

Two year adverse outcomes of the magnetic levitated centrifugal continuous flow circulatory pump versus the axial continuous-flow pump for advanced heart failure

A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Due to advances in technology and medical devices, intra-thoracic left ventricular assisted devices such as the fully magnetically levitated centrifugal-flow pump may now prolong the life of patients with advanced heart failure. However, several concerns have been raised about pump thrombosis and durability of the device. We aimed to systematically compare the two year outcomes of magnetic levitated centrifugal continuous flow circulatory pump versus the axial continuous flow pump for advanced heart failure.

Methods: Following the PRISMA guideline, online databases were searched for relevant trials based on centrifugal continuous flow circulatory pump and axial continuous flow pump in patients with advanced heart failure. The adverse clinical outcomes reported at 2 years follow-up were considered as the endpoints. This analysis was carried out by the RevMan 5.3 software whereby odds ratios (OR) and 95% confidence intervals (CI) were generated.

Results: A total number of 1011 patients with advanced heart failure was included. At 2 years, pump thrombosis was not significantly different between the two groups, with OR: 0.43, 95% CI: 0.06-3.29; P=.42. However, pump replacement was significantly higher with the axial continuous-flow pump with OR: 0.36, 95% CI: 0.15-0.84; P=.02. Stroke, sepsis and bleeding events were not significantly different. In addition, outcomes such as right heart failure, cardiac arrhythmia, the need for right ventricular assisted device, respiratory failure, renal failure and hepatic dysfunction were also not significantly different.

Conclusions: At a follow-up time period of 2 years, pump replacement was significantly higher with the axial continuous-flow pump in comparison to the magnetic levitated centrifugal continuous flow circulatory pump. However, no significant difference was observed with the other adverse outcomes.

Abbreviations: AHF = advanced heart failure, CI = confidence intervals, INR = International normalized ratio, LVAD = left ventricular assisted device, OR = odds ratios.

Keywords: advanced heart failure, axial continuous flow pump, centrifugal continuous flow circulatory pump, pump replacement, pump thrombosis, right heart failure, sepsis, stroke

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BT and HY contributed equally to this work and they are co-first authors.

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All data and materials used in this research are freely available in electronic databases (MEDLINE, EMBASE, Cochrane database, http://www.ClinicalTrials. gov). References have been provided.

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1. Introduction

Heart Failure is becoming a critical concern in this aging population.^[1] Any acute or chronic diseased condition can lead to heart failure and death in advanced cases. Due to advances in technology and medical devices, intra-thoracic left ventricular assisted devices^[2] such as the fully magnetically levitated centrifugal-flow pump are expected to prolong the life of patients with advanced heart failure. However, several concerns have been raised about pump thrombosis and durability of the device.

In 2016, the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3) showed that the fully magnetically levitated centrifugal-flow pump device was not associated with pump thrombosis at 6 months follow-up, and pump malfunction was not a major issue.^[2] However, the device was seldom assessed on a long-term basis.

Since the MOMENTUM 3 Trial was continued up to two years, and other trials which were based on a 2 year follow-up time period were also recently published, we aimed to systematically compare the two year outcomes of centrifugal continuous flow circulatory pump versus the axial continuous flow pump for advanced heart failure through this meta-analysis.

2. Methods

2.1. Searched databases and searched strategies

This analysis was based on studies which were randomized controlled trials, and therefore, the Preferred Reporting Items for Systematic Reviews and Meta-analyzes (PRISMA) guideline was followed during the search of studies.^[3]

Electronic/Online databases including the bibliographic database of life sciences and biomedical information: Medical Literature Analysis and Retrieval System Online (MEDLINE), the biomedical and pharmacological bibliographic database of published literature designed to support information managers and pharmacovigilance: Excerpta Medica dataBASE (EMBASE), Cochrane Central and http://www.ClinicalTrials.gov were carefully searched for relevant trials based on centrifugal continuous flow circulatory pump and axial continuous flow pump in patients with advanced heart failure by using the following searched terms:

- (a) Centrifugal continuous flow circulatory pump versus axial continuous flow pump;
- (b) Magnetic levitated centrifugal continuous flow circulatory pump versus axial continuous flow pump;
- (c) Centrifugal continuous flow circulatory pump and advanced heart failure;
- (d) Axial continuous flow pump and advanced heart failure;
- (e) Centrifugal continuous flow circulatory pump;
- (f) Axial continuous flow pump;
- (g) Magnetic levitated centrifugal continuous flow circulatory pump;
- (h) Magnetic levitated centrifugal continuous flow circulatory pump and advanced heart failure;
- (i) Advanced heart failure and circulatory flow pump;
- (j) Continuous flow left ventricular assisted devices;
- (k) Left ventricular assisted device (LVAD) and advanced heart failure;
- (l) Heart failure and assisted ventricular devices;

- (m) LVAD and heart failure;
- (n) LVAD and advanced heart failure.

Each of the above mentioned electronic databases [MEDLINE, EMBASE, Cochrane Central, http://www.ClinicalTrials.gov] was searched for relevant English publications using the respective above mentioned search terms.

