Systematic Review

Contemporary outcomes of continuous-flow biventricular assist devices

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Background: Significant right ventricular failure (RVF) complicating left ventricular assist device (LVAD) placement has been reported at 10–30%. Although primarily indicated for left ventricular failure, ventricular assist devices (VADs) have become utilized in a biventricular setup to combat right ventricular failure (RVF) following LVAD implantation. With the advent of continuous-flow LVADs (CF-LVADs) superseding their pulsatile predecessors, the shift towards CF-biventricular assist devices (CF-BiVADs) come with the prospect of improved outcomes over previous pulsatile BiVADs. We aim to review the literature and determine the outcomes of CF-BiVAD recipients.

Methods: A systematic review was performed to determine the outcomes of CF-BiVADs. Pre-operative demographics and device configuration data was collected. Primary outcomes evaluated were short-term survival, long-term survival, duration of support, and survival to transplant. Secondary outcomes evaluated included intensive care unit (ICU) and hospital length of stay (ICU-LOS and HLOS, respectively), pump thrombosis, pump exchange. Median and interquartile range was reported where appropriate. A major limitation was the likely overlap of cohorts across publications, which may have contributed to some selection bias.

Results: Of 1,282 screened, 12 publications were evaluated. Sample size ranged from 4 to 93 CF-BiVAD recipients, and follow-up ranged from 6 to 24 months. Mean age ranged from 34 to 52 years old. Forty-five percent of CF-BiVADs had right atrial (RA-) inflow cannulation, with the remaining being right ventricular (RV). Thirty-day survival was a median of 90% (IQR 82–97.8%) and 12-month survival was a median of 58.5% (IQR 47.5–62%). Where reported, rate of pump thrombosis (predominantly the right VAD) was a median of 31% (IQR 14–36%), although pump exchange was only 9% (IQR 1.5–12.5%).

Conclusions: RVF post-LVAD implantation is a high morbidity and mortality complication. There is no on-label continuous-flow RVAD currently available. Thus, the modifications of LVADs for right ventricular support to combat pump thrombosis has resulted in various techniques. BiVAD recipients are predominantly transplant candidates, and complications of pump thrombosis and driveline infection whilst on wait-list are of great consequence. This study demonstrates the need for an on-label CF-BiVAD.

Keywords: Biventricular assist device (BiVAD); heart failure; continuous-flow

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Introduction

Heart failure refractory to medical therapy has been treated with short- and long-term mechanical circulatory support since the 1960s. The first implantations of a left ventricular assist device (LVAD) as well as the first use of extra-corporeal life support (ECLS) heralded an innovative approach to mechanical circulatory support that has transformed the approach to heart failure. These advances have significantly improved survival to transplant, and evolved into a destination therapy for those indicated (1).

Although primarily indicated for left ventricular failure (LVF), ventricular assist devices (VADs) have become utilized in a biventricular set up to combat right ventricular failure (RVF) following LVAD implantation. Significant RVF complicating LVAD placement has been reported at 10–30% (2,3), and the need for either temporary or permanent mechanical right ventricular support occurs in 6–11% of LVAD recipients (2,4). Development of right heart failure following implantation of LVAD is shown to increase mortality six-fold and is a major contributor to prolonged hospitalization and re-hospitalization (5,6). Multiple studies have attempted to predict those patients requiring mechanical RV support post-LVAD (6-10), though they remain inadequately validated secondary to poor sensitivity and specificity (11,12).

Implantation of right-sided mechanical support can be temporary or permanent, and concomitant or delayed. Although temporary devices are aimed at avoiding the need for durable VAD implantation, they often still lead to a deferred right ventricular assist device (RVAD). Importantly, delayed implantation of permanent right ventricular mechanical devices has a significantly higher risk of mortality and morbidity than concomitant implantation (13). Survival following biventricular assist device insertion is reported to be 56% at 1-year (14).

A permanent and on-label long-term mechanical solution for right ventricular devices does not exist outside of use of the Total Artificial Heart (TAH) and the BerlinHeart Excor—a pulsatile device that may be used as biventricular support in Europe. However, the TAH does not fall into the classification of biventricular assist device (BiVAD) as it replaces the failing ventricles as opposed to assisting them (15). Hence, without an on-label solution, clinicians have resorted to using left-sided continuous-flow ventricular assist devices (VADs) in the right sided position for patients with severe biventricular failure (16).

The transition to continuous flow (CF) devices was accelerated by results of studies demonstrating mechanical problems—thrombosis, pump failure, system membrane rupture—occurred more frequently in pulsatile devices (17). Furthermore, in a randomized control trial comparing CF to pulsatile LVADs, it was found that the overall composite end-point of 2-year survival free of disabling stroke or re-operation was significantly better in the CF group (17). Continuous-flow devices have since superseded pulsatile devices. They have been shown to have at least equal survival to transplant, but also longer duration of support (18). The first use of a durable continuous-flow VAD in the right side was described in 2004, in a biventricular configuration (19) and since then, CF-BiVADs have progressively become the device configuration of choice. An INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) report published in 2017 recorded a total of 22,866 mechanical support devices implanted from 2006-2016. Of these, 616 were continuous-flow BiVADs (CF-BiVADs) (2.7%) and 349 pulsatile BiVADs (1.5%) (20). The latest INTERMACS report showed that the proportion of CF-BiVADs had dramatically replaced the use of pulsatile devices (3.9% *vs.* 0.1%, respectively), with BiVAD implantation composing 4.1% of all durable devices (21).

Without a dedicated, on-label solution for severe biventricular failure in the VAD market, there have been various ad-hoc techniques to RVAD or BiVAD implantation. Each of these have their own unique pitfalls and advantages. This review aims to evaluate the overall outcomes of BiVADs, in particular the now widely accepted continuous-flow devices that have superseded pulsatile flow devices.

Methods

Literature search strategy

Six databases were used to perform electronic searches including Ovid MEDLINE, EMBASE, PubMed, Cochrane Database of Systematic Reviews (CDSR), SCOPUS and Database of Abstracts of Review of Effectiveness (DARE). These databases were searched from their dates of inception to December 2020. The search strategy included a combination of keywords and MeSH headings including biventricular assist devices OR BiVAD (Figure S1). Predefined selection criteria were used to assess all relevant articles that were identified.

Selection criteria

Outlined below are the inclusion and exclusion criteria for our search. Long-term data was defined as 2 years or more follow-up post-operatively.

Inclusion criteria: (I) continuous flow right and left ventricular devices; (II) prospective and retrospective studies; (III) case series, meta-analyses; (IV) pre- or post-transplant patients.

