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Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials

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Aims Studies have compared safety and efficacy of percutaneous left ventricular assist devices (LVADs) with intra-aortic balloon pump (IABP) counterpulsation in patients with cardiogenic shock. We performed a meta-analysis of controlled trials to evaluate potential benefits of percutaneous LVAD on haemodynamics and 30-day survival.

Methods and results Two independent investigators searched Medline, Embase, and Cochrane Central Register of Controlled Trials for all controlled trials using percutaneous LVAD in patients with cardiogenic shock, where after data were extracted using standardized forms. Weighted mean differences (MDs) were calculated for cardiac index (CI), mean arterial pressure (MAP), and pulmonary capillary wedge pressure (PCWP). Relative risks (RRs) were calculated for 30-day mortality, leg ischaemia, bleeding, and sepsis. In main analysis, trials were combined using inverse-variance random effects approach. Two trials evaluated the TandemHeart and a recent trial used the Impella device. After device implantation, percutaneous LVAD patients had higher CI (MD 0.35 L/min/m^2, 95% CI 0.09–0.61), higher MAP (MD 12.8 mmHg, 95% CI 3.6–22.0), and lower PCWP (MD −5.3 mm Hg, 95% CI −9.4 to −1.2) compared with IABP patients. Similar 30-day mortality (RR 1.06, 95% CI 0.68–1.66) was observed using percutaneous LVAD compared with IABP. No significant difference was observed in incidence of leg ischaemia (RR 2.59, 95% CI 0.75–8.97) in percutaneous LVAD patients compared with IABP patients. Bleeding (RR 2.35, 95% CI 1.40–3.93) was significantly more observed in TandemHeart patients compared with patients treated with IABP.

Conclusion Although percutaneous LVAD provides superior haemodynamic support in patients with cardiogenic shock compared with IABP, the use of these more powerful devices did not improve early survival. These results do not yet support percutaneous LVAD as first-choice approach in the mechanical management of cardiogenic shock.

Keywords Cardiogenic shock • Cardiac-assist device • Intra-aortic balloon pump • Outcome • Meta-analysis

Introduction

Cardiogenic shock is a state of inadequate tissue perfusion due to cardiac dysfunction.[1] Despite the fact that prognosis of patients with cardiogenic shock has improved over time due to aggressive reperfusion strategies, in-hospital mortality from cardiogenic shock remains about 50%.[2–8]

Although recent guidelines supported the use of intra-aortic balloon pump (IABP) counterpulsation as method of first choice for mechanical assistance in cardiogenic shock,[1,9] the efficacy of routine IABP use adjunctive to primary percutaneous coronary intervention in cardiogenic shock was recently questioned.[10,11] The recent introduction of percutaneous left ventricular assist devices (LVADs) is very promising since these more powerful devices have the potential to reverse cardiogenic shock and to lower the unacceptably high short-term mortality rates.[12,13] These LVADs might be a better alternative as compared to IABP in the mechanical treatment of cardiogenic shock.[10,14]

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The TandemHeart (TandemHeart, Cardiac Assist, Pittsburgh, PA, USA) is a percutaneous left atrial-to-femoral arterial LVAD, driven by a low-speed centrifugal continuous flow pump.[15] The Impella (Impella LP2.5, Abiomed Europe GmbH, Aachen, Germany) LVAD is a catheter-based, impeller-driven, axial flow pump which pumps blood directly from the left ventricle into the ascending aorta.[13]

Several controlled trials have compared safety and efficacy of these percutaneous LVADs with IABP.[16–18] However, the trials were underpowered to adequately evaluate potential benefit on 30-day outcome. We pooled data from these trials and compared (i) differences in haemodynamic parameters following device implantation, (ii) 30-day mortality, and (iii) adverse events in patients receiving percutaneous LVAD vs. those treated with IABP. Aim of the study was to present an overview on the current status of percutaneous assist devices in the management of cardiogenic shock.