2.2. Inclusion and exclusion criteria

Trials were included if:

- (a) They compared centrifugal continuous flow circulatory pump versus axial continuous flow pump;
- (b) They involved only patients with advanced heart failure;
- (c) They reported adverse clinical outcomes;
- (d) They had a follow-up time period of two years.

Trials were excluded if:

- (a) They were review articles, meta-analyses, observational studies or case-control studies;
- (b) They did not involve patients with advanced heart failure;
- (c) They did not report adverse clinical outcomes;
- (d) They had a follow-up time period of less than 2 years;
- (e) They were duplicated trials.

2.3. Types of participants, outcomes and follow-up time periods

All the participants which were included in this analysis were patients with advanced heart failure.

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The outcomes which were assessed included (Table 1):

- (a) Pump thrombosis;
- (b) Pump replacement;
- (c) Any stroke;
- (d) Ischemic stroke;
- (e) Hemorrhagic stroke;
- (f) Other neurological events;
- (g) Any bleeding;
- (h) Bleeding requiring re-operation;

Table 1

Types of participants,	outcomes reported and follow-up time periods.
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Trials	Outcomes reported	Follow-up time period	Type of patients
Mehra, 2018 ^[5]	Suspected or confirmed pump thrombosis, pump thrombosis resulting in re-operation	2 years	Advanced heart failure
	for pump replacement or removal of device, any stroke, hemorrhagic stroke, ischemic		
	stroke, disabling stroke, other neurological event, any bleeding, bleeding requiring		
	surgery, gastrointestinal bleeding, sepsis, LVAD drive-line infection, local infection not		
	associated with LVAD, right heart failure, any cardiac arrhythmia, ventricular arrhythmia,		
	supraventricular arrhythmia, respiratory failure, renal dysfunction, hepatic dysfunction		
Rogers, 2017 ^[6]	Bleeding events, bleeding events requiring re-operation, bleeding events requiring	2 years	Advanced heart failure
	transfusion, gastrointestinal bleeding, cardiac arrhythmia, hepatic dysfunction, sepsis,		
	Drive-line-exit-site infection, stroke, ischemic cerebrovascular event, hemorrhagic		
	cerebrovascular event, renal dysfunction, respiratory dysfunction, right heart failure,		
	need for right ventricular assist device, pump replacement, pump replacement owing to		
	pump thrombosis, device malfunction or failure, death		
Slaughter, 2009 ^[7]	Pump replacement, stroke, ischemic stroke, hemorrhagic stroke, LVAD-related infection,	2 years	Advanced heart failure
	local-non-LVAD infection, sepsis, bleeding, bleeding requiring blood transfusion,		
	bleeding requiring surgery, other neurologic event, right heart failure, managed with		
	right ventricular assisted device, cardiac arrhythmia, respiratory failure, renal failure,		
	hepatic dysfunction, LVAD thrombosis		

LVAD = left ventricular assisted device.

- (i) Bleeding requiring blood transfusion;
- (j) Gastrointestinal bleeding;
- (k) Sepsis;
- (l) Left ventricular assisted device (LVAD) drive-line infection;
- (m) Local infection not associated with LVAD;
- (n) Right heart failure;
- (o) Any cardiac arrhythmia;
- (p) Need for right ventricular assisted device;
- (q) Respiratory failure;
- (r) Renal failure;
- (s) Hepatic dysfunction.

A follow-up time period of 2 years was considered relevant to this analysis.

2.4. Data extraction and quality assessment

Relevant data including the patients' enrollment time period, the total number of participants assigned to the experimental and control groups, the baseline features of the participants, the total number of events reported, the outcomes which were assessed and the follow-up time periods were independently extracted by two reviewers (BT and HY).

Any disagreement which followed was resolved by consensus. Quality assessment was carried out with reference to the criteria suggested by the Cochrane Collaboration.^[4]

2.5. Statistical analysis

This analysis was carried out by the RevMan 5.3 software whereby odds ratios (OR) and 95% confidence intervals (CI) were generated.

Heterogeneity was assessed by:

- The Q statistic test whereby a *P* value less than .05 was considered as statistically significant;
- The I² statistic test whereby the heterogeneity was increased with an increased I² value; that is, the lower the I² value, the lower the heterogeneity.

A fixed effects model ($I^2 < 50\%$) or a random effects model ($I^2 > 50\%$) was used based on the I^2 value which was obtained.

In addition, sensitivity analysis was carried out by an exclusion method, whereby each study was excluded one by one and a new analysis was carried out each time to ensure that consistent results were obtained throughout.

Since this analysis included a small volume of study, publication bias was visually assessed through funnel plots which were generated by the RevMan software.

2.6. Ethical approval

This meta-analysis was based on previously conducted studies and did not contain any studies with human participants or animals performed by any of the authors.

3. Results

3.1. Searched outcomes

A total number of 265 publications were obtained. Following an initial assessment, 237 publications were eliminated since they were not related to the scope of this research. Twenty-eight (28) full-text articles were assessed for eligibility.

