intra-aortic balloon pump.

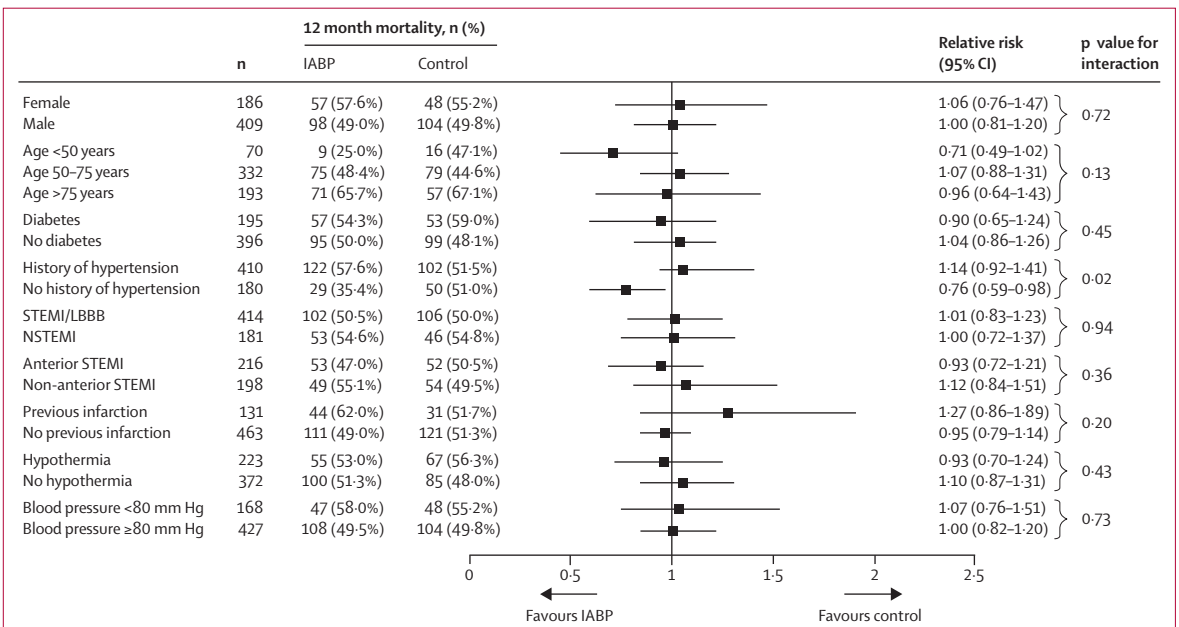

Figure 3: **Subgroup analyses for all patients with 12 month follow-up**
Relative risk and 95% CIs for predefined subgroups and the post-hoc subgroups hypothermia versus no hypothermia and baseline systolic blood pressure less than 80 mm Hg versus 80 mm Hg or higher. STEMI=ST-elevation myocardial infarction. LBBB=left bundle branch block. NSTEMI=non-ST-elevation myocardial infarction. IABP=intra-aortic balloon pump.

assignment and subgroup factors. A two-tailed p<0·05 was regarded as significant. Statistical analyses were done with SAS statistical package (version 9.3).

This trial is registered at ClinicalTrials.gov, NCT00491036.

Role of the funding source

This investigator-initiated trial was designed by the principal investigator and modified and approved by the steering committee.[14] The funding sources had no involvement in the study design, data interpretation, drafting of the report, and the final decision to publish, as reported previously.[14] Data were maintained at the coordinating research organisation, the Institut für Herzinfarktforschung, which independently undertook all statistical analyses. The principal investigator and the steering committee had unrestricted data access after database closure; the principal investigator prepared the first draft of the report, and controlled the decision to publish. The steering committee vouches for the integrity and completeness of the data and the statistician for the accuracy of data analysis.

