Outcome of Pre-transplant Left Ventricular Assist Device as Bridge to Heart Transplant in Patient with Fixed and non Fixed Pulmonary Hypertension : Systematic Review and Meta-analysis

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COI Disclosure

Febry Krisna, MD:

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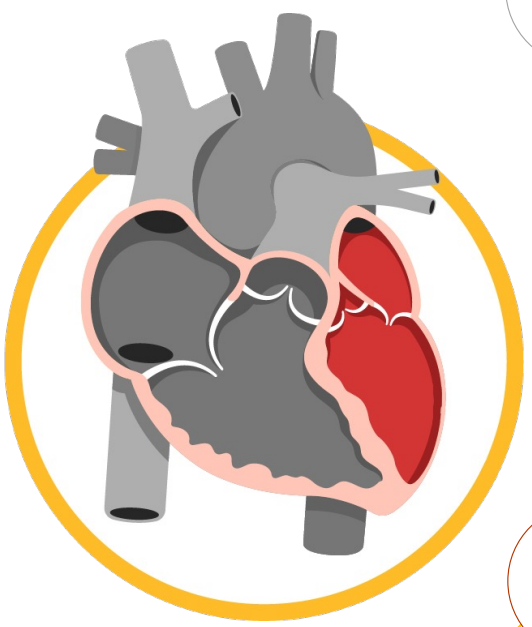
BACKGROUND

Advanced Heart Failure

Persistent symptoms despite maximal therapy



- Severe and persistent symptoms of heart failure (NYHA III or IV)
- Severe cardiac dysfunction
- Episodes of pulmonary or systemic congestion requiring high-dose i.v. diuretics
- Severe impairment of exercise capacity

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ESC European Society of Cardiology

European Heart Journal (2021) 42, 3599–3726
doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

Recommendations	Class[a]	Level[b]
Patients being considered for long-term MCS must have good compliance, appropriate capacity for device handling and psychosocial support.[414–416]	I	C
Heart transplantation is recommended for patients with advanced HF, refractory to medical/device therapy and who do not have absolute contraindications.	I	C
Long-term MCS should be considered in patients with advanced HFrEF despite optimal medical and device therapy, not eligible for heart transplantation or other surgical options, and without severe right ventricular dysfunction, to reduce the risk of death and improve symptoms.[378,396,397,401,402,404,417]	IIa	A
Long-term MCS should be considered in patients with advanced HFrEF refractory to optimal medical and device therapy as a bridge to cardiac transplantation in order to improve symptoms, reduce the risk of HF hospitalization and the risk of premature death.[398–400,402,404]	IIa	B
Renal replacement therapy should be considered in patients with refractory volume overload and end-stage kidney failure.	IIa	C
Continuous inotropes and/or vasopressors may be considered in patients with low cardiac output and evidence of organ hypoperfusion as bridge to MCS or heart transplantation.[389,390]	IIb	C
Ultrafiltration may be considered in refractory volume overload unresponsive to diuretic treatment.[391,392]	IIb	C

Advanced Heart Failure → Pulmonary Hypertension (Group 2 PH)

- PASP ≥ 50 mm Hg
- TPG ≥ 15 or PVR ≥ 3

↓

Vasodilator challenge

↓

If fails to achieve acceptable hemodynamics → ***irreversible***

Listing Criteria for Heart Transplantation: International Society for Heart and Lung Transplantation Guidelines for the Care of Cardiac Transplant Candidates—2006

- Pulmonary artery hypertension and elevated PVR should be considered as a relative contraindication to cardiac transplantation when the PVR is >5 Wood units or the PVRI is >6 or the TPG exceeds 16 to 20 mm Hg
- If the PAS exceeds 60 mm Hg in conjunction with any 1 of the preceding 3 variables, the risk of right heart failure and early death is increased
- If the PVR can be reduced to <2.5 with a vasodilator but the systolic blood pressure falls <85 mm Hg, the patient remains at high risk of right heart failure and mortality after cardiac transplantation

