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I have received research funding from, and provided consultancy to, manufacturers of smoking cessation medication. I have no connections with any manufacturers of electronic cigarettes.

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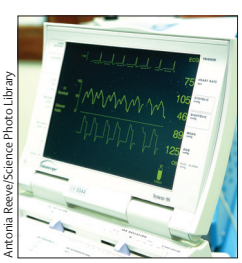
Is the intra-aortic balloon pump leaking?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Combined invasive and pharmacological treatment strategies have improved outcomes in acute myocardial infarction (MI) substantially. However, mortality in cardiogenic shock, which occurs in about 7% of patients admitted with acute MI, continues to be associated with high mortality (40–50%).[1] Yet trials in the emergency setting of acute MI complicated by cardiogenic shock are exceptionally difficult to conduct. Therefore, Holger Thiele and colleagues should be commended for the rigorous IABP-SHOCK II trial, which is the largest trial in this setting to date. In *The Lancet*, Thiele and colleagues report the 12 month follow-up.[2]

The underlying mechanism in cardiogenic shock is depression of myocardial contractility due to extensive MI, leading to a vicious cycle of reduced cardiac output, low blood pressure, reduced coronary blood flow, and ongoing reduction in contractility and cardiac output.[3] Despite compensatory mechanisms such as peripheral vasoconstriction and redistribution of circulation to the vital organs, this leads to multiple organ failure. The principal concept behind mechanical cardiac assistance in cardiogenic shock is to support the compromised circulation. The intra-aortic balloon pump (IABP) has long been the most accessible and frequently used mechanical cardiac assist device in the catheterisation laboratory. The IABP is a catheter-mounted balloon positioned in the descending aorta, usually through a percutaneous femoral approach. Counterpulsation is achieved by rapid inflation (diastole) and deflation (systole) of the balloon synchronised to the cardiac cycle. It augments diastolic coronary and systemic blood flow, and reduces systolic afterload, peak left ventricular wall stress, and myocardial oxygen consumption. Only a small increase of cardiac output is reported (0·5 L/min).

In 2012, Thiele and colleagues[4] reported the 30 day outcomes of IABP-SHOCK II, a randomised, open-label, multicentre trial that randomly assigned 600 patients with acute MI complicated by cardiogenic shock and treated with early revascularisation (percutaneous coronary intervention [96%] and coronary artery bypass graft [4%]) to either IABP therapy or no IABP therapy. All other intensive care unit treatment was standardised according to guidelines. There were no differences in the primary efficacy endpoint of 30 day mortality (IABP group 40%, no IABP group 41%; relative risk [RR] 0·96, 95% CI 0·79–1·17) or safety endpoints. Moreover there were no differences in lactate concentrations, dose and duration of catecholamine therapy, and renal function.

The newly published 12 month results[2] extend and strengthen the short-term findings. Mortality was mainly determined in the acute phase, but mortality thereafter was still substantial. 12 month mortality did not differ between groups (IABP group 52%, no IABP group 51%; RR 1·01, 95% CI 0·86–1·18) and there were no meaningful differences in the subgroup analyses. Importantly, no divergence in the mortality curves was observed, as was seen with the long-term results of the earlier trials SHOCK and BCIS-1.[5,6] Furthermore, there were no significant differences between groups in the frequency of reinfarction, stroke, functional class, or quality of life

indices. The authors conclude that IABP concomitant to early revascularisation does not reduce short-term or long-term mortality in acute MI complicated by cardiogenic shock, and survivors have a good quality of life.

IABP-SHOCK II provides a high level of evidence. On the basis of the established definition of cardiogenic shock from the landmark SHOCK trial, the 30 day mortality rates in IABP-SHOCK II were similar to those in the early revascularisation group of SHOCK (47%) and the placebo group of the TRIUMPH trial (42%), suggesting inclusion of patients with similarly severe cardiogenic shock.[5,7] Furthermore, IABP-SHOCK II was robust in terms of power, in view of the sample size and inclusion of more than 300 primary endpoint events. Although there might be concern about asymmetry in crossovers and difference in use of left ventricular assist devices, the results from the per-protocol and as-treated analyses at 30 days and 12 months did not differ from the intention-to-treat analyses.