	Univariable		Stepwise multivariable	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Single vessel coronary artery disease	0·68 (0·51–0·92)	0·01	..	..
Mechanical ventilation	1·23 (0·98–1·55)	0·07	..	..
Cold, clammy skin and extremities	1·55 (1·11–2·17)	0·01	..	..
Current smoking	0·63 (0·49–0·81)	0·0004	..	..
History of arterial hypertension	1·33 (1·03–1·72)	0·03	..	..
Haemoglobin per 1 mmol/L	0·87 (0·81–0·94)	0·0004	..	..
Haematocrit per 10%	0·83 (0·72–0·96)	0·01	..	..
Sinus rhythm	0·78 (0·60–1·01)	0·06	..	..
ST-elevation myocardial infarction	0·76 (0·60–0·95)	0·02	..	..
Age, per 10 years	1·33 (1·20–1·47)	<0·0001	1·25 (1·12–1·39)	<0·0001
History of stroke	2·18 (1·53–3·11)	<0·0001	2·00 (1·37–2·93)	0·0004
Baseline serum lactate, per 10 mmol/L	1·43 (1·29–1·57)	<0·0001	1·24 (1·10–1·39)	0·001
Baseline creatinine, per 100 µmol/L	1·38 (1·24–1·54)	<0·0001	1·23 (1·08–1·40)	0·002
Altered mental status	1·73 (1·30–2·30)	0·0002	1·57 (1·15–2·16)	0·005
Oliguria (<30 mL/h)	1·73 (1·38–2·18)	<0·0001	1·40 (1·08–1·82)	0·01
pH <7·36 at admission	1·58 (1·24–2·01)	0·0002	1·35 (1·02–1·79)	0·04
Left bundle branch block	1·84 (1·37–2·47)	0·0002	1·41 (1·01–1·98)	0·04

All baseline patient variables related to mortality in univariable analysis, defined by p<0·10. The first nine variables entered into the model were not independently associated with mortality in the stepwise multivariable model.

Table 2: **Predictors of 12 month mortality in univariable and stepwise multivariable Cox regression analysis**

See Online for appendix

Results

Between June 16, 2009, and March 3, 2012, 600 patients of 790 initially screened were randomly assigned to IABP (n=301) or control (n=299). Figure 1 shows revascularisation, study protocol compliance, and follow-up. 12 month follow-up was complete in 595 (99%) patients. The baseline characteristics were well balanced between treatment groups.[11] The median age was 70 years (IQR 58–77) and 413 (69%) were male. 270 (45%) underwent cardiopulmonary resuscitation before randomisation, 463 (77%) had multivessel coronary artery disease, 538 (90%) reported catecholamine use before randomisation and 22 (4%) levosimendan use, and median left ventricular ejection fraction was 35% (IQR 25–45). In the 330 (55%) patients with data available, the median time from onset of angina to randomisation was 4:19 h (IQR 2:32–11:13) and from onset of shock to randomisation was 2:17 h (IQR 1:19–3:56). The median duration of IABP support was 3·0 days (IQR 2·0–4·0, range 1–16 days). IABP insertion was done in 37 (12%) patients before revascularisation.

Mortality did not differ significantly between the IABP and the control group at 6 months (48·7% *vs* 49·2%, relative risk [RR] 0·99, 95% CI 0·85–1·16, p=0·91) and 12 months after randomisation (51·8% *vs* 51·4%, RR 1·01, 95% CI 0·86–1·18, p=0·91; table 1, figure 2). For the long-term follow-up at 12 months there was only minor variation in the RR estimates when the analyses were restricted to the per-protocol population (52·5% *vs* 50·0%, RR 1·05, 95% CI 0·89–1·23, p=0·55) or to the as-treated population (51·0% *vs* 52·3%, RR 0·97, 95% CI 0·82–1·14, p=0·68; appendix). Subgroup analyses confirmed the consistency of the results among all predefined and post-hoc defined subgroups except for patients without a history of hypertension (figure 3). Mortality did not differ significantly between IABP before and after PCI insertion in the IABP group at 12 month follow-up (54·6% *vs* 48·8%, p=0·53).

Multivariable modelling revealed that older age, history of stroke, baseline serum lactate, creatinine concentration, oliguria, altered mental status, pH lower than 7·36, and left bundle branch block at admission were independent risk factors for mortality (table 2). IABP support and time from angina or shock onset to randomisation were not predictive of survival.

We noted no significant differences in recurrent infarction, stroke, requirement for internal cardioverter defibrillator (ICD), or additional revascularisation procedures at 12 month follow-up (table 1).

In assessment of functional status and quality of life, the NYHA class was recorded in 253 (88%) of the 286 1-year survivors (127 [89%] of 142 in the IABP and 126 [88%] of 144 in the control group). Of these 233 (92%) were in NYHA class I or II (115 [91%] of 127 in the IABP and 118 [94%] of 126 in the control group, p=0·36). Similarly, the CCS class was recorded in 252 (88%) of the 286 1-year survivors (127 [89%] of 142 in the IABP and 125 [87%] of 144 in the control group). Of these 125 (98%) of 127 versus 124 (99%) of 125 were in CCS class I or II (p=1·00). The EQ-5D-3L index value was assessed for 274 (95%) survivors with 0·9 indicating moderate to good quality of life. Quality of life assessment did not differ between treatment groups with respect to the five dimensions and the EQ VAS (figure 4).