ESC European Society of Cardiology
European Heart Journal (2021) **42**, 3599–3726
doi:10.1093/eurheartj/ehab368
ESC GUIDELINES

Indications
Advanced HF[376]
No other therapeutic option, except for LVAD as BTT
Contraindications
Active infection[a]
Severe peripheral arterial or cerebrovascular disease
Pharmacologic irreversible pulmonary hypertension (LVAD should be considered to reverse elevated pulmonary vascular resistance with subsequent re-evaluation to establish candidacy)
Malignancy with poor prognosis (a collaboration with oncology specialists should occur to stratify each patient as regards their risk of tumour progression or recurrence which increases with the use of immunosuppression)
Irreversible liver dysfunction (cirrhosis) or irreversible renal dysfunction (e.g. creatinine clearance <30 mL/min/1.73 m^2). Combined heart-liver or heart-kidney transplant may be considered
Systemic disease with multiorgan involvement
Other serious comorbidity with poor prognosis
Pre-transplant BMI >35 kg/m^2 (weight loss is recommended to achieve a BMI <35 kg/m^2)
Current alcohol or drug abuse
Psychological instability that jeopardizes proper follow-up and intensive therapeutic regime after heart transplantation
Insufficient social supports to achieve compliant care in the outpatient setting

AIM

To evaluate the outcomes of the LVAD use as bridge-to-transplant (BTT) in patients with Group 2 PH.