Further eliminations following assessment of the full-text articles were due to the following reasons:

- They were review articles (n=2);
- They were not based on the comparison of centrifugal flow circulatory pump versus the axial continuous flow pump (n = 14);
- They did not report the adverse clinical outcomes (n=2);
- They had a follow-up time period of less than 2 years (n=1);
- They were duplicated trials (n=6).

Finally, only three (3) trials^[5-7] were selected and confirmed for this meta-analysis as shown in Figure 1.

3.2. General and baseline features of the participants

A total number of 1011 patients with advanced heart failure was included in this analysis whereby 621 participants were assigned to the centrifugal continuous flow circulatory pump whereas 390 participants were assigned to the axial continuous flow pump as shown in Table 2. All the three studies were randomized controlled trials and the time period for patients' enrollment was between years 2005 and 2015.

Following the bias risk assessment with reference to the Cochrane Collaboration, all the trials were allotted a grade A which implied a low risk of bias as shown in Table 2.

The baseline features of the participants were listed in Table 3. The patients had a mean age ranging from 59.0 to 66.2 years. Most of the participants were male patients with advanced heart failure having an average left ventricular ejection fraction ranging from 16.2 to 17.4%. The percentage of patients with ischemic cause of heart failure, with a history of stroke or atrial fibrillation, bridging for cardiac transplantation and their respective cardiac index which were reported in the original studies were listed in Table 3. According to Table 3, there was no significant difference in baseline features observed between patients who were assigned to either of the two groups.

The recommended anticoagulants which were used included: daily aspirin (81 mg to 100 mg) and warfarin monitored by an International Normalized Ratio (INR) between 2.0 and 3.0.

The frequency of regular follow-up was at 1 month, then 3 months, then 6 months after discharge, and then every 6 months until 2 years (Study Mehra2018).

3.3. Main results of this analysis

At 2 years, when centrifugal continuous flow circulatory pump was compared with the axial continuous-flow pump in patients with advanced heart failure, pump thrombosis was not significantly different between the two groups, with OR: 0.43, 95% CI: 0.06–3.29; P = .42 (Fig. 2). However, pump replacement was significantly higher with the axial continuous-flow pump with OR: 0.36, 95% CI: 0.15–0.84; P = .02 as shown in Figure 2.

At 2 year follow-up, stroke including 'any stroke' (OR: 1.32, 95% CI: 0.40 - 4.35; P = .65), ischemic stroke (OR: 1.14, 95% CI: 0.37 - 3.54; P = .82) and hemorrhagic stroke (OR: 1.40, 95% CI: 0.36 - 5.46; P = .62) were not significantly different with either the centrifugal flow circulatory or the axial continuous-flow pump as shown in Figure 3. Other neurological events were also not significantly different (OR: 1.57, 95% CI: 1.01 - 2.44; P = .05) as shown in Figure 4.

In addition, sepsis, left ventricular assisted device (LVAD) drive-line infection, and local infection not associated with LVAD

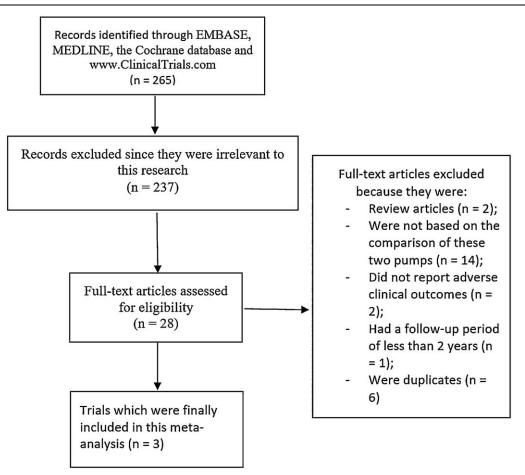


Figure 1. Flow diagram representing the study selection.

Table 2					
The General Featu	res of the trials.				
	Type of	No of patients	No of patients	Year of	Bias risk

	Type of	No of patients	No of patients	Year of	Bias risk
Trials	study	with CCFCP (n)	with ACFP (n)	patients' enrollment	score
Mehra, 2018	RCT	190	176	2014–2015	А
Rogers, 2017	RCT	297	148	2010-2012	А
Slaughter, 2009	RCT	134	66	2005–2007	А
Total no of patients (n)		621	390		

ACFP = axial continuous-flow pump, CCFCP = centrifugal continuous flow circulatory pump, RCT = randomized controlled trials.

Table 3	
Baseline features of the participants.	

Features	Mehra, 2018	Rogers, 2017	Slaughter, 2009
	CP/FP	CP/FP	CP/FP
Age (years)	61.0/59.0	63.9/66.2	62.0/63.0
Males (%)	78.9/81.2	76.4/77.7	81.0/92.0
LVEF (%)	17.2/17.4	17.1/16.2	17.0/16.8
ICHF (%)	42.1/50.0	57.9/60.1	66.0/68.0
HOS (%)	8.40/11.4	19.2/16.2	16.0/17.0
Cardiac Index	2.0/2.0	-	2.0/2.1
HAF (%)	42.6/47.2	-	-
BTT (%)	25.8/23.9	_	-

BTT=bridge to transplantation, CP=centrifugal continuous flow circulatory pump, FP=axial continuous-flow pump, yrs: years, HAF=history of atrial fibrillation, HOS=history of stroke, ICHF= ischemic cause of heart failure, LVEF=left ventricular ejection fraction. Note that cardiac index was measured in liters/min/m² of body-surface area.

were also not significantly different at 2 years follow-up with OR: 1.19, 95% CI: 0.86–1.65; P=.29, OR: 1.24, 95% CI: 0.84–1.84; P=.28 and OR: 1.24, 95% CI: 0.93–1.65; P=.15 respectively as shown in Figure 4.