Discussion

In this prospective, randomised trial of patients with cardiogenic shock complicating acute myocardial infarction, IABP support did not increase 6 and 12 month survival compared with control, supporting the short-term 30 day follow-up data (panel). Despite early revascularisation and optimum medical therapy in both groups, mortality was still slightly higher than 50% at 1 year follow-up. Nevertheless, for survivors, the self-reported quality of life was moderate to good.

There are several possible explanations for the absence of benefit. Although experimental and clinical studies have shown haemodynamic improvements with IABP, its effect on cardiac output is only modest with an absolute increase in cardiac output of 0·5 L/min.[6] Furthermore, most trials investigating haemodynamic IABP effects had no control group.[6] In the IABP-SHOCK I randomised pilot trial, no significant differences between IABP and control were observed in cardiac power output, left ventricular stroke work index, and systemic vascular resistance.[20] Interestingly, there

was a significant increase in cardiac power output, a haemodynamic measure correlating well with mortality,[21] in both groups indicating that initial haemodynamic improvements might be more affected by revascularisation as well as fluid and inotropic optimisation than by IABP effects. Notably, however, there is currently no evidence that the use of catecholamines, levosimendan, fluids, or assist devices leads to improved survival. In IABP-SHOCK II, no detailed haemodynamic monitoring data were available. However, there were no effects on markers of systemic inflammation or serum lactate as a measure of tissue hypoxia, thereby providing pathophysiological explanations for the lack of mortality benefit.[11] The results were fairly consistent for all subgroups studied except for patients without a history of hypertension. However, data for any subgroup, in particular in a negative trial, are only hypothesis-generating. Furthermore, the results of the current trial with its long-term follow-up are in line with previous registry data in the PCI era and two small randomised trials in the fibrinolytic and PCI era, which were all negative for surrogate and combined clinical endpoints.[7,19,22]

We cannot entirely rule out the possibility that a potential beneficial effect of IABP on clinical endpoints is confined to patients in whom the support was started before revascularisation.[23] Mortality did not differ significantly between patients in whom IABP was started before and after revascularisation. However, pre-PCI IABP was done in less than 15% of patients and therefore no definitive conclusions can be drawn. Currently, data from observational studies are conflicting with one small retrospective registry trial in 48 patients with cardiogenic shock showing a benefit of pre-PCI implantation,[23] whereas in a more recent trial in 173 patients, IABP insertion before PCI led to increased creatine kinase concentrations and had no effect on mortality.[24]

A negative trial usually raises a question of power. Although we cannot definitively rule out a type II error, the absolute difference of only 0·4% in mortality rates between the groups together with the lack of benefit for any of the other outcome variables and a trend towards more recurrent infarctions in the IABP group compared with control make any clinically meaningful positive effect of IABP unlikely. The event rate in the control group was lower than the value initially used in the sample size calculation (41·3% *vs* 56·0%), which might have further affected statistical power.

In the current trial there was an additional absolute 10% mortality increase at 12 months by comparison with the 30 day results. This difference is slightly higher by comparison with the only other large randomised cardiogenic shock trial that reported long-term follow-up (SHOCK trial), which had mortality rates of 46·7% at 30 days and 53·3% at 12 months in the early revascularisation group.[3,12,13] These data confirm that mortality in cardiogenic shock is mainly determined in the early phase, although the risk of death is still substantial after the acute phase. Functional status for survivors is relatively good. Similar to the SHOCK trial, about 90% of survivors were in NYHA class I/II.[13] In the current trial, more detailed quality of life assessment was done with a standardised questionnaire. Health-related quality of life states consisting of five dimensions and a visual analogue scale were similar to a general population survey.[25] The absence of a survival benefit at long-term follow-up in the present study contrasts with the SHOCK trial and is probably explained by the different interventions. Revascularisation might have long-term