Exclusion criteria: (I) non-English language titles without adequate translation; (II) pneumatic or pulsatile ventricular assist devices; (III) single ventricular assist device; (IV) paediatric population (<17 years); (V) small case series (n<4); (VI) case reports, abstracts, conference presentations, editorials, reviews, and expert opinions.

Data extraction and critical appraisal

Patient-level data was extracted from article texts, tables and figures (JF, KW, NM). Discrepancies were discussed between reviewers and a consensus was reached.

Outcomes of interest

Primary outcomes evaluated were short- and long-term survival, duration of support, and survival to transplant. Secondary outcomes assessed were complications including pump thrombosis, pump exchange, bleeding, stroke, infection, and intensive care unit (ICU) and hospital length of stay.

Statistical analysis

Due to the limited numbers of BiVAD recipients, likelihood of duplication, and varying end-points measured, a meta-analysis was not able to be performed. Results are presented comparing demographics, methods of BiVAD implantation, survival, and complications. Where data is sufficiently reported, means and medians are provided to assess overall outcomes.

Results

Quality of studies

The literature search identified a total of 1,612 studies. After exclusion of duplicates and irrelevant studies, 59 publications were selected for full-text review. Fourteen studies with a total of 399 CF-BiVAD recipients were reviewed. One study was a systematic review (16), and all others were observational studies. Three studies were registry reviews, one Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), one European Registry of patients with Mechanically Assisted Circulatory Support (EUROMACS), and one of the United Network for Organ Sharing (UNOS) database. A further three studies were multi-center observational studies and the remaining seven publications were case series. All studies were retrospective reviews of prospectively collected data. Reported follow-up duration ranged from a mean of four to twenty-one months. Most studies, however, did not report a mean/median follow-up period. Number of participants ranged from 4 to 93 receiving continuous-flow BiVADs. Although multiple studies included a greater number of BiVAD recipients, all but one (22) did not report on outcomes of CF-BiVADs separately, and thus were not included in the analysis. Quality assessment of each study was performed using the GRADE system and can be seen in *Table 1*.

Basic demographics and pre-operative status

Mean age ranged from 34 to 52 years old (*Table 2*), and gender was predominantly male (74–100%). Where reported (11 of 14 papers), BiVAD recipients were primarily implanted for bridge to transplant (BTT), ranging from 47–100%, except in one study, where BTT was only 27% of recipients. In this study, bridge to candidacy/decision was also 27% (23). INTERMACS profile—which characterizes severity of cardiogenic shock (*Figure 1*)—demonstrated that most BiVAD recipients were critically unwell with 65–100% of recipients INTERMACS 1 or 2. A median of 24% (IQR 11–34%) patients were bridged from ECMO (9/14 studies reported). Non-ischaemic cardiomyopathies were the predominant etiology, with dilated cardiomyopathy being the most commonly reported subtype (37–92%).

Devices, techniques and configurations

Although device numbers were not consistently reported, most studies delineated which devices were utilized on their participants (*Table 3*). Eleven of these studies (15,16,23-31) utilized the HeartWare HVAD (Medtronic, Minnesota MN) whereas only three studies reported the use of the HeartMate 3 (Abbott, Chicago, IL) (27,32,33) (*Figure 2*). Timing of RVAD implantation as either concomitant with LVAD versus delayed was reported in most studies

Table 1 Study methods

Paper	Study type	Follow up period	Number of patients	Years of review	GRADE score
Marasco, 2020, "*International experience using a durable, centrifugal-flow ventricular assist device for biventricular support*"	Multi-centre retrospective cohort review	24 months	93; 12 institutions contributed	2009 to 2017	++++
McGiffin, 2020, "*The results of a single-centre experience with HeartMate 3 in a biventricular configuration*"	Case series	18 months	12	May 2017 to April 2020	+++
Maynes, 2020, "*Right atrial versus right ventricular HeartWare HVAD position in patients on biventricular HeartWare HVAD support: a systematic review*"	Systematic Review	117.5d (4 months) (30–342.5)	56; identified 1,288 papers, included: 13 papers	–	++++
Vierecke, 2019, "*Results of primary biventricular support: an analysis of data from the EUROMACS registry*"	EUROMACS Registry review—retrospective review of prospectively collected data	18 months	22	Jan 2011 to Oct 2017	+++
Arabia, 2018, "*Biventricular support with intracorporeal, continuous flow, centrifugal ventricular assist devices*"	INTERMACS Registry review—retrospective review of prospectively collected data	5.08 months (157.5 days)	38; 19 institutions contributed	Jun 2006 to Jun 2015	++++
Shah, 2018, "*Multicenter experience with the durable biventricular assist device*"	Multi-centre retrospective cohort review	6 months (unreported)	46; 6 institutions (of surgeons >5 BiVADs)	Oct 2011 to Jun 2017	++++
Lavee, 2018, "*An international multicenter experience of biventricular support with HeartMate 3 ventricular assist systems*"	Multi-centre retrospective cohort review	21 months	14; 6 centres	Mar 2016 to Jan 2018	+++
Eulert-Grehn, 2018, "*Two implantable continuous-flow ventricular assist devices in a biventricular configuration: technique and results*"	Case series	12 months (unreported)	39	Sept 2009 to Oct 2017	+++
Tran, 2018, "*Durable biventricular support using right atrial placement of the HeartWare HVAD*"	Case series	Unreported	11	Jun 2014 to May 2016	+++
Levin, 2016, "*Outcomes of contemporary mechanical circulatory support device configurations in patients with severe biventricular failure*"	retrospective analysis of UNOS database	6 months (unreported)	28 CF-BiVAD (408 BiVAD/TAH)	Jan 2010 to Jun 2014	+++
Maltais, 2016, "*Surgical considerations and challenges for bilateral continuous flow durable device implantation*"	Case series	6 months (unreported)	4	Dec 2013 to Aug 2014	++
Shehab, 2016, "*Long-term biventricular HeartWare ventricular assist device support - case series of right atrial and right ventricular implantation outcomes*"	Case series	Census date Feb 2015	13	Aug 2011 to Oct 2014	+++

Table 1 (*continued*)

Table 1 (*continued*)

Paper	Study type	Follow up period	Number of patients	Years of review	GRADE score
Marasco, 2014, "*Long-term right ventricular support with a centrifugal ventricular assist device placed in the right atrium*"	Case series	6 months (unreported)	4	–	++
Krabatsch, 2011, "*Biventricular circulatory support with two miniaturised implantable assist devices*"	Case series	6–12 months (unreported)	17	Sept 2009 to Nov 2010	+++

INTERMACS, Interagency Registry of Mechanically Assisted Circulatory Support; EUROMACS, European Registry for patients with Mechanically Assisted Circulatory Support; UNOS, United Network Organ Sharing; BiVAD, biventricular assist device; CF-BiVAD, continuous flow biventricular assist device; TAH, total artificial heart.