Moreover, similar events representing 'any bleeding' and gastrointestinal bleeding were observed with OR: 0.83, 95% CI: 0.62–1.11; P=.21 and OR: 1.02, 95% CI: 0.75–1.38; P=.92 respectively as shown in Figure 5. Bleeding requiring re-operation and bleeding requiring blood transfusion were also not significantly different with OR: 0.99, 95% CI: 0.54–1.79; P=.97 and OR: 1.25, 95% CI: 0.30–5.29; P=.76 respectively as shown in Figure 6.

Right heart failure (OR: 1.30, 95% CI: 0.98–1.72; P=.07), Cardiac arrhythmia (OR: 0.93, 95% CI: 0.71–1.20; P=.56), the need for right ventricular assisted device (OR: 0.75, 95% CI: 0.38–1.49; P=.41), Respiratory failure (OR: 1.12, 95% CI:

	centrifugal continuous flow circula	tory pump a:	xial continuous-flo	w pump		Odds Ratio	Odds Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFO
.1.1 Pump thrombo	osis							
Mehra2018	2	190	27	176	15.9%	0.06 [0.01, 0.25]		
Rogers2017	19	297	16	148	26.1%	0.56 [0.28, 1.13]		
Slaughter2009	5	134	0	66	6.3%	5.65 [0.31, 103.70]	-	*
Subtotal (95% CI)		621		390	48.3%	0.43 [0.06, 3.29]		
Total events	26		43					
Heterogeneity: Tau ² =	= 2.49; Chi ² = 11.21, df = 2 (P = 0.004); l ²	= 82%						
Test for overall effect:	: Z = 0.81 (P = 0.42)							
1.1.2 Pump replacem	nent							
Rogers2017	23	297	20	148	27.0%	0.54 [0.28, 1.01]		
Slaughter2009	12	134	20	66	24.7%	0.23 [0.10, 0.50]		
Subtotal (95% CI)		431		214	51.7%	0.36 [0.15, 0.84]	◆	
Total events	35		40					
Heterogeneity: Tau ² = Test for overall effect:	= 0.24; Chi ² = 2.79, df = 1 (P = 0.09); l ² = : Z = 2.37 (P = 0.02)	64%						
Total (95% CI)		1052		604	100.0%	0.36 [0.16, 0.81]	•	
Total events	61		83					
Heterogeneity: Tau ² =	= 0.54; Chi ² = 13.84, df = 4 (P = 0.008); l ²	= 71%						,
Test for overall effect:	: Z = 2.47 (P = 0.01)						avours [CCFCP] Favours [ACFP	
Test for subgroup diffe	erences: Chi ² = 0.02, df = 1 (P = 0.88), I ²	= 0%				1		1
Risk of bias legend								
(A) Random sequence	e generation (selection bias)							
(B) Allocation conceal	Iment (selection bias)							
(C) Blinding of particip	pants and personnel (performance bias)							
	ne assessment (detection bias)							
	me data (attrition bias)							
(F) Selective reporting	g (reporting bias)							
(G) Other bias								

Figure 2. Comparing pump thrombosis and pump replacement between the centrifugal continuous flow circulatory pump versus the axial continuous flow pump.

0.84-1.49; P=.46), Renal failure (OR: 1.11, 95% CI: 0.76–1.61; P=.59) and Hepatic dysfunction (OR: 0.72, 95% CI: 0.38–1.35; P=.30) were not significantly different in these patients with advanced heart failure at 2 years follow-up as shown in Figure 7. The results of this analysis have been listed in Table 4.

Sensitivity analysis showed consistent results in all of the

subgroups. Publication bias was visually assessed as shown in

Figure 8.

4. Discussion

This current analysis showed that in patients with advanced heart failure, pump replacement was significantly higher with the axial continuous flow pump in comparison to the centrifugal continuous flow circulatory pump at 2 years. However, other outcomes including pump thrombosis, stroke, bleeding events, infections and different organ dysfunctions were not significantly different.