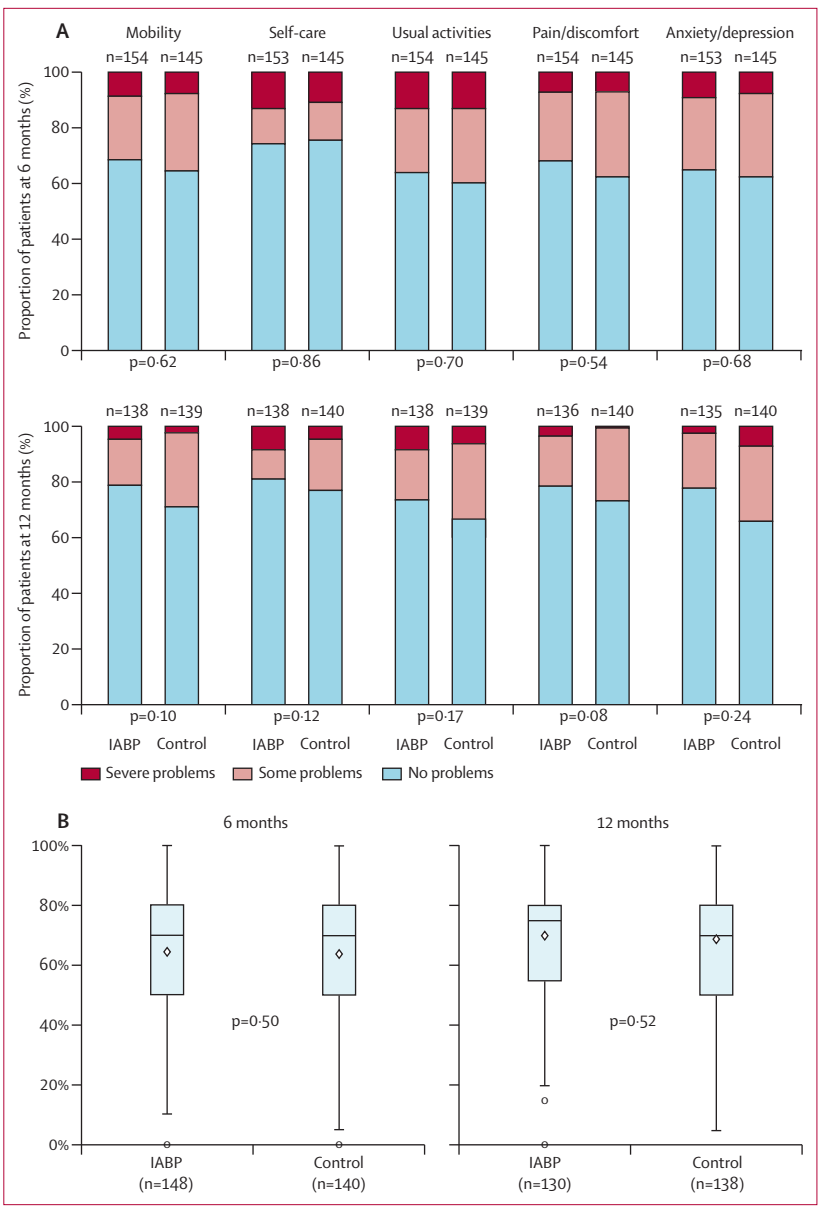

Figure 4: **Quality of life at 6 and 12 month follow-up for patients alive**
(A) Health-related quality of life states in the five dimensions of mobility, self-care, usual activities, pain or discomfort, and anxiety or depression for patients in the IABP and control groups. (B) Box plot of the visual analogue scale of self-rated health for patients in the IABP and control groups. IABP=intra-aortic balloon pump.

Panel: **Research in context**

Systematic review

To further evaluate the relative effect of IABP versus control we did an updated meta-analysis of studies comparing the two interventions in patients with cardiogenic shock complicating acute myocardial infarction. We searched Medline, Embase, Central (the Cochrane Controlled Clinical Trials Register), ClinicalTrials.gov, and proceedings from major cardiology scientific sessions for randomised controlled trials comparing IABP versus control in cardiogenic shock with an early revascularisation strategy. Studies with comparison of IABP to an active assist device and studies in the fibrinolytic era were excluded. We used the keywords "cardiogenic shock", "shock", "assist device", "intraaortic balloon pump", "infarction", and "randomised". The search was limited to studies published between Jan 1, 1980, and Aug 7, 2013.

The clinical endpoint death for the 12 month follow-up was analysed. In addition to the IABP-SHOCK II trial we identified only one small randomised pilot trial leading to a total of 640 patients, of which follow-up was available for 627 patients.[19] We pooled results using a random effects model. Data synthesis and statistical analyses were done with the Cochrane Collaboration Review Manager (RevMan, version 5.1.1). There were no significant differences in the risk of death (relative risk 1·03, 95% CI 0·88–1·19, p=0·75).

Interpretation

In this pooled analysis, mortality with IABP was not superior to that with control treatment without mechanical support in patients in cardiogenic shock undergoing early revascularisation.

mortality effects by salvaging myocardium, whereas IABP support does not have an effect on myocardial damage.[26] The fairly low rate of ICD implantations of 10% might be explained by a survivor selection bias and reflects the favourable functional status of survivors. Patients surviving might have left ventricular function at follow-up above established cutoff criteria for ICD implantation. In IABP-SHOCK II, no additional information about left ventricular function and remodelling at follow-up was available.