Primarily based on two previously reported meta-analyses and acknowledging the conflicting evidence from registries, joint American Heart Association and American College of Cardiology guidelines and European Society of Cardiology guidelines recently downgraded the class of recommendation and level of evidence for IABP therapy in acute MI complicated by cardiogenic shock from IB and IC ("should be used"), respectively, to IIaB and IIbB ("may/can be used").[8–10] With findings in concordance with the previous meta-analyses, IABP-SHOCK II endorses the downgraded recommendations. Although the results of IABP-SHOCK II question the usefulness of IABP therapy in cardiogenic shock, there still might be an indication for initial stabilisation of severely compromised patients, especially in centres without facilities for early revascularisation, as an adjunct to thrombolytic therapy, or to allow transport to specialised tertiary centres.

Most importantly, this successfully undertaken trial should encourage further research, since mortality in cardiogenic shock is still unacceptably high. Mechanical cardiac assistance remains an appealing treatment strategy. Perhaps the more powerful percutaneous left ventricular assist devices (eg, extracorporeal membrane oxygenation, Impella, TandemHeart) could reduce the use of high-dose inotropic drugs or vasopressors, and improve in-hospital and long-term outcome.[11] An important issue will be the identification of patients who might benefit from device therapy versus those who could be harmed. Another area of interest is the optimum treatment strategy for coronary multivessel disease in cardiogenic shock. The upcoming European multicentre CULPRIT-SHOCK trial (NCT01927549) will compare culprit-vessel treatment with complete revascularisation.

Finally, research into pharmacological therapy counteracting haemodynamic deterioration and systemic inflammatory response syndrome warrants further evaluation. This research includes optimising the strategy for use of inotropic drugs and vasopressors. Recent novel insight into the role of the massive release of monocytes in the systemic inflammatory response after acute MI might also lead to new therapeutic options in cardiogenic shock (ie, specific β-receptor blockers).[12]

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JJP has taken part in a medical advisory board for Abbott Vascular and acted as a consultant for Miracor. KDS declares that he has no conflicts of interest.

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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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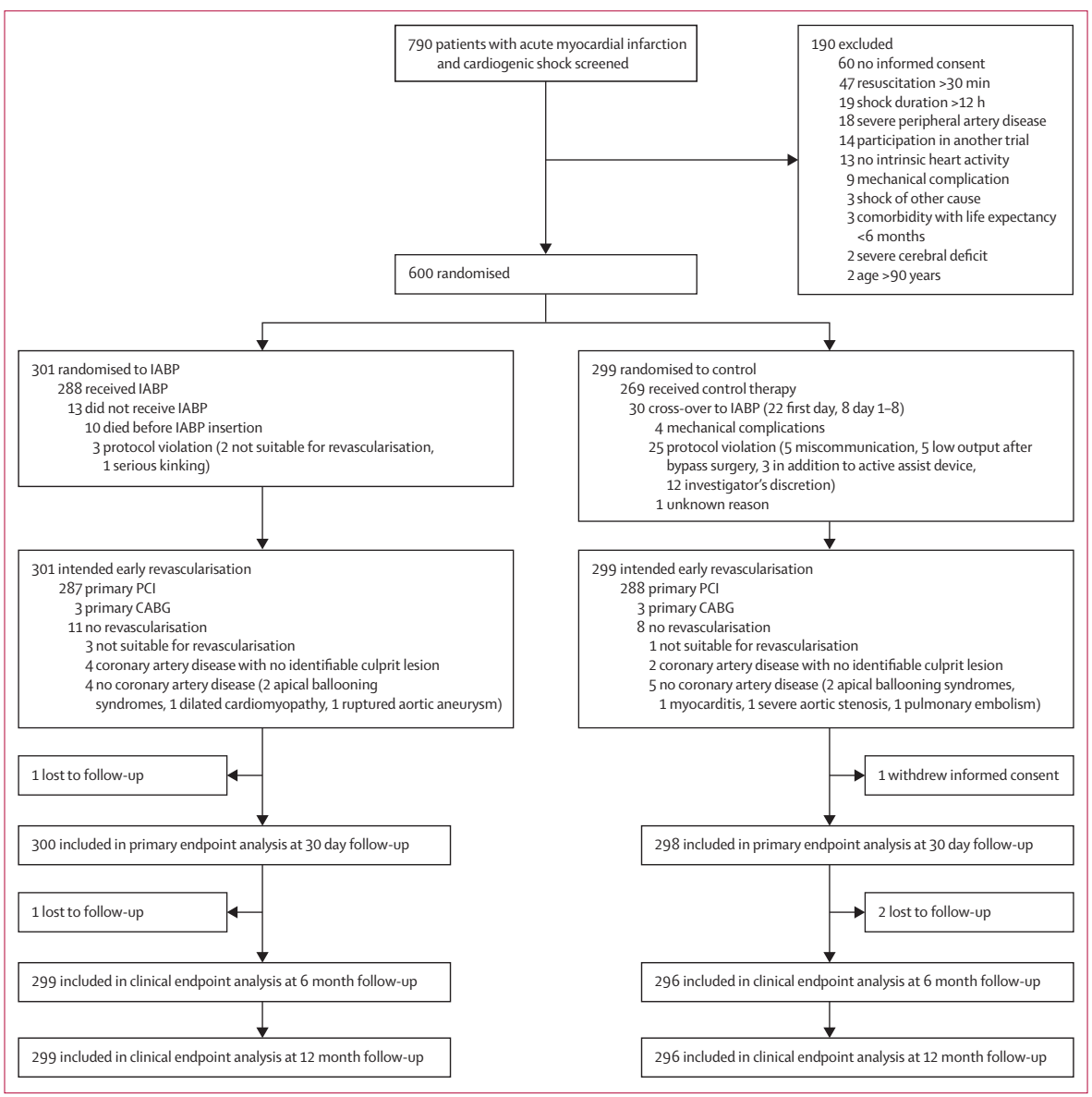