(12 of 14) and was predominantly implanted concomitantly (median 82%, IQR 62–84%). Where it was delayed, the median time to implantation was 16.5 days (IQR 10.8–24.9 days). Cannulation strategy for the RVAD inflow cannula was described in 12 of the 14 studies, and this varied widely with some reporting only RV-cannulation (25,28) whilst others reported an exclusively RA-cannulation approach (26,29,33). In total, 147 had RA-compared with 182 RV-inflow cannula cannulation.

Primary outcomes—survival, duration of support, and survival to transplant

Duration of support was reported in eleven of fourteen papers (*Table 4*) and was a median of 237 days (IQR 163–309 days). Short-term survival was reported as either 1-month or 30-day survival in ten out of fourteen studies, with a median of 91% (IQR 82–100%). However, only three studies reported survival to discharge, and these were far less successful, ranging from 50–69%. The 12-month survival was reported in 8 of 14 studies evaluated and ranged from 44–92%, with a median of 59% (IQR 52.5–65.3%). Survival to follow-up was reported in the rest, ranging from 47–91% (median 69.5%, IQR 58.8–75%). Only two studies reported follow-up to 24 months (30,31), reporting 54% and 56% survival. Survival to transplant was described in all but one study, and ranged quite significantly, from 3–75% (median 42%, IQR 18–50%).

Secondary outcomes—complications

ICU length of stay was reported in four studies and had a range of 7–29 days (median 16.5, IQR 12.3–21.5), whilst hospital length of stay (also only reported in the same four studies) ranged from 30 to 53 days (median 41, IQR 36.8–45.5) (*Table 5*). Most studies (12 out of 15) reported their pump thrombosis rate, and this varied widely, from 0–75% (median 30%, IQR 16–34%). Pump exchange was lower, with a median 8% (IQR 3–11%). Other complications including infection, bleeding, return to theatre, and neurological sequelae were inconsistently reported. These were not comparable across studies, with events per patient year, events per 100 patient months, and percentage affected reported.

Discussion

Our review demonstrated great variability in study type, follow-up, end-points, device type and configuration making it a challenge to effectively assess the contemporary outcomes of CF-BiVADs.

Study type ranged from registry reviews of INTERMACS, EUROMACS, and UNOS, as well as single- and multi-center cohorts and case series. With likely a great overlap in patient-data recruitment into registries, as well as heterogeneity in end-points, results were thus not compiled to perform a meta-analysis.

Short-term survival was predominantly reported at 30-day, and as an encouraging median of 91%. However, the survival to discharge reported in only three studies was far less, ranging from 50% to 69%. This is unsurprising given median hospital length of stay was 41 days. This highlights the protracted and complicated post-operative course of BiVAD recipients, where routine post-operative

Table 2 Demographics and pre-op status

PAPER	Age	Gender	INTERMACS	Bridge from ECMO	Primary/secondary device	CM
Marasco, 2020, "*International experience using a durable, centrifugal-flow ventricular assist device for biventricular support*"	Mean: 47.4 years old (SD 12.9)	70/93 male (75%)	Int 1–2: 61% Int 1: 35% Int 2: 26% Int 3: 8% Int 4: 6% Unknown: 25%	34% IABP 5%	–	Ischaemic 15% Non-ischaemic 85% DCM 48%
McGiffin, 2020, "*The results of a single- centre experience with HeartMate 3 in a biventricular configuration*"	Mean: 44 years old (17 to 63)	12/12 male (100%)	Int 1–2: 12/12 (100%) Int 1: 1/12 (8%) Int 2: 11/12 (92%)	1/12 (8%)	All primary	Non-ischaemic CM 11/12 (92%) 6/12 DCM (50%) 1/12 Ischaemic CM (8%)
Maynes, 2020, "*Right atrial versus right ventricular HeartWare HVAD position in patients on biventricular HeartWare HVAD support: a systematic review*"	Median: 51 years old IQR 33.8 to 57.0	40/50 male (80%)	Int 1–2: 38/56 (88.4%)	9/12 (75%)	–	Non-ischaemic CM: 42/56 (85.7%) Cardiogenic shock: 1/56 (1.8%)
Vierecke, 2019, "*Results of primary biventricular support: an analysis of data from the EUROMACS registry*"	Median: 58 years old IQR 39 to 62	20/22 male (91%)	Int 1: 2 (9%) Int 2: 9 (41%) Int 3: 8 (36%) Int 4: 3 (14%)	3/22 (14%)	All primary	DCM 8/22 (38%) Non-ischaemic CM: 15/22 (68.2%)
Arabia, 2018, "*Biventricular support with intracorporeal, continuous flow, centrifugal ventricular assist devices*"	Median: 47.02 years old (SD 13.6)	28/38 male (73.7%)	Int 1–2: 30/38 (78.9%)	4/38 (11%)	31 first device (81.6%) 5-prior LVAD (13.2%) 2-prior BiVAD (5.2%)	DCM 14/38 (36.8%) Non-ischaemic CM: 33/38 (86.8%)
Shah, 2018, "*Multicenter experience with the durable biventricular assist device*"	Median: 46 years old IQR 19 to 67	36/46 male (78%)	Int 1: 32/46 (70%) Int 2: 10/46 (22%) Int 3: 4/46 (8%)	12/46 (26%) IABP 44%	All primary	Non-ischaemic CM: 37/46 (80%) Ischaemic CM: 6/46 (13%)
Lavee, 2018, "*An international multicenter experience of biventricular support with HeartMate 3 ventricular assist systems*"	Median: 48.5 years old (17 to 73)	13/14 male (93%)	Int 1: 2/14 (14%) Int 2: 9/14 (64%) Int 3: 3/14 (21%)	–	–	Non-ischaemic CM: 10/14 (71%) DCM: 7/14 (50%) Ischaemic CM: 4/14 (29%)

Table 2 (*continued*)

Table 2 (*continued*)