Methods

Trial inclusion

All controlled trials using percutaneous LVAD in patients with cardiogenic shock were included. Follow-up duration had to be at least 30 days. Using Cochrane Central Register of Controlled Trials, Embase, and Medline (Pubmed U.S. National Library of Medicine), we performed a literature search from inception to April 2009 using the following search terms: 'heart-assist device' OR 'shock, cardiogenic', as well as using the terms separately as text words.[19] A methodological filter was used to limit the results to clinical trials in humans.[19] No language restrictions were used. Two investigators (J.M.C. and C.A.U.) then independently retrieved potentially eligible reports for evaluation. Both investigators independently examined design, patient population, and interventions in the reports. In case of disagreement, this was resolved in consultation with a third reviewer (R.T.D.). Trials without control group and trials using surgical LVADs were excluded. In addition, references of included trials were checked, www.clinicaltrials.gov was searched, conference proceedings were checked. and experts were contacted to ensure that no potentially eligible studies were missed. Quality of the reports was assessed in terms of randomization, adequateness of sequence generation, concealment of allocation, blinding, and handling of patient attrition.[20,21] Data were extracted by two independent investigators (J.M.C. and C.A.U.) using standardized forms.

Study outcomes

Thirty-day all-cause mortality was a priori specified as our primary clinical outcome, as this is the most common clinical endpoint in the literature on cardiogenic shock. Secondary outcomes were the following prespecified haemodynamic parameters: cardiac index (CI), mean arterial pressure (MAP), and pulmonary capillary wedge pressure (PCWP), all measured within 2 h after device implantation. Safety outcomes were chosen a posteriori, and included the following reported device-related adverse events during support: leg ischaemia, major bleeding, and fever and/or sepsis. On the basis of incomplete data reported in the studies, we also evaluated occurrence of thrombocytopenia and haemolysis when reported.

Statistical analysis

All data were analysed with MIX (MIX 1.7, Kitasato Clinical Research Center, Sagamihara, Kanagawa, Japan)[22] and SPSS (SPSS 15.0, SPSS Inc., Chicago, IL, USA) software. Categorical variables were presented in numbers and in percentages. Continuous variables were presented as mean $\pm$ standard deviation. For continuous variables reported as median and interquartile range, the mean and standard deviation were estimated. The mean was estimated by the formula $x = (a + 2m + b)/4$ using the values of the median (m), P25 and P75 (a and b, respectively).[23] The estimator sd = IQR/1.35 was used to estimate standard deviation (sd) from the interquartile range (IQR).[21] Weighted mean difference (MD) was used to compare continuous variables and was calculated for the pooled study population. The final results were presented as weighted MD with the associated 95% CI. Relative risk (RR) of unadjusted 30-day mortality and adverse events was calculated for each study and for the pooled study population. The final results were presented as unadjusted RR with the associated 95% CI. Heterogeneity between trials, defined as variation among the results of individual trials beyond that expected from chance, was assessed with Cochran's Q-statistic and I^2 statistic. Both inverse variance weighted fixed effect model and a random effects model were used for comparison based on MD and RR. Conclusions were drawn based on the random effects models. All statistical tests were analysed two-tailed and a P-value of <0.05 was considered statistically significant.

Results

Three trials met our inclusion criteria and were included in this study (*Figure 1*). Study characteristics are presented in *Table 1*. All three trials randomly assigned patients to treatment with percutaneous LVAD or IABP counterpulsation. Two randomized controlled trials compared the TandemHeart device with IABP,[16,17] and one randomized controlled trial compared the Impella with IABP counterpulsation.[18] One trial reported adequate sequence generation,[16] while two trials omitted description of methods for sequence generation.[17,18] Methods for allocation concealment were not adequately reported. Complete follow-up was available in all included trials.

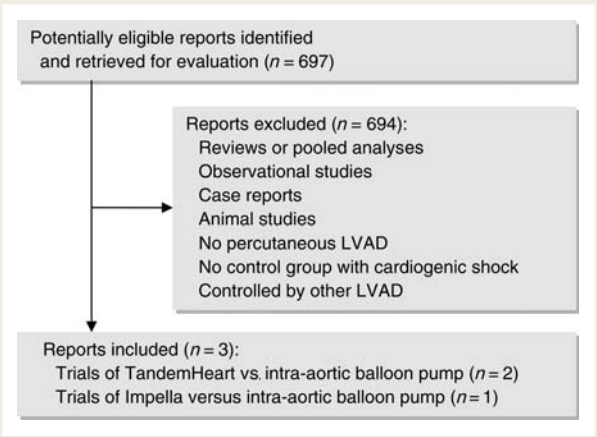

Figure 1 Identification of trials. LVAD, left ventricular assist device.