centr tudy or Subgroup	ifugal continuous flow circu Events	latory pump Total	axial continuous-flo Events		Waight	Odds Ratio M-H, Random, 95% Cl	Odds Ratio M-H, Random, 95% Cl
.1.1 Any stroke	Events	Total	Events	TOLAT	weight	W-H, Random, 95% G	M-H, Randolli, 95% Cl
lehra2018	19	190	33	176	12.3%	0.48 [0.26, 0.88]	
lenrazu 18 logers2017	88	297		148	12.3%	3.04 [1.75, 5.28]	· · · ·
laughter2009	24	134	8	66	12.5%	1.58 [0.67, 3.74]	
ubtotal (95% CI)	24	621	0	390	35.7%	1.32 [0.40, 4.35]	
otal events	131		59				-
leterogeneity: Tau ² = 0.99; Cl est for overall effect: Z = 0.46	hi² = 19.57, df = 2 (P < 0.0001 6 (P = 0.65)); I² = 90%					
.1.2 Ischemic stroke							
lehra2018	12	190	23	176	11.6%	0.45 [0.22, 0.93]	_ _
logers2017	52	297	12	148	12.0%	2.41 [1.24, 4.66]	
laughter2009	11	134	4	66	9.1%	1.39 [0.42, 4.53]	
ubtotal (95% CI)		621		390	32.8%	1.14 [0.37, 3.54]	\leftarrow
otal events	75		39				
leterogeneity: Tau ² = 0.81; Cl est for overall effect: Z = 0.22	hi² = 11.27, df = 2 (P = 0.004) 2 (P = 0.82)	; I² = 82%					
.1.3 Hemorrhagic stroke							
1ehra2018	8	190	16	176	10.8%	0.44 [0.18, 1.05]	
logers2017	44	297	6	148	10.8%	4.12 [1.71, 9.90]	
ilaughter2009	15	134	5	66	9.8%	1.54 [0.53, 4.43]	
ubtotal (95% CI)		621		390	31.5%	1.40 [0.36, 5.46]	
otal events	67		27				
	ni² = 12.72, df = 2 (P = 0.002)	l² = 84%					
est for overall effect: Z = 0.49	9 (P = 0.62)						
otal (95% CI)		1863		1170	100.0%	1.28 [0.70, 2.35]	•
otal events	273		125				
eterogeneity: Tau ² = 0.69; C	ni² = 43.89, df = 8 (P < 0.0000	1); I² = 82%				F	.01 0.1 1 10
est for overall effect: Z = 0.80	(P - 0.42)					0.	Favours [CCFCP] Favours [ACFP]

Figure 3. Comparing stroke between the centrifugal continuous flow circulatory pump versus the axial continuous flow pump.

5	ntinuous flow circulate		ial continuous-flo			Odds Ratio	Odds Ratio
tudy or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.1 Other neurological events							
lehra2018	22	190	15	176	6.0%	1.41 [0.70, 2.80]	
ogers2017	25	297	7	148	3.8%	1.85 [0.78, 4.39]	
laughter2009	29	134	10	66	4.6%	1.55 [0.70, 3.40]	
ubtotal (95% CI)		621		390	14.4%	1.57 [1.01, 2.44]	◆
otal events	76		32				
eterogeneity: Chi ² = 0.24, df = 2 (P =							
est for overall effect: Z = 1.98 (P = 0.0	5)						
1.2 Sepsis							
ehra2018	26	190	24	176	9.4%	1.00 [0.55, 1.82]	_ + _
ogers2017	70	297	23	148	10.3%	1.68 [1.00, 2.82]	
aughter2009	48	134	26	66	9.8%	0.86 [0.47, 1.58]	
ubtotal (95% CI)		621		390	29.5%	1.19 [0.86, 1.65]	*
otal events	144		73				
eterogeneity: Chi ² = 3.09, df = 2 (P =	0.21); l² = 35%						
est for overall effect: Z = 1.05 (P = 0.2	9)						
1.3 LVAD drive-line infection							
ehra2018	45	190	34	176	11.8%	1.30 [0.78, 2.14]	
laughter2009	47	134	21	66	8.0%	1.16 [0.62, 2.17]	
ubtotal (95% CI)		324		242	19.8%	1.24 [0.84, 1.84]	◆
otal events	92		55				
eterogeneity: Chi ² = 0.08, df = 1 (P =	0.78); l² = 0%						
est for overall effect: Z = 1.08 (P = 0.2	8)						
1.4 Local infection not associated v	with LVAD						
ehra2018	70	190	60	176	17.3%	1.13 [0.73, 1.73]	
ogers2017	58	297	23	148	10.8%	1.32 [0.78, 2.24]	+
aughter2009	65	134	27	66	8.2%	1.36 [0.75, 2.47]	
ubtotal (95% CI)		621		390	36.3%	1.24 [0.93, 1.65]	◆
otal events	193		110				
eterogeneity: Chi ² = 0.33, df = 2 (P =	0.85); I ² = 0%						
est for overall effect: Z = 1.44 (P = 0.1	5)						
otal (95% CI)		2187		1412	100.0%	1.27 [1.07, 1.51]	•
otal events	505		270				
eterogeneity: Chi ² = 4.80, df = 10 (P =							
est for overall effect: $Z = 2.70$ (P = 0.0							0.01 0.1 1 10 10
est for subgroup differences: $Chi^2 = 1$.		- 0%					Favours [CCFCP] Favours [ACFP]

Figure 4. Comparing sepsis between the centrifugal continuous flow circulatory pump versus the axial continuous flow pump.