PAPER	Age	Gender	INTERMACS	Bridge from ECMO	Primary/secondary device	CM
Eulert-Grehn, 2018, "*Two implantable continuous-flow ventricular assist devices in a biventricular configuration: technique and results*"	Mean: 52 years old (21 to 73)	–	–	–	–	DCM: 17/39 (44%) Ischaemic CM: 13 (33%)
Tran, 2018, "*Durable biventricular support using right atrial placement of the HeartWare HVAD*"	Mean: 42.3 years old (19 to 57)	9/11 male (82%)	Int 1/2: 11/11 (100%) Int 1: 7/11 (64%) Int 2: 4/11 (36%)	–	–	Ischaemic CM: 1/11 (9%) Non-ischaemic CM: 10/11 (91%)
Levin, 2016, "*Outcomes of contemporary mechanical circulatory support device configurations in patients with severe biventricular failure*"	Median: 45.5±16.5 years old	21/28 male (75%)	–	IABP: 2/28 (7%)	–	Ischaemic CM 5/28 (18%) Non-Ischaemic CM 23/28 (82%)
Maltais, 2016, "*Surgical considerations and challenges for bilateral continuous flow durable device implantation*"	Mean: 34 years old (18 to 63)	–	Int 1: 2/4 Int 2: 1/4 Int 3: 1/4	1/4	–	Viral 1/4 Post-partum 1/4 Ischaemic 1/4 Familial 1/4
Shehab, 2016, "*Long-term biventricular HeartWare ventricular assist device support - case series of right atrial and right ventricular implantation outcomes*"	Mean: 45 years old (SD 11)	10/13 male (77%)	Int 1: 10/13 (77%) Int 2: 3/13 (23%)	ECMO 5/13 (38%) IABP 2/13 (15%)	–	DCM: 11/13 (85%)
Marasco, 2014, "*Long-term right ventricular support with a centrifugal ventricular assist device placed in the right atrium*"	Mean: 36 years old (17 to 56)	2/4 female 2/4 male	–	2/4	Primary 3/4 Secondary 1/4	Post-partum CM 1/4 Lymphocytic CM 1/4 DCM 2/4
Krabatsch, 2011, "*Biventricular circulatory support with two miniaturised implantable assist devices*"	Mean: 51.8 years old (29 to 73)	15/17 male (88%)	Int 1/2: 11/17 (65%) Int 3/4: 5/17 (30%)	–	–	DCM: 9/17 (53%) Ischaemic CM: 4/17 (24%)

IQR, inter-quartile range; INTERMACS, Interagency Registry of Mechanically Assisted Circulatory Support; CM, cardiomyopathy; DCM, dilated cardiomyopathy; Int, INTERMACS; ECMO, extra-corporeal membrane oxygenation; IABP, intra-aortic balloon pump.

Profile	Title	Description
1	Critical cardiogenic shock	Life-threatening hypotension refractory to IV inotropes. "crash and burn"
2	Progressive decline	IV inotropes required with worsening end-organ function. "sliding on inotropes"
3	Inotrope dependent	Stable blood pressure and end-organ function but failure to wean from IV inotropes. "dependent stability"
4	Resting symptoms	Daily symptoms of congestion at rest or with ADLs. High doses of diuretics
5	Exertion intolerant	Unable to engage in any activity above ADLs
6	Exertion limited	Can participate in minor activities but quickly fatigues. "walking wounded"
7	Advanced NYHA III	Comfortable with meaningful activity, limited to mild exertion

Figure 1 INTERMACS profiles. INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; NYHA, New York Heart Association; IV, intra-venous; ADLs, activities of daily living.

Table 3 Devices, configurations and technique

PAPER	Device	Concomitant (C) *vs.* delayed (D) RVAD	Time to RVAD	Cannulation	Indication (BTT, BTD, DT)
Marasco, 2020, "*International experience using a durable, centrifugal-flow ventricular assist device for biventricular support*"	HeartWare HVAD	C: 77/93 (83%) D: 16/93 (17%)	Mean 23.3 d (SD 20.7 d) Median 18 d (IQR 7–35 d)	RA: 32/88 (36%) RV: 56/88 (64%)	BTT: 47%
McGiffin, 2020, "*The results of a single-centre experience with HeartMate 3 in a biventricular configuration*"	HeartMate 3	C: 6/12 (50%) D: 6/12 (50%)	–	RA: 12/12 (100%)	BTT: 12/12 (100%)
Maynes, 2020, "*Right atrial versus right ventricular HeartWare HVAD position in patients on biventricular HeartWare HVAD support: a systematic review*"	HeartWare HVAD	C. 48/56 (85.7%) D. 8/56 (14.3%)	Total: 12 d (IQR 7–14) RA-HVAD 10 d (IQR 7–14) RV-HVAD 12 d (IQR 8–30)	RA: 21/56 (37%) RV: 35/56 (63%)	BTT 40/46 (87%) DT 6/46 (13%)
Vierecke, 2019, "*Results of primary biventricular support: an analysis of data from the EUROMACS registry*"	HeartWare HVAD	–	–	–	BTR: 0 BTT 6 (27%) DT 6 (27%) BTD 6 (27%) Rescue 1 (5%)
Arabia, 2018, "*Biventricular support with intracorporeal, continuous flow, centrifugal ventricular assist devices*"	HeartWare HVAD, HeartMate II	C: 38/38 (100%)	–	RA: 13/32 (41%) RV: 19/32 (59%)	BTT 28/38 (73.7%) BTD 8/38 (21%) DT 2/38 (5.3%)

Table 3 (*continued*)

Table 3 (*continued*)

PAPER	Device	Concomitant (C) *vs.* delayed (D) RVAD	Time to RVAD	Cannulation	Indication (BTT, BTD, DT)
Shah, 2018, "*Multicenter experience with the durable biventricular assist device*"	HeartWare HVAD	C: 31/46 (67%) D: 15/46 (33%)	15 d (13 to 30)	RA: 23/46 (50%) RV: 23/46 (50%)	BTT 38/46 (83%) DT 8/46 (17%)
Lavee, 2018, "*An international multicenter experience of biventricular support with HeartMate 3 ventricular assist systems*"	HeartMate 3	C: 8/14 (57%) D: 6/14 (43%)	45.6 d (9 to 112)	RA: 12/14 (86%) RV: 1/14 (7%) Ventricular excision and TAH Config: 1/14 (7%)	–
Eulert-Grehn, 2018, "*Two implantable continuous-flow ventricular assist devices in a biventricular configuration: technique and results*"	HeartWare HVAD HeartMate 3	C: 22/39 (56%) D: 17/39 (44%)	–	RA: 17/36 (47%) RV: 19/36 (53%)	–
Tran, 2018, "*Durable biventricular support using right atrial placement of the HeartWare HVAD*"	LVAD: HeartWare HVAD 10/11; HeartMate 2 1/11 RVAD: HeartWare HVAD 11/11	C: 9/11 (82%) D: 2/11 (18%)	D: Within 1 week	RA: 11/11	
Levin, 2016, "*Outcomes of contemporary mechanical circulatory support device configurations in patients with severe biventricular failure*"	–	–	–	–	BTT 100%
Maltais, 2016, "*Surgical considerations and challenges for bilateral continuous flow durable device implantation*"	HeartWare HVAD	C: 3/4 D: 1/4	D: 1/4–77 d	RV: 4/4 (diaphragmatic) RA: 1/4 (Redo)	BTT 4/4
Shehab, 2016, "*Long-term biventricular HeartWare ventricular assist device support - case series of right atrial and right ventricular implantation outcomes*"	HeartWare HVAD	C: 11/13 (85%) D: 2/13 (15%)	D: 7 d	RA: 6/13 (46%) RV: 7/13 (54%)	BTT 13/13 (100%)
Marasco, 2014, "*Long-term right ventricular support with a centrifugal ventricular assist device placed in the right atrium*"	LVAD: 3/4 HeartWare HVAD; 1/4 VentrAssist RVAD: 4/4 HeartWare HVAD	C: 1/4 D: 3/4	D: 3/4–18 d mean (7 to 33)	RA: 4/4	BTT: 4/4
Krabatsch, 2011, "*Biventricular circulatory support with two miniaturised implantable assist devices*"	HeartWare HVAD	C: 14/17 (82%) D: 3/17 (18%)	–	RV: 17/17 (100%) RA: 1/17 (switched from RV)	BTT: 13/17 (76%) DT: 4/17 (24%)