Baseline characteristics

Baseline characteristics and baseline haemodynamic parameters of patients included in the randomized controlled trials are presented in *Table 2*. In the study by Thiele *et al.*[16] 41 patients with revascularized acute myocardial infarction complicated by cardiogenic shock were included for randomization (21 patients assigned to LVAD and 20 patients assigned to IABP). Burkhoff *et al.*[17] randomized 33 patients with cardiogenic shock caused by acute myocardial infarction or decompensated chronic heart failure (19 patients assigned to LVAD and 14 patients assigned to IABP). Seyfarth *et al.*[18] randomized 26 patients with acute myocardial infarction complicated by cardiogenic shock (13 patients assigned to LVAD and 13 patients assigned to IABP).[18] In total, 100 patients were included for meta-analysis, of whom 53 patients were treated with LVAD and 47 patients were treated with IABP. Almost all patients were treated with inotropes or vasopressors, mechanical ventilation, and percutaneous coronary intervention.

Table 1 Study characteristics of included trials

	Thiele *et al.*[16]	Burkhoff *et al.*[17]	Seyfarth *et al.*[18]
Percutaneous LVAD used	TandemHeart	TandemHeart	Impella LP2.5
Control	IABP	IABP	IABP
Total number of patients	41	33	26
Setting	Single-centre	Multi-centre	Two-centre
Inclusion period	2000–2003	2002–2004	2004–2007
Randomization	Yes	Yes	Yes
Sequence generation	Drawing envelopes	Not reported	Not reported
Concealment of allocation	Sealed envelopes[a]	Not reported	Not reported
Blinding	Not possible	Not possible	Not possible
Handling of patient attrition	Complete follow-up	Complete follow-up	Complete follow-up

[a]Not reported whether the envelopes were opaque and sequentially numbered.
IABP, intra-aortic balloon pump; LVAD, left ventricular assist device.

Haemodynamic parameters following device implantation

Haemodynamic parameters measured after device implantation as well as results obtained from both fixed effect models and random effects models showing the pooled MDs between haemodynamic parameters of LVAD patients compared with IABP patients are presented in *Table 3*. In the random effects model, patients treated with a percutaneous LVAD had higher CI (MD 0.35 L/min/m^2, 95% CI 0.09–0.61, $P < 0.01$), higher MAP (MD 12.8 mmHg, 95% CI 3.6–22.0, $P < 0.01$), and lower PCWP (MD −5.3 mmHg, 95% CI −9.4 to −1.2, $P < 0.05$) compared with patients treated with IABP (*Figure 2*).

Table 2 Baseline characteristics

	Thiele *et al.*[16]		Burkhoff *et al.*[17]		Seyfarth *et al.*[18]	
	LVAD ($n = 21$)	IABP ($n = 20$)	LVAD ($n = 19$)	IABP ($n = 14$)	LVAD ($n = 13$)	IABP ($n = 13$)
Age, years ± SD	63 ± 10	66 ± 10	66 ± 14	60 ± 11	65 ± 10	67 ± 19
Male, *n* (%)	16 (76)	15 (75)	14 (74)	9 (64)	8 (62)	11 (85)
Hypertension, *n* (%)	19 (90)	15 (75)			7 (54)	9 (69)
Diabetes mellitus, *n* (%)	11 (52)	11 (55)			5 (39)	3 (23)
Smoking, *n* (%)	9 (43)	6 (30)			8 (62)	7 (54)
Hypercholesterolaemia, n (%)	11 (52)	9 (45)			8 (62)	7 (54)
Multivessel disease, *n* (%)	13 (62)	14 (70)			9 (69)	10 (77)
LVEF ± SD (%)	26 ± 9	27 ± 7	19 ± 14	22 ± 9	28 ± 14	31 ± 16
AMI, *n* (%)	21 (100)	20 (100)	11 (58)	10 (71)	13 (100)	13 (100)
Anterior MI, *n* (%)	18 (86)	13 (65)			7 (54)	8 (62)
Peak creatine kinase (U/L) ± SD	5307 ± 4297	4395 ± 3987			4067 ± 6104	4971 ± 5211
Inotropes or vasopressors, *n* (%)	21 (100)	20 (100)	19 (100)	14 (100)	11 (84)	12 (92)
Mechanical ventilation, *n* (%)	20 (95)	20 (100)			12 (92)	12 (92)
Primary PCI, *n* (%)	20 (95)	19 (95)			12 (92)	12 (92)
Haemodynamics						
CI ± SD (L/min/m^2)	1.8 ± 0.4	1.6 ± 0.5	1.8 ± 0.4	1.8 ± 0.6	1.7 ± 0.5	1.7 ± 0.6
MAP ± SD (mmHg)	62 ± 14	65 ± 13	70 ± 16	67 ± 15	78 ± 16	72 ± 17
PCWP ± SD (mmHg)	20 ± 4	26 ± 7	25 ± 8	28 ± 6	22 ± 8	22 ± 7

AMI, acute myocardial infarction; CI, cardiac index; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; PCI, percutaneous coronary intervention; PCWP, pulmonary capillary wedge pressure.