Figure 1: **Trial profile**
IABP=intra-aortic balloon pump. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting.

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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

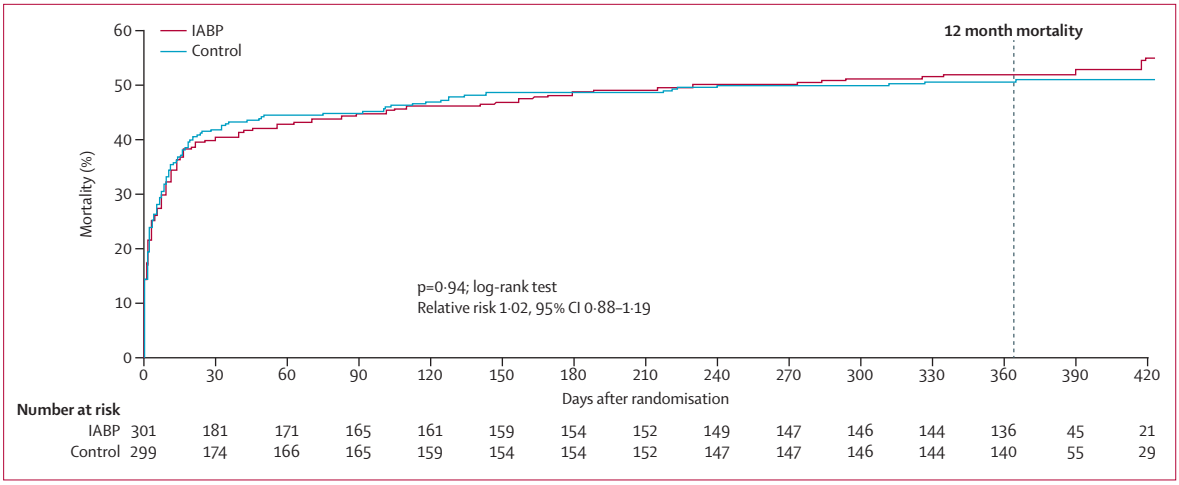

Figure 2: **Time-to-event curves for all-cause mortality up to 12 months**
Event rates represent Kaplan-Meier estimates. Two patients in the IABP group died at days 388 and 419 postrandomisation, which is represented in the Kaplan-Meier curves. IABP=intra-aortic balloon pump.