METHODS

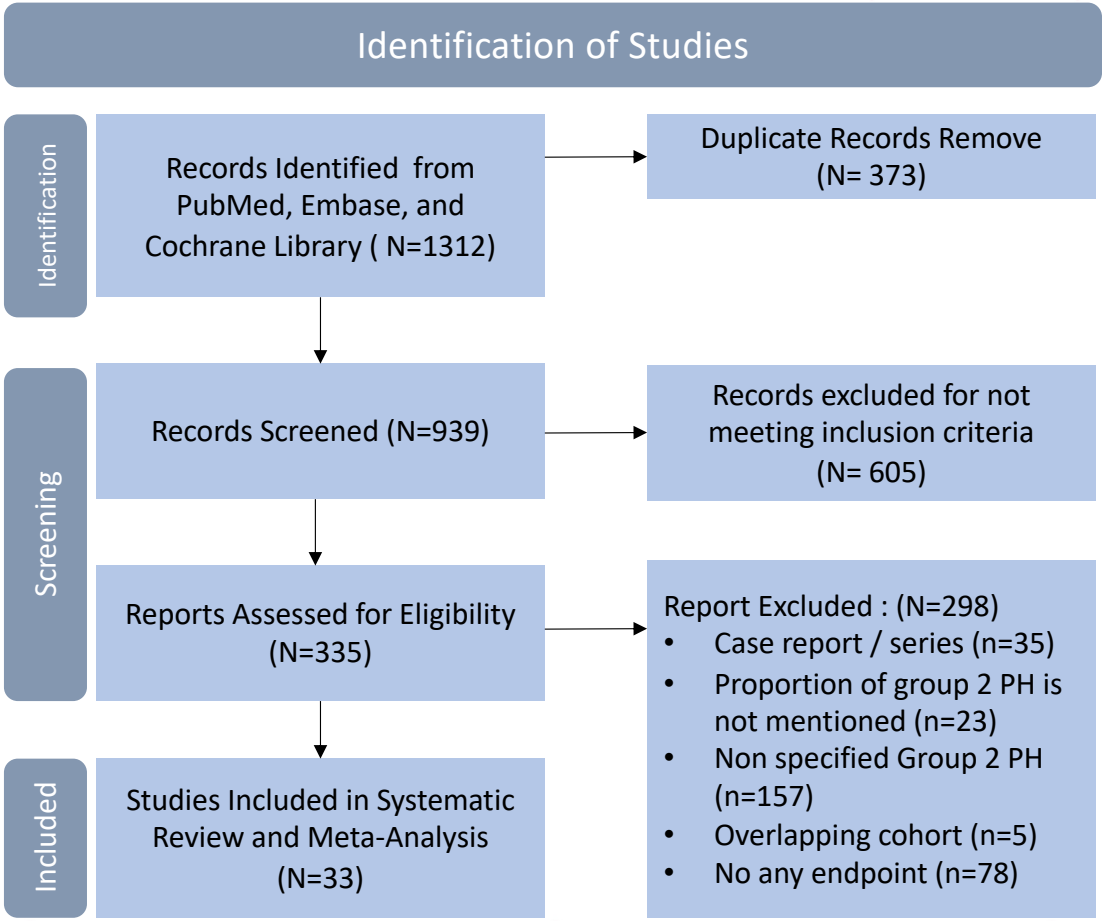
PROSPERO : CRD42023472951

Inclusion criteria

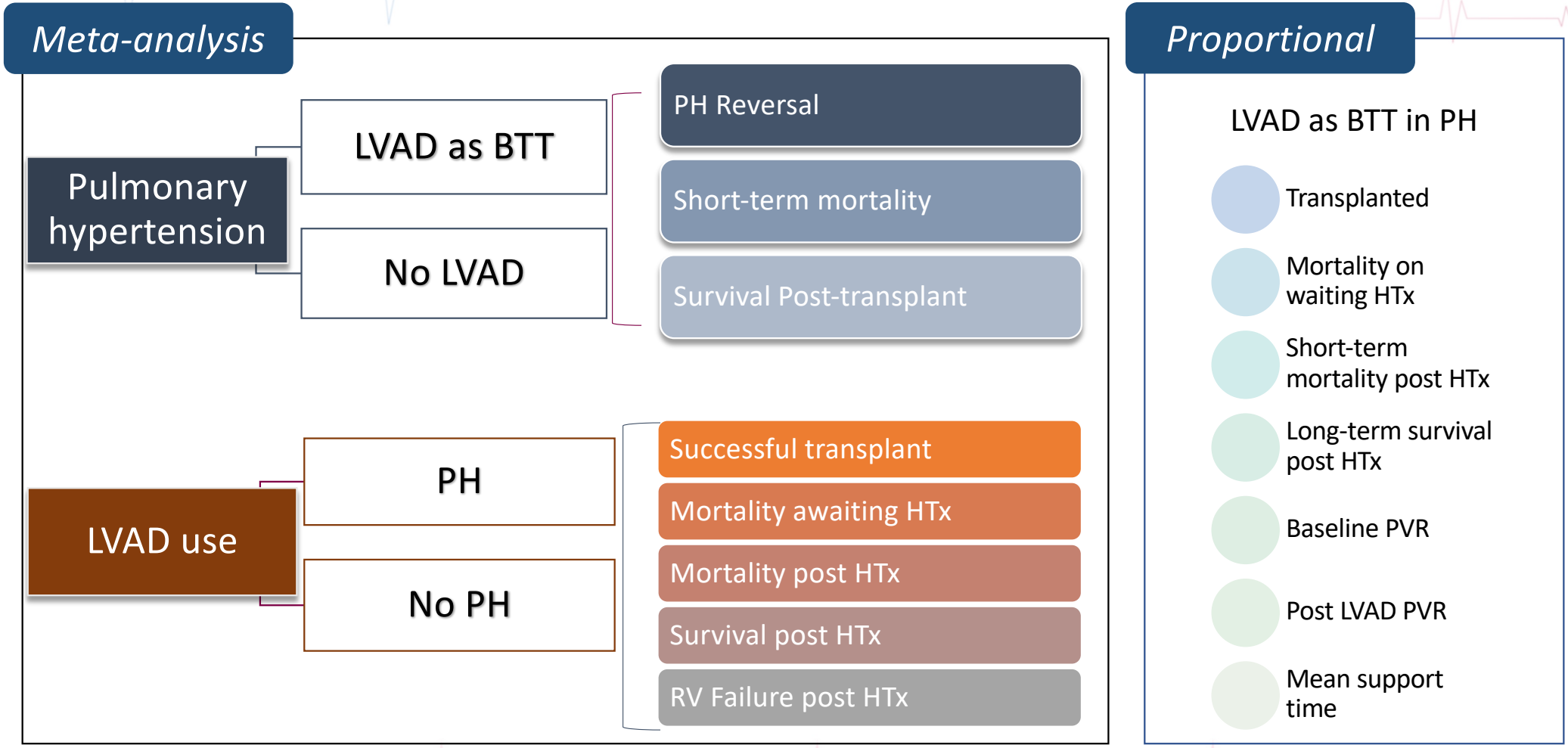
- Population :
  - ➢ Patient with advanced heart failure and Pulmonary Hypertension (group 2 PH)
  - ➢ Patient with LVAD as BTT
- Intervention : LVAD implantation as a bridge-to-transplant
- Control : did not undergo LVAD implantation
- Provide any outcomes of primary outcomes