Table 3 **Meta-analysis of outcomes**

	Thiele *et al.*[16]		Burkhoff *et al.*[17]		Seyfarth *et al.*[18]		Pooled (fixed effect model)			Pooled (random effects model)		
	LVAD (*n* = 21)	**IABP (*n* = 20)**	**LVAD (*n* = 19)**	**IABP (*n* = 14)**	**LVAD (*n* = 13)**	**IABP (*n* = 13)**	**Mean difference/ relative risk**		***P*-value**	**Mean difference/ relative risk**		***P*-value**
Haemodynamics												
CI ± SD (L/min/m^2)	2.3 ± 0.6	1.8 ± 0.4	2.2 ± 0.6	2.1 ± 0.2	2.2 ± 0.6	1.8 ± 0.7	0.35	(0.14; 0.55)	<0.001	0.35	(0.09; 0.61)	<0.01
MAP ± SD (mmHg)	76 ± 10	70 ± 16	91 ± 16	72 ± 12	87 ± 18	71 ± 22	12.1	(6.3; 17.9)	<0.001	12.8	(3.6; 22.0)	<0.01
PCWP ± SD (mmHg)	16 ± 5	22 ± 7	16 ± 4	25 ± 3	19 ± 5	20 ± 6	−6.2	(−8.0; −4.3)	<0.001	−5.3	(−9.4; −1.2)	<0.05
Clinical outcome												
30-day mortality, *n* (%)	9 (43)	9 (45)	9 (47)	5 (36)	6 (46)	6 (46)	1.06	(0.68; 1.66)	0.80	1.06	(0.68; 1.66)	0.80
Reported adverse events												
Leg ischaemia, *n* (%)	7 (33)	0 (0)	4 (21)	2 (14)	1 (8)	0 (0)	2.59	(0.75; 8.97)	0.13	2.59	(0.75; 8.97)	0.13
Bleeding, *n* (%)	19 (90)	8 (40)	8 (42)	2 (14)			2.35	(1.40; 3.93)	<0.01	2.35	(1.40; 3.93)	<0.01
Fever of sepsis, *n* (%)	17 (81)	10 (50)	4 (21)	5 (36)			1.38	(0.88; 2.15)	0.16	1.11	(0.43; 2.90)	0.83

CI, cardiac index; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure.

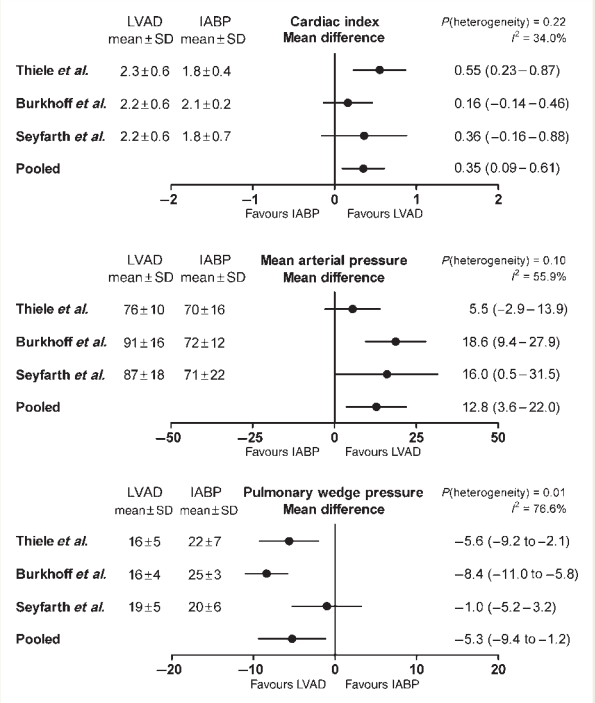

Figure 2 Meta-analysis showing the mean difference in haemodynamic parameters with use of percutaneous left ventricular assist devices. Random effects models were used for meta-analysis. Weighted mean differences with 95% confidence intervals are presented on the right of the figure. IABP, intra-aortic balloon pump; LVAD, left ventricular assist device.