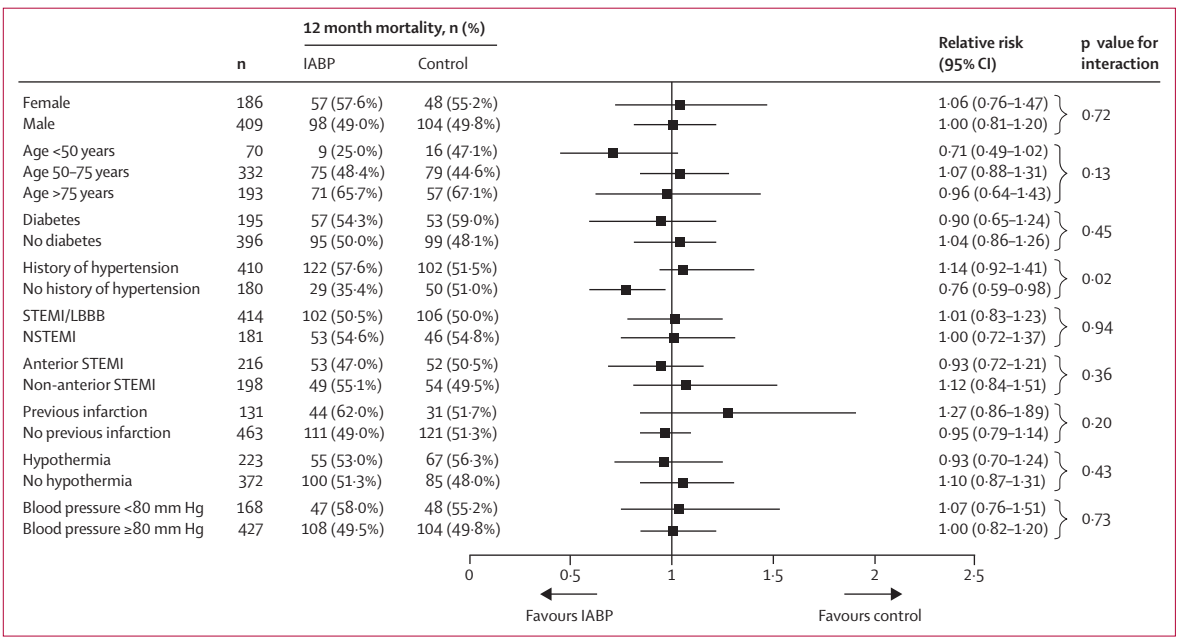

Figure 3: **Subgroup analyses for all patients with 12 month follow-up**
Relative risk and 95% CIs for predefined subgroups and the post-hoc subgroups hypothermia versus no hypothermia and baseline systolic blood pressure less than 80 mm Hg versus 80 mm Hg or higher. STEMI=ST-elevation myocardial infarction. 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