Exclusion criteria

- Experimental animal models / basic science
- Review/Meta-analysis
- Secondary research papers
- Case report and case series
- Duplicate population



Systematic review, Meta-analysis, Proportional meta-analysis


Meta-analysis
Pulmonary hypertension
LVAD as BTT
No LVAD
PH Reversal
Short-term mortality
Survival Post-transplant
LVAD use
PH
No PH
Successful transplant
Mortality awaiting HTx
Mortality post HTx
Survival post HTx
RV Failure post HTx
Proportional
LVAD as BTT in PH
Transplanted
Mortality on waiting HTx
Short-term mortality post HTx
Long-term survival post HTx
Baseline PVR
Post LVAD PVR
Mean support time

RESULTS AND DISCUSSION

RISK OF BIAS ASSESMENT

Author	Selection				Comparability		Outcome			Score
	1	2	3	4	1	2	1	2	3	
Liden 2009	*	*	*	*	*	-	*	*	*	8
Al-Kindi 2016	*	*	*	*	*	-	*	*	*	8
Kumarasinghe 2018	*	*	*	*	*	*	*	*	*	9
Ando 2019	*	*	*	*	*	-	*	*	*	8
Schummer 2017	*	*	*	*	*	-		-	*	6
Frutos 2020	*	*	*	*	*	-	*	*	*	8
Alba 2010	*	*	*	*	*	-	-	-	*	6
Kutty 2013	*	*	*	*	*	*	-	-	*	7
Mikus 2011	*	*	*	*	*	*	*	*	*	9
Moayedifar 2018	*	*	*	*	*	*	*	*	*	9
Nair 2010	*	*	*	*	*	-	*	*	*	8
Tsukashita 2015	*	*	*	*	*	-	*	*	*	8
Smedira 1996	*	*	*	*	-	-	*	*	*	8
Uriel 2019	*	*	*	*	-	-	*	*	*	7
Grupper 2022	*	*	*	*	-	-	-	-	*	5
Tremblay 2021	*	*	*	*	-	-	-	-	*	5
Ruan 2022	*	*	*	*	-	-	-	-	*	5
Anegawa 2023	*	*	*	*	-	*	-	-	*	6
Torre-Amione 2010	*	*	*	*	-	-	*	*	*	7
Etz 2007	*	*	*	*	-	*	*	*	*	8
Han 2018	*	*	*	*	-	-	*	*	*	7
John 2010	*	*	*	*	*	-	-	-	*	6
Zolty 2008	*	*	*	*	-	-	-	-	*	5
Saidi 2012	*	*	*	*	*	-	-	-	*	6
Atluri 2011	*	*	*	*	-	-	-	-	*	5
Gupta 2014	*	*	*	*	-	*	-	-	*	6
Kettner 2011	*	*	*	*	-	*	-	-	*	6
Al-Sarie 2016	*	*	*	*	-	*	-	-	*	6
Zimpfer 2006	*	*	*	*	*	*	*	*	*	9
Bhashyam 2008	*	*	*	*	-	*	-	-	*	6
Dorazilova 2012	*	*	*	*	-	*	*	*	*	8
Houston 2015	*	*	*	*	-	*	-	-	*	6
Doss 2015	*	*	*	*	-	*	-	-	*	6