30-Day mortality

Reported absolute 30-day all-cause mortality as well as results obtained from both fixed effect model and random effects model showing the RR are presented in *Table 3*. In the pooled study population, 24 patients (45%) treated with LVAD and 20 patients (43%) treated with IABP did not survive 30 days of follow-up ($P = 0.80$). The pooled estimate of the RR revealed no significant difference in 30-day mortality using percutaneous LVAD compared with IABP (RR 1.06, 95% CI 0.68–1.66) (*Figure 3*).

Adverse events

Reported adverse events as well as results obtained from both fixed effect models and random effects models showing the RR are presented in *Table 3*. Using a random effects model, similar incidence rates of leg ischaemia were observed using percutaneous LVAD when compared with IABP (RR 2.59, 95% CI 0.75–8.97, $P = 0.13$) (*Figure 4*). Bleeding (RR 2.35, 95% CI 1.40–3.93, $P < 0.01$) was more frequently reported as a complication related to the TandemHeart. Furthermore, Thiele *et al.* reported that fresh frozen plasma ($P < 0.01$) and platelets ($P < 0.05$) were more often required in the TandemHeart group. However, Burkhoff *et al.* found no significant difference in thrombocytopenia, but these investigators did find a trend towards more haemolysis with higher peak values in plasma-free haemoglobin in patients treated with the Tandemheart ($P = 0.10$).

No reports were found on Impella-related incidence of bleeding and fever and/or sepsis. However, a trend was reported for more packed red blood cells (Impella 2.6 ± 2.7 units vs. IABP 1.2 ± 1.9 units, $P = 0.2$) and fresh frozen plasma (Impella 1.8 ± 2.5 units vs. IABP 1.0 ± 1.7 units, $P = 0.4$) administered to Impella patients. Haemolysis was assessed by measurements of free haemoglobin, which was significantly higher in Impella patients ($P < 0.05$).

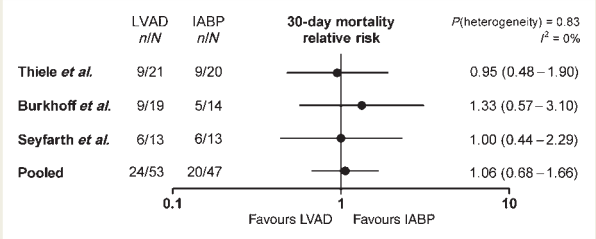

Figure 3 Meta-analysis showing the relative risk of crude 30-day mortality with use of percutaneous left ventricular assist devices. Random effects model was used for meta-analysis. Relative risks with 95% confidence intervals are presented on the right of the figure. IABP, intra-aortic balloon pump; LVAD, left ventricular assist device.

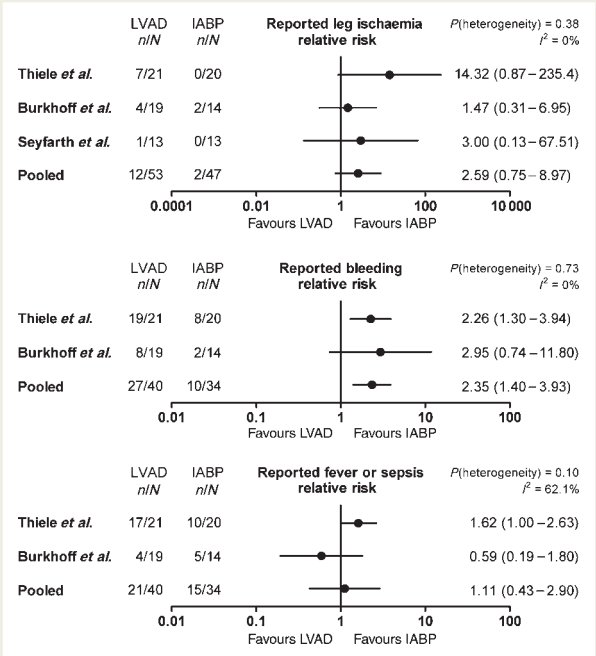

Figure 4 Meta-analysis showing the relative risk of adverse events with use of percutaneous left ventricular assist devices. Random effects models were used for meta-analysis. Relative risks with 95% confidence intervals are presented on the right of the figure. IABP, intra-aortic balloon pump; LVAD, left ventricular assist device.