RVAD, right ventricular assist device; LVAD, left ventricular assist device; BiVAD, biventricular assist device; RA, right atrial; RV, right ventricular; BTT, bridge to transplant; BTD, bridge to decision; DT, destination therapy.

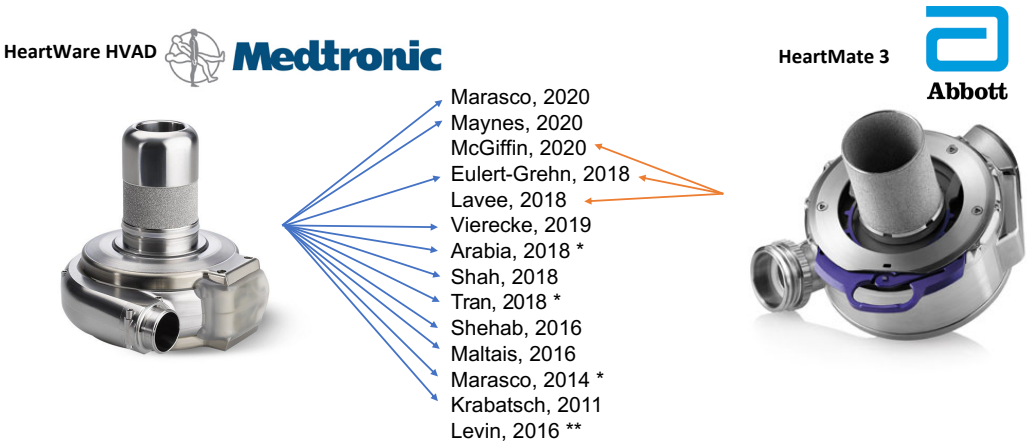

Figure 2 Devices evaluated by studies.

Table 4 Results—primary outcomes

Paper	Duration of support	30-d survival	Long-term survival	Survival to transplant
Marasco, 2020, "*International experience using a durable, centrifugal-flow ventricular assist device for biventricular support*"	Total median 176 d: RA 107 d; RV 215 d	–	12 months 56%; 24 months 47%	17/93 (18%) at 24 months
McGiffin, 2020, "*The results of a single-centre experience with HeartMate 3 in a biventricular configuration*"	Mean 349 d (43 to 1,108 d)	30 d 12/12 (100%)	12 months 11/12 (92%); 18 months 11/12 (92%); 1/12 (8%) explanted at 7 months	5/12 (42%) at 18 months
Maynes, 2020, "*Right atrial versus right ventricular HeartWare HVAD position in patients on biventricular HeartWare HVAD support: a systematic review*"	Total 156 d (IQR 66 to 351), 351 d (IQR 136 to 626), 135 d (IQR 61 to 244)	30 d 51/56 (91%)	12 months 75%: RA 91.7% (95% CI: 77.3–100); RV 66.2% (95% CI: 48.9–89.6)	16/35 (45.7%): RA 10/14 (71.4%); RV 6/21 (28.6%)
Vierecke, 2019, "*Results of primary biventricular support: an analysis of data from the EUROMACS registry*"	–	–	12 months 55%	–
Arabia, 2018, "*Biventricular support with intracorporeal, continuous flow, centrifugal ventricular assist devices*"	–	30 d 34/38 (89%)	6 months 68%; 12 months 62%	6 months 25%
Shah, 2018, "*Multicenter experience with the durable biventricular assist device*"	237 d median (IQR 89 to 350)	30 d 31/46 (67%); survival to DC 23/46 (50%); C: 61% *vs.* D: 27% survival to discharge	12 months 21/46 (45%); 18/46 (39%) at latest f/u	20/46 (43%); time to Tx 261 d (IQR 175–348)
Lavee, 2018, "*An international multicenter experience of biventricular support with HeartMate 3 ventricular assist systems*"	266 d (95 to 636)	–	9/14 (64%) at latest f/u	1/14 (7%)

Table 4 (*continued*)

Table 4 (*continued*)

Paper	Duration of support	30-d survival	Long-term survival	Survival to transplant
Eulert-Grehn, 2018, "*Two implantable continuous-flow ventricular assist devices in a biventricular configuration: technique and results*"	–	30 d: 73% (concomitant); 71% (delayed)	6 months 22/39 (56%): 55% (primary); 57% (delayed). 12 months 17/39 (44%): 45% (primary); 41% (delayed)	1/39 (3%) transplanted at 8 mo
Tran, 2018, "*Durable biventricular support using right atrial placement of the HeartWare HVAD*"	Mean 392 d (17 to 808); median 255 d	91–100% (unreported)	10/11 (91%) at latest f/u	7/11 (64%)
Levin, 2016, "*Outcomes of contemporary mechanical circulatory support device configurations in patients with severe biventricular failure*"	97.5 d (52.5 to 151)	1 month survival 82%	6 months survival 57%	Tx 6 months post-BiVAD 21/28 (75%); 83% 6 months survival post-transplant
Maltais, 2016, "*Surgical considerations and challenges for bilateral continuous flow durable device implantation*"	Mean 154 d (118 to 183)	1 month survival 4/4	3/4 at latest f/u	3/4 (75%)
Shehab, 2016, "*Long-term biventricular HeartWare ventricular assist device support - case series of right atrial and right ventricular implantation outcomes*"	Median 269 d (IQR 93 to 426)	30 d survival 13/13 (100%); survival to discharge 9/13 (69%)	12 months 8/13 (62%), 24 months 7/13 (54%)	5/11 (38%) at median 513 d support
Marasco, 2014, "*Long-term right ventricular support with a centrifugal ventricular assist device placed in the right atrium*"	Mean 503 d (117 to 772)	1 month survival 4/4	3/4 at latest f/u	2/4 (50%) 1/4 pending Tx
Krabatsch, 2011, "*Biventricular circulatory support with two miniaturised implantable assist devices*"	Mean 170 d (SD 163)	30 d survival 14/17 (82%); survival to discharge 10/17 (59%)	8/17 (47%) at latest f/u	1/17 (6%) transplanted (280 d)

RA, right atrial; RV, right ventricular; Tx, transplant; RVAD, right ventricular assist device; DC, discharge; f/u, follow-up.

markers of success are less relevant and accurate.