Risk of death varied substantially among patients with cardiogenic shock complicating myocardial infarction. An objective and readily available measure to assess mortality risk for individual patients is crucial to guide treatment. However, no easy score for risk prediction is currently available and used in clinical practice. Several previous analyses revealed different clinical, laboratory, angiographic, and haemodynamic measures as predictors mainly for short-term but also partly for long-term mortality in patients with cardiogenic shock undergoing early revascularisation by PCI.[12,27–30] In the current analysis, outcome predictors were similar to those in previous analyses including age, history of stroke, oliguria, left bundle branch block, and creatinine concentration. Of note, the readily available baseline serum lactate indicating the severity of end-organ hypoxia was one of the strongest predictors of long-term mortality. Previous trials in cardiogenic shock did not measure serum lactate systematically and the measure was therefore not used in multivariable modelling. Baseline serum lactate together with age and oliguria might therefore be integrated in mortality risk assessment in clinical practice.

This study has several strengths, including its size, multicentre design, recruitment of a broad risk, real world population managed with current, guideline-supported drugs and interventional techniques, and near complete clinical follow-up. In view of the broad inclusion criteria less than a quarter of initially screened patients were not eligible for the trial, suggesting broad generalisability of the results in interventionally treated patients with cardiogenic shock. Owing to the low number of surgically treated patients the effects of IABP might not be applicable to patients undergoing immediate bypass surgery. Masking of treatment allocation was not possible because of the nature of the intervention. However, several methods to avoid bias were implemented, such as a central randomisation system, a masked clinical event committee, and high standard requirements concerning the experience of centres and investigators.

In conclusion, this randomised, multicentre trial showed that IABP support did not reduce 12 month mortality in patients with cardiogenic shock complicating myocardial infarction undergoing early revascularisation. Quality of life was good for survivors of cardiogenic shock at 6 and 12 months.

Contributors

HT, UZ, KW, and GS designed the study, analysed and interpreted data, and revised the report. SD, IE, GF, and all other authors contributed to implementation of the study, enrolment and follow-up of patients, and reviewed the report. SS did all statistical analysis. HT wrote the first draft and submitted the final version of the report. All authors have seen the final submitted Article and agree with its contents.

Conflicts of interest

HT reports receiving consulting fees from Lilly, grant support on behalf of his institution from Lilly and Terumo, and lecture fees from AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Lilly, the Medicines Company, and Terumo. JH reports receiving lecture fees from Siemens and Abbott Vascular, and grant support from Siemens. SD reports receiving consulting fees from Osprey Medical and AstraZeneca and lecture fees from Boehringer Ingelheim, Bayer, Maquet, and Terumo. MB reports receiving consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, MSD, Novartis, Pfizer, Sanofi-Aventis, and Servier, and lecture fees from AstraZeneca, AWD Dresden, Bayer, Berlin Chemie, Boehringer Ingelheim, Daiichi Sankyo, MSD, Novartis, Pfizer, Sanofi-Aventis, and Servier. GR reports receiving lecture fees from Maquet Cardiovascular. SS reports holding a board membership on the ethics committee of Landesärztekammer Baden-Württemberg, receiving payment for manuscript preparation by Biosense Webster, Grupo Ferrer, and Nycomed, and money received on behalf of his institution's clinical research organisation from Abbott Vascular, AstraZeneca, Bayer Schering, Bayer Vital, Biotronik GmbH, Bristol-Myers Squibb, Boehringer Ingelheim, Cordis, Daiichi Sankyo, Diagenics GmbH, Enverdis, Lilly, GlaxoSmithKline, Guidant, IKKF GmbH, Impulse Dynamics, Medtronic, Merck & Co, MSD, Novartis GmbH, Roche Diagnostics, Sanofi-Aventis, Schering-Plough, Siemens AG, St Jude Medical, Takeda Pharma, Trommsdorff GmbH, and Vifor Pharma. UZ reports holding board membership at Daiichi Sankyo and Lilly, and receiving consulting and lecture fees from Daiichi Sankyo, Lilly, and the Medicines Company. KW reports holding board membership at Biotest and Servier, receiving grant support on behalf of his institution from Biotest and Servier, and lecture fees from Biotest, Brahms, Maquet Cardiovascular, and Servier. We declare no other potential conflicts of interest relevant to this Article.

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