Discussion

This is the first meta-analysis of controlled trials comparing percutaneous LVAD with IABP, presenting a survey of available data. Our main findings were 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. Moreover, patients treated with a percutaneous LVAD tended to have a higher incidence of leg ischaemia and device-related bleeding.

The main limitation of an IABP is the lack of active cardiac support: the IABP requires a certain residual level of left ventricular function. As an alternative, percutaneous LVADs are promising devices since these provide active circulatory support. This meta-analysis indeed confirms that a percutaneous LVAD is a more powerful device than IABP, which is clearly reflected by a better haemodynamic profile after implantation.

Although both types of percutaneous LVADs improved the haemodynamic profile, it is disappointing that both devices did not improve 30-day outcome when compared with current routine treatment including IABP. Besides, it is important to note that both percutaneous LVADs are currently about 10 times as expensive as an IABP catheter.

We reported similar complication rates within both types of percutaneous LVADs. However, it might be possible that the Impella is a safer device than the TandemHeart due to its smaller catheter size, potentially resulting in a lower incidence of leg ischaemia or groin bleeding,[24] although this is not clearly demonstrated by this meta-analysis. 17 French cannulas were used in TandemHeart patients and 13 French sheaths were used in Impella patients, whereas most IABPs are currently introduced using 8 French sheaths. Although the way of vascular closure was not consistently reported in the trials, this could also be a factor involved in the development of vascular complications. Whether haemolysis is a clinically significant problem associated with Impella use, has to be investigated further.

Some limitations of our meta-analysis need to be acknowledged. First, we compared different types of percutaneous LVADs (i.e. TandemHeart and Impella) with IABP. However, there was no heterogeneity between TandemHeart and Impella studies in 30-day mortality and in most secondary study outcomes. Because the small number of trials included could possibly lead to a type II error of the heterogeneity test, all conclusions were based on results obtained from random effects models. Second, the number of patients included in this meta-analysis was small. However, we included all available trials and we did not even observe a trend in a reduced 30-day mortality rate associated with LVAD use. The results from this meta-analysis suggest that potential benefit of percutaneous LVADs on 30-day survival might be very limited. Owing to the small sample size, there is a probability of missing a clinically meaningful benefit if one exists (type II error).[25] However, given a total sample size of 100 patients, an observed *P*-value (α) of 0.80, and a presumed effect size of at least 10% (event rate of 45% in IABP patients and 40% in percutaneous LVAD patients), *post hoc* analysis showed that the probability for type II error (β) does not exceed 12%. A third limitation was that we did not have access to individual patient data. It may be very well possible that subgroups of cardiogenic shock patients might benefit from percutaneous LVAD therapy, but we could not perform these analyses given the limited number of patients included in the currently available reports. A final limitation was that the included trials were not described in sufficient detail to judge adequateness of randomization, so that we were not able to exclude the potential risk of bias in these trials.

Hopefully, further technical improvements on percutaneous LVAD systems, together with enhanced experience with these devices, will improve prognosis of cardiogenic shock patients in the future. A larger, adequately powered, randomized controlled trial using the Impella device is necessary to provide more definite information about potential benefit on 30-day survival. Some investigators have shown the feasibility of introduction of surgical LVADs in patients with acute myocardial infarction complicated by cardiogenic shock.[26] A major problem of implanting a surgical LVAD includes apical cannulation in infarcted myocardium. The recent development of a micropump, inserted via a mini-thoracotomy and providing substantial left ventricular support, is very promising, but has to be investigated in larger studies and in the setting of cardiogenic shock.[27]

In conclusion, in patients presenting with cardiogenic shock, the use of a percutaneous LVAD provides superior haemodynamic support compared with the use of IABP. However, a better haemodynamic profile associated with percutaneous LVAD use did not result into a reduced 30-day mortality rate. Furthermore, a higher rate of adverse events was encountered by the higher invasive nature of LVAD, especially of the TandemHeart device. Larger randomized controlled trials using the Impella device are needed to better evaluate clinical outcome and adverse events. Until now, we cannot recommend to replace IABP counterpulsation by the more powerful percutaneous LVAD for the treatment of cardiogenic shock patients who do not respond sufficiently to pharmacologic therapy.

Conflict of interest: none declared.

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