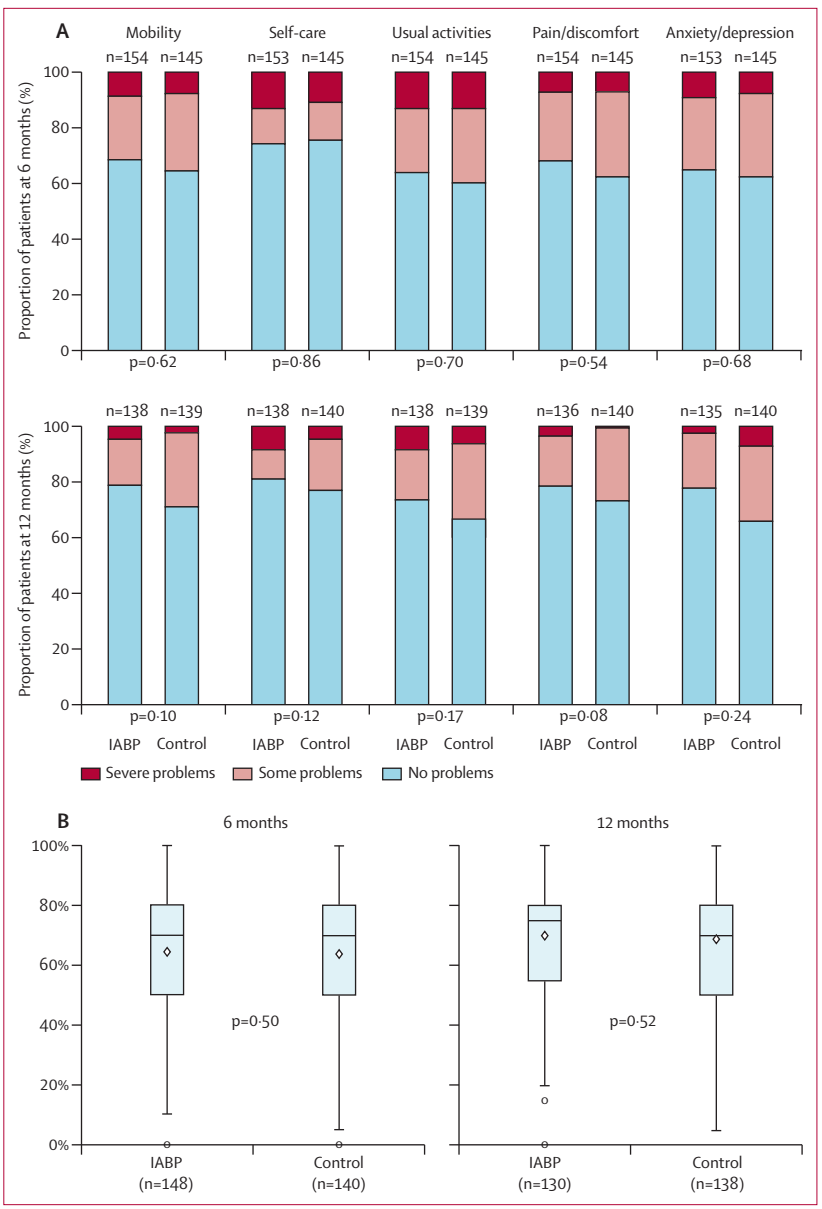

Figure 4: **Quality of life at 6 and 12 month follow-up for patients alive**
(A) Health-related quality of life states in the five dimensions of mobility, self-care, usual activities, pain or discomfort, and anxiety or depression for patients in the IABP and control groups. (B) Box plot of the visual 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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condemning many users to reverting to lethal cigarettes.

We do not think we could have done more to eliminate the risk of our work being used to open the market for nicotine e-cigarettes in New Zealand, as Rehab Auf suggests. Our study was done independently of any industry influence, in a transparent manner. To have adjusted the study sample size in light of the recorded abstinence rates was not possible, because the analysis plan did not allow for interim analyses. Auf asserts the ability of e-cigarettes to reduce the number of cigarettes smoked should not be regarded as a harm reduction measure. The argument rests on a concern that e-cigarettes might be used by people who would not otherwise have used nicotine products. This assertion is founded on the US Centers for Disease Control and Prevention report showing a doubling of e-cigarette use by never smoking US middle school students between 2011 and 2012 in which "use" was defined as greater than or equal to 1 day use in the past 30 days, and only 20% of ever e-cigarette users reported ever using conventional cigarettes.[3]

Christopher Doyle and colleagues imply involvement of the tobacco industry in our trial, which we refute. We do not think that our discussion favoured e-cigarettes over patches or "glossed over" differences in adverse events. We believe our treatment of the data was appropriately conservative. Indeed, we stated that a higher number and proportion of adverse events occurred in the nicotine e-cigarette group than in the patches group.[1]

Dual use is a valid concern. What is as yet unknown is whether it is largely a temporary state before quitting.

We did not suggest that e-cigarettes should be funded for tobacco control in any country, including developing countries, where the tobacco burden is greatest. However, we note that smoking cessation treatment is a recognised element of comprehensive approaches to global tobacco control.[4] E-cigarettes are unlikely to be funded by governments as cessation aids, but if regulated as consumer products they could potentially decrease government spending on smoking cessation medicines.

We declare that we have received no support from any companies for the submitted work and have no non-financial interests that might be relevant to the submitted work. ML, via his company Health New Zealand, previously did research funded by Ruyan (an e-cigarette manufacturer). CB and HM have done research on Ruyan e-cigarettes funded by Health New Zealand, independently of Ruyan. HM has received honoraria for speaking at research symposia, has received benefits in kind and travel support from, and has provided consultancy to, the manufacturers of smoking cessation drugs. NW has provided consultancy to the manufacturers of smoking cessation drugs, received honoraria for speaking at a research meeting and received benefits in kind and travel support from a manufacturer of smoking cessation drugs. JW has provided consultancy to the manufacturers of smoking cessation medications.

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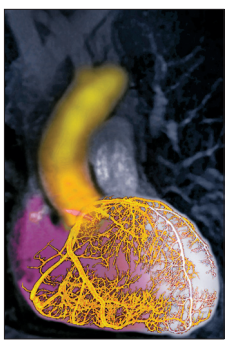
Management of acute myocardial infarction

The ischaemic myocardium should have more priority in the management of acute myocardial infarction.