Long-term survival was less consistently reported, ranging from 6 to 24 months, and survival to follow-up—where a time-interval was often not specified. Duration of follow-up was seldom longer than 12 months which reflects the relatively diminutive number of BiVAD recipients, the largely bridge to transplant cohort, as well as the novel nature of continuous-flow devices in this configuration. Nonetheless, survival when reported at 12 months was 59%, significantly lower than at 30-day, and highlights how critically unwell this cohort is. BiVAD implantation confers double the risk of mortality at 12 months compared with LVAD alone (20,34), however, no singular factor has been identified as to why BiVADs are associated with higher mortality. Several studies have shown that certain indices of RVF including right atrial pressure (RAP) and serum bilirubin secondary to hepatic congestion are independent risk factors. Therefore, it may be the chronicity of RVF and the associated end-organ dysfunction (or sequalae of delayed utilisation in acute RHF)—rather than the device and its potential complications—which contribute the greatest to post-operative mortality (35).

Demographics across cohorts were relatively similar, and this was most demonstrable with the etiology of cardiomyopathy and INTERMACS profile. Across all studies, most candidates suffered a non-ischaemic cardiomyopathy. Severity of heart-failure was most consistently measured with the INTERMACS profile, and BiVAD recipients were predominantly INTERMACS 1-2. Once again, this impacts survival; BiVAD compared with

Table 5 Results—secondary outcomes

Paper	ICU-LOS/H-LOS	RTT <30 d	Infections	Bleeding	Neurological Injury	Device malfunction/ pump thrombosis	Pump-exchange
Marasco, 2020, "*International experience using a durable, centrifugal- flow ventricular assist device for biventricular support*"	–	–	24/93 (26%)	33/93 (36%)	13/93 (14%)	Device malfunction 17/93 (18%); pump thrombosis 8/93 (9%) (all RVAD)	7/93 (8%): 1 LVAD, 6 RVAD
McGiffin, 2020, "*The results of a single-centre experience with HeartMate 3 in a biventricular configuration*"	–	–	Driveline wound: 3/12 (25%)	All bleeding: 11/12 (92%); GIB 2/12 (2%)	0/12 (0%)	Pump thrombosis 3/12 (25%), all RVAD	1/12 (8%)
Maynes, 2020, "*Right atrial versus right ventricular HeartWare HVAD position in patients on biventricular HeartWare HVAD support: a systematic review*"	–	12/19 (63.2%) for POB	–	GIB: total 15/56; RA 10/35; RV 5/21	–	Pump thrombosis total 9/30 (30%): RA 3/10; RV 6/20	–
Vierecke, 2019, "*Results of primary biventricular support: an analysis of data from the EUROMACS registry*"	–	–	Freedom from infection =61% (12 months)	Freedom from bleeding =82% (12 months)	Freedom from neurological events: 76% (12 months)	Freedom from device malfunction/ thrombosis =95% (18 months)	–
Arabia, 2018, "*Biventricular support with intracorporeal, continuous flow, centrifugal ventricular assist devices*"	–	–	3 months: 15 events (rate 62.1); 3–24 months: 14 events (rate 13.2)	3 months: 16 events (rate 66.3); 3–24 months: 10; events per 100 patient-months (rate 9.5)	3 months: 2 events (rate 8.3); 3–24 months: 3 events (rate 2.8)	Device malfunction 26%: 3 months: 9 events (rate 37.3); 3–24 months: 6 events (rate 5.7)	4/38 (11%)
Shah, 2018, "*Multicenter experience with the durable biventricular assist device*"	ICU LOS 19 d (IQR 8–39); C: 12 d (IQR 7–23); D: 42 d (IQR 28–48); HLOS 43 d (IQR 25–59)	–	27/46 (59%), undefined	GIB 14/46 (30%)	10/46 (22%)	LVAD thrombosis 3/46 (7%); RVAD thrombosis 17/46 (37%)	5/46 (11%) for PT (RVADs)
Lavee, 2018, "*An international multicenter experience of biventricular support with HeartMate 3 ventricular assist systems*"	–	–	5/14 (36%), driveline wound infection 1/14 (7%)	GIB 1/14 (7%)	1/14 (7%)	2/14 pump thrombosis (14%)	2/14 (14%)

Table 5 (*continued*)

Table 5 (*continued*)

Paper	ICU-LOS/H-LOS	RTT <30 d	Infections	Bleeding	Neurological Injury	Device malfunction/ pump thrombosis	Pump-exchange
Eulert-Grehn, 2018, "*Two implantable continuous-flow ventricular assist devices in a biventricular configuration: technique and results*"	–	–	–	–	–	12 RVAD pump thromboses 12/39 (31%); 5 rTPA; 1 pump exchange; 4 deaths due to pump thrombosis	1/39 (3%)
Tran, 2018, "*Durable biventricular support using right atrial placement of the HeartWare HVAD*"	ICU-LOS median 7 d; HLOS median 30 d	–	–	GIB 2/11 (18%)	3/11 (27%) ICH	4/11 (36%), thrombosis	1/11 (9%) pump exchange
Levin, 2016, "*Outcomes of contemporary mechanical circulatory support device configurations in patients with severe biventricular failure*"	–	–	–	–	–	–	–
Maltais, 2016, "*Surgical considerations and challenges for bilateral continuous flow durable device implantation*"	–	–	–	1/4	0/4	3/4 (75%) pump thrombosis	2/4
Shehab, 2016, "*Long-term biventricular HeartWare ventricular assist device support - case series of right atrial and right ventricular implantation outcomes*"	ICU-LOS median 14 d (IQR 8–36); HLOS median 53 d (IQR 33–70)	–	7/13 (54%) total; DSWI 2/13 (15%); driveline infection 1/13 (8%)	3/13 (23%)	2/13 (15%)	4/13 (31%) RVADs thrombosis: 1/7 RA; 3/6 RV	0/13 (0%)
Krabatsch, 2011, "*Biventricular circulatory support with two miniaturised implantable assist devices*"	ICU-LOS mean 29 d (SD 30.8); HLOS mean 39 d	6/17 (35%) for POB	1/17 (6%), mediastinitis	6/17 (35%) post-op bleeding; GIB 2/17 (12%)	–	–	–
Marasco, 2014, "*Long-term right ventricular support with a centrifugal ventricular assist device placed in the right atrium*"	–	2/4	2/4	3/4	–	0/4	0/4

ICU-LOS, intensive care unit length of stay; HLOS, hospital length of stay; RTT, return to theatre; POB, post-operative bleeding; DSWI, deep sternal wound infection; GIB, gastro-intestinal bleeding; RA, right atrial; RV, right ventricular; ICH, intra-cerebral haemorrhage; LVAD, left ventricular assist device; RVAD, right ventricular assist device; PT, pump thrombosis.