The possible reasons for pump replacement were pump thrombosis in a minority of patients, damage of the device lead, system related technical events such as communication fault leading to electrical failure, pump malfunction, sepsis including drive line infection, heart failure, persistent low pump flow due to obstructive outflow graft-twist or severe hemolysis.^[5–6] In study Slaughter et al^[7] of the 59 participants who were implanted with a pulsatile-flow LVAD, 21 pumps were replaced in 20 of the

participants whereas among the 133 participants who were implanted with a continuous flow LVAD, 13 pump replacement were reported among 12 participants due to the breakage of the percutaneous lead, pump thrombosis and outflow elbow disconnection.

In this analysis, three randomized controlled trials were included. The Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy

	centrifugal continuous flow circulator	y pump	axial continuous-flo	w pump		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
I.1.1 Any bleeding							
Mehra2018	81	190	90	176	29.5%	0.71 [0.47, 1.07]	
Rogers2017	178	297	90	148	26.5%	0.96 [0.64, 1.44]	+
Slaughter2009 Subtotal (95% CI)	148	134 621	54	66 390	56.0%	Not estimable 0.83 [0.62, 1.11]	•
Fotal events	407		234				
· ·	.08, df = 1 (P = 0.30); l ² = 7%						
Test for overall effect: Z	z = 1.26 (P = 0.21)						
I.1.2 Gastrointestinal	bleeding						
Mehra2018	51	190	47	176	19.6%	1.01 [0.63, 1.60]	- + -
Rogers2017	104	297	51	148	24.3%	1.02 [0.68, 1.55]	- + -
Subtotal (95% CI)		487		324	44.0%	1.02 [0.75, 1.38]	•
Fotal events	155		98				
Heterogeneity: Chi ² = 0	.00, df = 1 (P = 0.96); I ² = 0%						
Fest for overall effect: Z	2 = 0.11 (P = 0.92)						
Fotal (95% CI)		1108		714	100.0%	0.91 [0.74, 1.13]	
Fotal events	562		332				
Heterogeneity: Chi ² = 1	.97, df = 3 (P = 0.58); l ² = 0%						
Fest for overall effect: Z							0.01 0.1 1 10 10 Favours [CCFCP] Favours [ACFP]
	ences: Chi ² = 0.89, df = 1 (P = 0.35), l ² = 0	0%					ravours [CCFCF] Favours [ACFP]

Figure 5. Comparing bleeding between the centrifugal continuous flow circulatory pump versus the axial continuous flow pump (part I).

	centrifugal continuous flow circula	tory pump ax	ial continuous-flo	w pump		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	I M-H, Random, 95% CI
.1.1 Bleeding requir	ing re-operation						
/lehra2018	23	190	30	176	20.5%	0.67 [0.37, 1.21]	
Rogers2017	45	297	27	148	21.6%	0.80 [0.47, 1.35]	
Slaughter2009 Subtotal (95% CI)	108	134 621	45	66 390	19.0% 61.1%	1.94 [0.99, 3.80] 0.99 [0.54, 1.79]	•
otal events	176		102				
Heterogeneity: Tau ² = Test for overall effect:	0.19; Chi ² = 6.09, df = 2 (P = 0.05); l ² = Z = 0.04 (P = 0.97)	67%					
.1.2 Bleeding requir	ing blood transfusion						
Rogers2017	45	297	33	148	22.0%	0.62 [0.38, 1.03]	
laughter2009	40	134	9	66	16.9%	2.70 [1.22, 5.96]	
ubtotal (95% CI)		431		214	38.9%	1.25 [0.30, 5.29]	
otal events	85		42				
leterogeneity: Tau ² = est for overall effect:	0.97; Chi ² = 9.45, df = 1 (P = 0.002); l ² = Z = 0.31 (P = 0.76)	= 89%					
otal (95% CI)		1052		604	100.0%	1.06 [0.62, 1.80]	•
otal events	261		144				
est for overall effect:	0.27; Chi ² = 15.49, df = 4 (P = 0.004); l ² Z = 0.22 (P = 0.83) rences: Chi ² = 0.09, df = 1 (P = 0.77), l ²						0.01 0.1 1 10 10 Favours [CCFCP] Favours [ACFP]

Figure 6. Comparing bleeding between the centrifugal continuous flow circulatory pump versus the axial continuous flow pump (part II).