Krischan Sjauw and Jan Piek[1] recently commented on the IABP-SHOCK trial (Nov 16, p 1638)[2] and correctly stated that the underlying mechanism of cardiogenic shock is depression of myocardial contractility, they argue that this is due to extensive acute myocardial infarction. We take the view that failure of contractility with or without cardiogenic shock is not necessarily determined by the extent of infarction but that both can result from sudden impairment of energy supply.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Tremendous headway has been made by interventionist cardiologists with coronary angiography, insertion of stents, bypass surgery, and the early infusion of thrombolytic agents—all with the aim of improving blood supply. But there have been few interventions directed specifically to the injured myocardium. Yet, it is a functioning myocardium that will determine survival. When there is an excessively high plasma free fatty acid (FFA) concentration, as in early acute myocardial infarction,[3] with inadequate glucose availability, normal oxidative metabolism is no longer possible, so ATP stores run down.

Improvement of coronary artery perfusion will not sustain contractility if the balance of substrates is awry. To put it simply, pumps deprived of energy do not work.

While further research into pharmacological therapy counteracting haemodynamic deterioration is certainly warranted, far more focus is needed on redressing the imbalance in myocardial metabolism that occurs during acute ischaemia. To this end, strategies to reduce adrenaline-stimulated tissue lipolysis and plasma FFA concentrations, such as the use of nicotinic acid analogues,[4] and to increase glucose availability,[5] seem to be the best bet. Glucose-insulin-potassium infusions also reduce circulating FFA by inhibiting its release from adipose tissue, as observed in the IMMEDIATE trial.[5] The focus should be on metabolic measures that maintain myocardial ATP concentrations and availability.

We declare that we have no conflicts of interest.

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Holger Thiele and colleagues[1] reported the 12-month results of intra-aortic balloon pump (IABP) in acute myocardial infarction complicated by cardiogenic shock. IABP effects on cardiogenic shock could be at two levels: on the amount of left ventricular mass affected by infarction and on the vascular peripheral bed tone. The dysfunction of one of these mechanisms would negatively affect the other. We are probably expecting too much of IABP efficacy.

As mentioned in Thiele and colleagues' report,[1] some clinical signs of ischaemic cardiogenic shock (ie, oliguria, serum lactate concentrations, creatinine concentrations, pH) were independent risk factors for mortality.[1] IABP could help if the shock is not already plain and clear; any subsequent increase of cardiac index is indirect—secondary to any improvement of cardiac perfusion and reduced afterload. The powerful reperfusive action of percutaneous coronary intervention could overlap with any myocardial effects of IABP, some other effects are related to the reduction of vascular resistances but during ischaemic cardiogenic shock peripheral vascular tone might be lost. In this scenario, IABP could not work properly.

Another important factor is time. A randomised trial[2] of early in-ambulance thrombolysis versus primary percutaneous coronary intervention showed no ischaemic cardiogenic shock among patients assigned to prehospital thrombolysis. Although time has no effect on 30-day survival, it is associated with the probability of developing ischaemic cardiogenic shock. Among patients randomised in the first 2 h after ischaemic myocardial infarction, cardiogenic shock was less frequent with lytic therapy compared with primary percutaneous coronary intervention, whereas rates were similar in patients randomised later than 2 h.[2] The pathophysiology of ischaemic cardiogenic shock does not allow us to wait until it is clinically clear. Concentrations of interleukin-6 and tumour necrosis factor have been shown to be elevated on admission in patients having myocardial infarction initially in Killip Class I and who later developed ischaemic cardiogenic shock.[3]

We favour an aggressive monitoring of ventricular function not only with haemodynamic data but also with myocardium thickness and contractility by echocardiography to detect initial signs of left ventricular failure, which causes 75% of ischaemic cardiogenic shock.[4,5] Serial echocardiography before ischaemic cardiogenic shock is the best and simplest method for monitoring changes in left ventricular systolic and diastolic function over time after infarction and primary percutaneous coronary intervention because the myocardium might recover function hours or days after reperfusion. Maybe the IABP could be used before it "leaks".

I declare that I have no conflicts of interest.