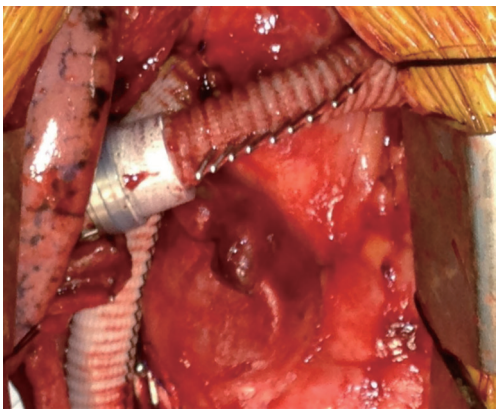

Figure 3 RVAD outflow graft (crossing the ascending aorta) crimped with hemaclips (reprinted with authors permission) (23).

LVAD recipients are by far more critically unwell and in cardiogenic shock—likely contributing to poorer long-term survival and survival to transplant. Although transplant would be the ideal management, their critical pre-operative condition and multi-organ dysfunction likely reduces their candidacy (24).

The indication of LVADs is significantly different to BiVAD implantation. The proportion of LVADs implanted for destination therapy has progressively increased from 46% in 2014 to 70% in 2019 (21). Most patients in this review were implanted with BiVADs with the intent of bridge to transplantation. However, there is discrepancy across global regions where locality impacts overall patient selection leading to heterogenous indications for VAD implantation across the international community. Whereas VADs are indicated as bridge to transplant, destination therapy and even bridge to candidacy (decision) in the USA and Europe, LVADs are not approved for destination therapy in Japan (36). The relevance of indication is heightened by the fact that wait-list times for heart transplantation vary widely with Japan having a median of more than 1,150 days (37). This is significantly higher than the global wait-list median of 144 days reported in 2014 (38). Thus, this is likely to affect candidacy for BiVAD support and patient selection across regions.

Continuous-flow devices hold several advantages over their pulsatile predecessors that are unique to the BiVAD setting. Pulsatile biventricular devices were initially utilized but were limited by their large size, requiring extensive pockets to be created in the abdominal wall, and with four cannulae exiting/entering the skin for externalized pumps, increasing risk of infection (28). Additionally, their drivers were bulkier and pumps more prone to thrombosis (17).

In our systematic review, complications were too inconsistently reported to be comparable. Of greatest interest is the incidence of pump thrombosis and need for pump-exchange. The median incidence of pump thrombosis was 30% across the larger cohorts studied with a subsequent 8% incidence of pump exchange. Although most pump thromboses reported were thrombolyzed to avert pump exchange, almost all thrombosis complications were of the RVAD. Pump thrombosis and exchange remains the main dilemma with BiVADs, whether continuous-flow or otherwise.

As it is primarily designed for the left ventricle, these LVADs implanted do not take into account the anatomy, geometry and physiology of the right ventricle. As such, the inlet is too long (primarily designed for LV apex cannulation) and pump flows too high [not accounting for the lower afterload of pulmonary vascular resistance (PVR) compared with systemic (SVR)]. The HeartWare HVAD for example accommodates for 600–3,500 dynes/sec/cm^5. However, PVR is generally <250 dynes, and banding procedures on the VAD outflow trunk are usually required to increase the afterload, and thus reduce the risk of pulmonary oedema from excessive flow to the pulmonary vasculature (28). Across our review, each study described a differing surgical approach, from: inlet cannulation, pump-placement, pump-speed variation, banding strategy, and even TV explantation. Within some studies, there were sub-group analyses comparing RA- and RV-cannulation.

Reducing outflow graft diameter with suture line, clips (*Figure 3*), bands, or utilizing an 8 mm outflow graft rather than the standard 10 mm diameter have all been described in both the HeartWare HVAD and HeartMate 3 (26,39). This increases resistance to the pump so that a lower PVR can be accommodated. Modifications of pump speed to accommodate for reduced PVR have been evaluated, but must be balanced against the increased risk of pump thrombosis at lower speeds. These are obviously model-specific, and thus modifications to one device are not uniformly applicable across other devices (40).

All studies describing their configuration detailed procedures to reduce the inflow-cannula intra-cavity distance, predominantly with felt-spacers. Furthermore, our review found that 45% of BiVAD recipients had RA-inflow cannulation compared with 55% RV-inflow cannulation of the RVAD. Higher rate of thrombosis has been most often found in RV-inflow cannulation (24), with the advent of RA-inflow cannulation designed to combat this complication.

With the offloading of both ventricles, the RV has been visualized to remodel on serial echocardiography, resulting in a reduced cavity size. As such, suction events become more frequent leading to a higher incidence of pump thrombosis. This has been dynamically demonstrated in multiple patients with occlusion of the inflow cannula by the interventricular septum on respiratory expiration (30).

TV-explantation was performed by a small case series of four patients by Maltais *et al.*, with the intent of reducing RVAD thrombosis with RV-inflow cannulation (25). However, not only does this preclude the possibility of RVAD removal in RV recovery, three out of four of their patients had pump-thrombosis nonetheless.

Delayed RVAD implantation occurred in 18% of cases across studies. Often this was preceded with a temporary mechanical support device to trial need for RVAD, as it was presumably an unexpected event. Nonetheless, delayed RVAD implantation is proven to have worse outcomes than planned (concomitant) RVAD implantation, although we could not accurately compare long-term outcomes in our study (4,24,41).

But there remain limitations to BiVADs that undoubtedly reduce survival and quality of life compared with LVAD alone, prompting many clinicians to avoid RVAD implantation with temporary devices if possible. There remain two separate drivelines, and if two different devices are implanted (occasionally in delayed RVAD implantation) having two separate controllers is of great inconvenience for the patient and care-team. Although risk of infection is increased with two drivelines, size is also of great significance. Solutions to extracorporeal power supply have been attempted. The Lion Heart study examining a completely implantable device without a driveline and requiring only transcutaneous power induction was associated with significant infection risk. This was thought to be secondary to volume and size of foreign material located within the chest (42). As devices become smaller, risk of infection is likely to decrease as well.