centrifu Study or Subgroup	gal continuous flow circu Events	latory pump a Total	axial continuous-flo Events		Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% Cl
1.1.1 Right heart failure	LVenta	Total	Lventa	Total	weight	WI-11, 1 IAEG, 33 /8 OI	M-11, 1 1xed, 55% C1
-	60	100	10	470	0.00/	4 00 10 70 4 001	
Mehra2018	60	190	48	176	8.9%	1.23 [0.78, 1.93]	
Rogers2017	114	297	40	148	8.6%	1.68 [1.09, 2.59]	
Slaughter2009	32	134	19	66	5.1%	0.78 [0.40, 1.51]	
Subtotal (95% CI)		621		390	22.5%	1.30 [0.98, 1.72]	•
Total events	206		107				
Heterogeneity: Chi ² = 3.74, df = 2 Test for overall effect: Z = 1.83 (F							
1.1.2 Any cardiac arrhythmia							
Mehra2018	71	190	70	176	11.9%	0.00 0 50 4 201	
						0.90 [0.59, 1.38]	
Rogers2017	112	297	61	148	13.2%	0.86 [0.58, 1.29]	
Slaughter2009	75	134	35	66	5.4%	1.13 [0.62, 2.03]	
Subtotal (95% CI)		621		390	30.5%	0.93 [0.71, 1.20]	₹
Total events	258		166				
Heterogeneity: $Chi^2 = 0.55$, df = 2 Test for overall effect: Z = 0.58 (F							
1.1.3 Need for right ventricular							
Mehra2018	6	190	8	176	2.1%	0.68 [0.23, 2.01]	
Rogers2017	8	297	5	148	1.7%	0.79 [0.25, 2.46]	
Slaughter2009	5	134	3	66	1.0%	0.81 [0.19, 3.51]	
Subtotal (95% CI)		621	-	390	4.8%	0.75 [0.38, 1.49]	
Total events	19		16			. / .	
Heterogeneity: $Chi^2 = 0.05$, df = 2 Test for overall effect: Z = 0.82 (F	2 (P = 0.98); I ² = 0%						
1.1.4 Respiratory failure							
Mehra2018	45	190	39	176	8.1%	1.09 [0.67, 1.78]	
Rogers2017	86	297	38	148	9.4%	1.18 [0.76, 1.84]	
Slaughter2009	50	134	24	66	5.3%	1.04 [0.57, 1.92]	
Subtotal (95% CI)	66	621	24	390	22.7%	1.12 [0.84, 1.49]	▲
Total events	181	021	101	000		1112 [0104, 1140]	ľ
Heterogeneity: Chi ² = 0.12, df = 2 Test for overall effect: Z = 0.74 (F	2 (P = 0.94); I ² = 0%		101				
1.1.5 Renal failure							
Mehra2018	25	190	18	176	4.2%	1.33 [0.70, 2.53]	-+ -
Rogers2017	44	297	18	148	5.3%	1.26 [0.70, 2.26]	
Slaughter2009	21	134	14	66	4.1%	0.69 [0.33, 1.46]	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)		621		390	13.7%	1.11 [0.76, 1.61]	—
Total events	90		50				
Heterogeneity: Chi ² = 2.01, df = 2 Test for overall effect: Z = 0.54 (F							
1.1.6 Hepatic dysfunction							
Mehra2018	8	190	7	176	1.8%	1.06 [0.38, 2.99]	
Rogers2017	14	297	12	148	4.0%	0.56 [0.25, 1.24]	— • +
Slaughter2009	0	134	0	66	7.070	Not estimable	
Subtotal (95% CI)	U	621	U	390	5.8%	0.72 [0.38, 1.35]	
		021	10	290	5.0%	0.72 [0.30, 1.35]	
Total events Heterogeneity: Chi² = 0.92, df = ⁻ Test for overall effect: Z = 1.03 (F			19				
Total (95% CI)		3726		2340	100.0%	1.06 [0.92, 1.22]	•
Total events	776		459				
Heterogeneity: Chi ² = 12.99, df =							· · · · · · · · · · · · · · · · · · ·
Test for overall effect: Z = 0.79 (F							0.01 0.1 1 10 100 Favours [CCFCP] Favours [ACFP]

Figure 7. Comparing the other adverse clinical outcomes between the centrifugal continuous flow circulatory pump versus the axial continuous flow pump.

Table 4Results of this analysis.

	OR with	P value	l ² value (%)
Outcomes analyzed	95% CI		
Pump thrombosis	0.43 [0.06–3.29]	.42	82
Pump replacement	0.36 [0.15-0.84]	.02	64
Any stroke	1.32 [0.40-4.35]	.65	90
Ischemic stroke	1.14 [0.37-3.54]	.82	82
Hemorrhagic stroke	1.40 [0.36-5.46]	.62	84
Other neurological events	1.57 [1.01-2.44]	.05	0
Any bleeding	0.83 [0.62-1.11]	.21	7
Bleeding requiring re-operation	0.99 [0.54-1.79]	.97	67
Bleeding requiring blood transfusion	1.25 [0.30-5.29]	.76	89
Gastrointestinal bleeding	1.02 [0.75-1.38]	.92	0
Sepsis	1,19 [0.86-1.65]	.29	35
LVAD drive-line infection	1.24 [0.84-1.84]	.28	0
Local infection not associated with LVAD	1.24 [0.93–1.65]	.15	0
Right heart failure	1.30 [0.98-1.72]	.07	47
Any cardiac arrhythmia	0.93 [0.71-1.20]	.56	0
Need for right ventricular assisted device	0.75 [0.38–1.49]		0
Respiratory failure	1.12 [0.84-1.49]	.46	0
Renal failure	1.11 [0.76–1.61]	.59	0
Hepatic dysfunction	0.72 [0.38–1.35]	.30	0