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Authors' reply

We thank Michael Oliver and Lionel Opie, and Roberto Gaeta for their interest in our work.[1]

Oliver and Opie point out that in the setting of infarct-related cardiogenic shock deregulations in energy supply, especially the accumulation of plasma free fatty acids and impaired glucose metabolism, are major determinants of contractility failure. They further argue that therapies directed towards correction of these metabolic changes (eg, glucose-insulin-potassium infusions) might positively affect clinical outcome. However, in the IMMEDIATE trial[2] of patients with suspected acute coronary syndromes cited by Oliver and Opie, glucose-insulin-potassium infusions did not reduce the rate of progression to myocardial infarction (primary endpoint), nor 30-day mortality, and should therefore not be over-interpreted.[1] We agree that the idea of counteracting metabolic disorders during acute ischaemia is plausible and should be a target for future research.

Gaeta argues that intra-aortic balloon counterpulsation (IABP) might be beneficial in the very early stages of evolving cardiogenic shock before it becomes clinically apparent. To detect the initial onset of shock, he suggests serial echocardiographic monitoring

of left ventricular function. Most patients with a final diagnosis of infarct-related cardiogenic shock already present in shock upon arrival in the hospital—ie, shock develops in the ambulatory setting. For obvious reasons, echocardiographic monitoring is not feasible in these patients. For patients who present in the hospital with acute myocardial infarction without shock we believe that the most important step to prevent progression to cardiogenic shock is prompt reperfusion and not serial echocardiographic monitoring with potential IABP insertion. After early reperfusion, close monitoring for signs of developing cardiogenic shock is indeed mandatory. However, once reperfused, progression to cardiogenic shock in a patient who was initially clinically stable is uncommon. It remains speculative if early IABP is beneficial in the small subset of patients who develop shock in the clinical course after reperfusion. Notably, the IABP-SHOCK II trial exclusively enrolled patients with overt cardiogenic shock (hypotension and signs of impaired organ perfusion).

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Unacceptable commercial interests

In his Offline (Nov 30, p 1768),[1] Richard Horton rightly rails against the acceptance of pharmaceutical and nutritional industry funding and promotion at the recent Developmental Origins of Health and Disease meeting in Singapore. In view of the leadership that Horton and *The Lancet* have shown in raising the profile of global health, the time is ripe for *The Lancet* to consider its own position on unacceptable promotion and the potential influence of commercial concerns, whose first interest is certainly not the health of the world population.

As an example, the US Institute of Medicine sent a copy of the *Lancet* special issue of the Global Burden of Disease Study (GBD) 2010 to members shrink-wrapped with a six-page advertising leaflet for an anti-obesity drug. Presumably, *The Lancet* and its publishers benefitted from this advertising being shrink-wrapped with the journal? It is difficult not to be struck by the coincidence of this advert accompanying the GBD 2010 report, which clearly advanced the notion that obesity and related problems are eclipsing issues such as maternal, infant, and child under nutrition as threats to global health and wellbeing.

We declare that we have no conflicts of interest.

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WHO guidelines on fluid resuscitation in children with shock

Randy Faris/Corbis

Deaths of children in hospitals often occur within 24 h of admission. Many of these deaths could be prevented if very sick children are identified soon after their arrival in the health-care facility and appropriate treatment started immediately. In response to this need, WHO developed and published Emergency Triage Assessment and Treatment guidelines, and included an abbreviated chapter in the *Pocket Book of Hospital Care for Children*, first edition in 2005.

In 2011, the Fluid Expansion as Supportive Therapy (FEAST) study examined the management of children with fever and signs of impaired perfusion in African hospitals and concluded that fluid boluses in children with shock were potentially harmful.[1]

In a comment published in the *BMJ* on Jan 14, 2014,[2] the researchers involved in the FEAST trial criticised WHO for not revising the relevant guidance—notably the *Pocket Book of Hospital Care for Children*, second edition.[3] The *Pocket Book*,[3] which is a compilation of hundreds of WHO recommendations, is widely used by doctors, nurses, and health-care workers responsible for the care of young children at first-level referral hospitals.

The results of the FEAST trial were shared with WHO and the expert group in 2011 (when the reviews for the second edition of the *Pocket Book* were already well underway). The results were clearly important, but several issues had to be taken into consideration before they could be incorporated into policy

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For the **Emergency Triage Assessment and Treatment guidelines** see http://www.who.int/maternal_child_adolescent/documents/9241546875/en/index.html