Some institutions are reticent to implement BiVAD support to transplant due to potentially worse outcomes than single device, increased cost, demanding and non-standardized implantation techniques, and reduced patient quality of life with double peripherals (43). However, in centers where transplant wait-list times are shorter, there may be less reluctance to place high-risk patients on BiVAD and thus ameliorate the risk of delayed insertion (43). In fact, BiVAD implantation has been recommended to be limited to BTT patients rather than destination therapy (DT), where non-survival outcomes are preferenced including quality of life and functionality (13). As such, higher risk profile groups (INTERMACS 1-2) are less likely to receive VAD support if BTT is unlikely, and LVAD for DT is becoming a more semi-elective procedure (44).

There remains the TAH as a viable alternative to BiVAD implantation. Studies show no difference in outcome between TAH *vs.* BiVAD thus far (20,45), and the single driveline is seemingly an attractive alternative. However, TAH requires explantation of the native ventricles, and thus excludes the potential for ventricular recovery, which was demonstrated to be 5% by Cleveland *et al.* 2011 (14). It is also bulkier, more expensive, and few centers have experience with its implantation and post-operative care, compared with utilizing an additional LVAD (44). Furthermore, being a pulsatile device, it requires a large driver that contains a noisy compressor and is significantly limiting in comparison with the BiVADs currently available (28). However, TAH does provide a role in patients with refractory arrhythmias, as well as those with restrictive cardiomyopathies where VAD placement would be complicated by small ventricular cavities.

Overall, the need for a biventricular assist device presents a conundrum. There is no dedicated long-term RV support device and in such severe biventricular failure, transplant would be the best option. The staged approach of RVAD implantation demonstrates the unpredictable nature of RVF post LVAD insertion. And, although most VAD recipients are indicated for destination therapy, the opposite trend is found with BiVADs recipients, whom are predominantly indicated as bridge to transplant.

Limitations

There was significant overlap in the cohorts studied, with many studies including populations from one another (23,27,28). In particular, there would be overlap of patient cohorts from various registries including UNOS, InterMACS, and EuroMACS, which likely introduces bias to the results. Unfortunately, these cohorts could not be separated to reveal the absolute number of patients. Additionally, small sample size bias may have affected study results—the largest being 93 CF-BiVAD recipients. Once again this demonstrates the novel nature of continuous-flow devices being utilized in this niche heart failure strategy. With no particular VAD designed for the right ventricle, the differing strategies of conforming an LVAD for RV use adds heterogeneity. This may have confounded the results

further with differing anticoagulation strategies post-operatively also described. Finally, there was no consistent indication algorithm for BiVAD implantation across studies—some studies having defined indications based upon RV failure parameters (40), whilst others deferred to surgeons' discretion (27).

Conclusions

Although these patients represent a small subset of cardiac failure patients requiring mechanical ventricular assistance, a dedicated CF-RVAD for a BiVAD configuration is greatly in need. The variety of alterations and adjustments to off-label use of varying LVADs demonstrates how unregulated practice can be. A purpose-designed device would greatly reduce error by standardizing practice whilst reducing risk of pump thrombosis. A dedicated BiVAD device would ideally taper to a single driveline, or better, a trans-cutaneous charge thus reducing infection risk and improving quality of life. Studies are promising in the advent of continuous-flow devices, and greater progress is now needed to accommodate for this cohort whilst awaiting definitive transplantation.

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Footnote

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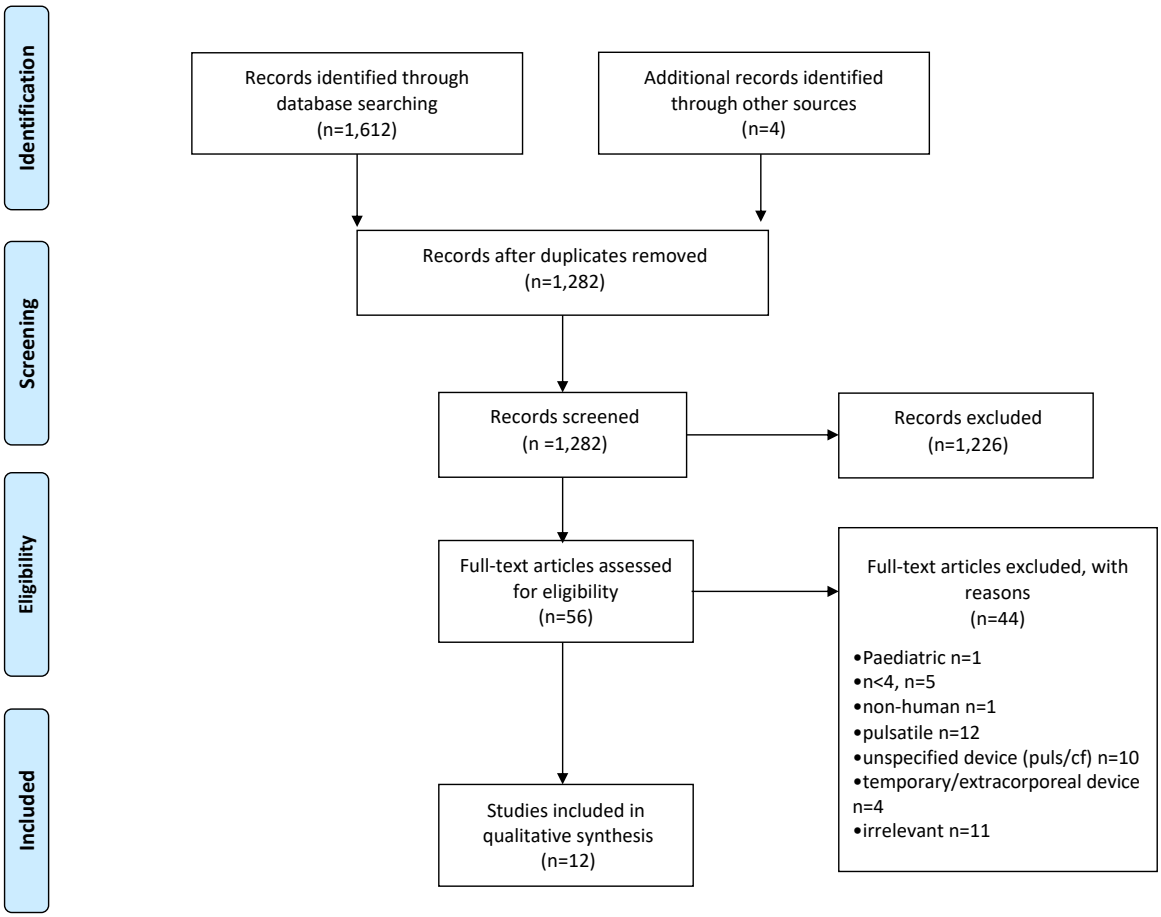

Figure S1 PRISMA flow diagram. cf, continuous flow; puls, pulsatile.

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