CI = confidence intervals, LVAD = left ventricular assisted device, OR = odds ratios.

with HeartMate 3 (MOMENTUM 3) having a follow-up time period of 2 years, is one among the trials which were used.^[2] However, the MOMENTUM 3 trial is a continuation of the previously published trial which had a follow-up period of only 6 months. Of the 294 participants with advanced heart failure which were included, 152 were assigned to the centrifugal continuous flow circulatory pump whereas 142 patients were assigned to the axial continuous flow pump. Similar to this current analysis, there was no significant difference in adverse outcomes, however, re-operation for pump malfunction or pump thrombosis was significantly higher with the axial continuous flow pump even at 6 months follow-up. Also, pump thrombosis occurred in 10.1% of the patients who were assigned to the axial continuous flow pump further supporting the fully magnetically levitated centrifugal-flow pump.

It would be interesting to know about the cost effectiveness of such devices. Recently, a Markov model was set up to assess the cost effectiveness of using these cardiac pump devices.^[8] All data were obtained from patients with advanced heart failure who were treated medically or with a continuous flow pump. Hospital claims were the source to determine the cost of such left ventricular assisted devices. When compared to patients who were managed medically, patients who were implanted with a continuous flow device had a higher 5 year cost (\$ 360,407 compared to \$ 62,856), quality adjusted life (1.87 vs 0.37 years) and life years. There was also a 75% reduction in incremental

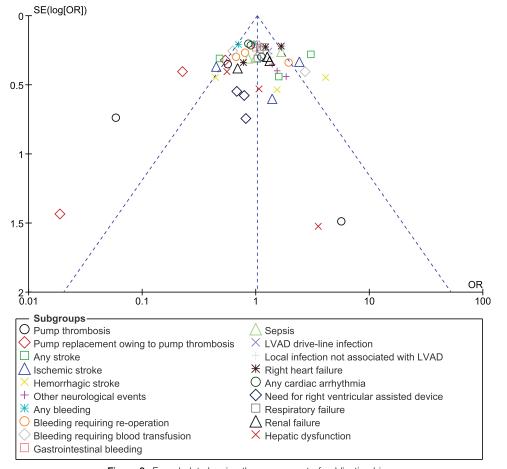


Figure 8. Funnel plot showing the assessment of publication bias.

cost effectiveness ratio compared to that for the pulsatile flow device.

Nevertheless, thrombus formation has been a major concern for patients who were implanted with those left ventricular assisted devices. Even if the HeartMate II (axial) and the HeartWare HVAD (centrifugal) are being continually used in patients with advanced heart failure,^[9] it is high-time to focus more on the potential complications^[10] in other to further expand this technology for the treatment of such patients. The impact of anticoagulation on the reduction of stent thrombosis in these patients should also be considered.^[11]

Moreover, even if our current study could not assess death outcome associated with these devices, the original studies showed a higher rate of death among those with a centrifugal flow device as compared to an axial flow device. To be more precise, in the ENDURANCE trial,^[6] a total number of 103 out of 297 patients who were implanted with the centrifugal flow device died compared to 39 death among 148 patients who were implanted with the axial flow device. Similarly, in another trial,^[7] 44% death occurred among those who were implanted with a continuous flow device compared to 27% death in the control group during a 2 year time period.

In comparison to previously published randomized controlled trials, this analysis consisted of a larger number of participants, giving an overview of the three trials. Also, all the trials had a similar follow-up period of 2 years, which might be another strength of this analysis, which would not be influenced by different follow-up time periods. At last, it should not be ignored that this idea is new in clinical medicine and in advanced progress of science and technology, and many research have yet to be carried out to better understand the clinical importance of these cardiac devices.

5. Limitations

Due to the limited number of participants in both groups, the results might have been affected. In addition, the total number of trials was limited in this analysis compared to other metaanalyses outside the scope of this topic. In addition, several subgroups showed a moderate to high level of heterogeneity, which might have affected the results. Other factors such as the duration of diseases, co-morbidities, and the use of different cardiac medications were not taken into consideration. A better analysis could also have been the comparison of adverse events from each individual pump and not classifying them by the type of flow.

6. Conclusions

At a follow-up time period of 2 years, pump replacement was significantly higher with the axial continuous-flow pump in comparison to the centrifugal continuous flow circulatory pump. However, no significant difference was observed with the other adverse outcomes. This hypothesis should be confirmed in future larger studies with even longer follow-up time periods.

Author contributions

Conceptualization: Bing Tang, Hua Yang. Data curation: Bing Tang, Hua Yang. Formal analysis: Bing Tang, Hua Yang. Funding acquisition: Bing Tang, Hua Yang. Investigation: Bing Tang, Hua Yang. Methodology: Bing Tang, Hua Yang. Project administration: Bing Tang, Hua Yang. Resources: Bing Tang, Hua Yang. Software: Bing Tang, Hua Yang. Supervision: Bing Tang, Hua Yang. Validation: Bing Tang, Hua Yang. Visualization: Bing Tang, Hua Yang. Writing – original draft: Bing Tang, Hua Yang. Writing – review & editing: Bing Tang, Hua Yang.

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