RESULTS AND DISCUSSION

CHARACTERISTICS OF STUDY

authors	study design	total population	PH		PVR Baseline		Total PH patients transplanted with LVAD	Type of LVAD use
			LVAD	no LVAD	LVAD	No LVAD		
Liden 2009	retrospective	33	11	22	4.3	4.3	11	HeartMate
Al-Kindi 2016	retrospective	1016	393	623	5.3	5.9	235	HeartMate II,HeartWare
Kumarasinghe 2018	retrospective	24	10	14	6.5	6.4	4	HeartWare
Ando 2019	retrospective	1040	798	242	3.7	3.8	798	HeartMate II,HeartWare
Schummer 2017	retrospective	8446	2179	6286	NA	NA	2179	HeartMate II,HeartWare
Frutos 2020	retrospective	19	7	12	5.9	6.2	6	HeartMate III, EXCOR, HeartWare
Alba 2010	retrospective	54	22	NA	4.4	NA	22	HeartMate II, Novacor
Kutty 2013	retrospective	29	17	NA	5.1	NA	9	HeartWare
Mikus 2011	retrospective	145	56	NA	3.61	NA	19	NA
Moayedifar 2018	retrospective	127	79	NA	5.4	NA	79	HeartMate II, Novacor, HVAD
Nair 2010	retrospective	58	44	NA	4.82	NA	36	HeartMate, Novacor
Tsukashita 2015	retrospective	227	45	NA	7.13	NA	30	HeartMate II,HeartWare
Smedira 1996	retrospective	63	47	NA	5	NA	38	HeartMate
Uriel 2019	retrospective	416	202	NA	4	NA	122	HeartMate II
Grupper 2022	retrospective	65	5	NA	6.55	NA	4	HeartMate II, HeartMate III
Tremblay 2021	retrospective	177	107	NA	NA	NA	60	HeartMate II, HeartMate III, HVAD
Ruan 2022	retrospective	78	42	NA	3.8	NA	33	HeartMate II, HeartMate III, HVAD
Anegawa 2023	retrospective	89	50	NA	4.36	NA	22	HeartMate II, HVAD, DuraHeart
Torre-Amione 2010	retrospective	23	9	NA	NA	NA	9	Novacor, HeartMate
Etz 2007	retrospective	10	10	NA	4.8	NA	5	INCOR
Han 2018	retrospective	83	53	NA	3	NA	17	HVAD. HMII
John 2010	retrospective	50	50	NA	3.6	NA	32	HeartMate II
Zolty 2008	retrospective	12	12	NA	7.6	NA	12	HeartMate II
Saidi 2012	retrospective	16	16	NA	3.4	NA	16	NA
Atluri 2011	retrospective	49	49	NA	NA	NA	38	NA
Gupta 2014	retrospective	35	35	NA	3.7	NA	24	NA
Kettner 2011	retrospective	11	11	NA	6.1	NA	7	NA
Al-Sarie 2016	retrospective	25	25	NA	4.5	NA	25	NA
Zimpfer 2006	retrospective	35	35	NA	5.1	NA	24	Novacor, DuraHeart, DeBakey
Bhashyam 2008	retrospective	15	15	NA	3.2	NA	9	NA
Dorazilova 2012	retrospective	65	12	NA	6.3	NA	7	HeartMate II
Houston 2015	retrospective	66	16	NA	5.1	NA	NA	HeartMate II
Doss 2015	retrospective	49	49	NA	3.7	NA	NA	HeartMate II, HeartWare

RESULTS AND DISCUSSION

OUTCOMES OF THE STUDY

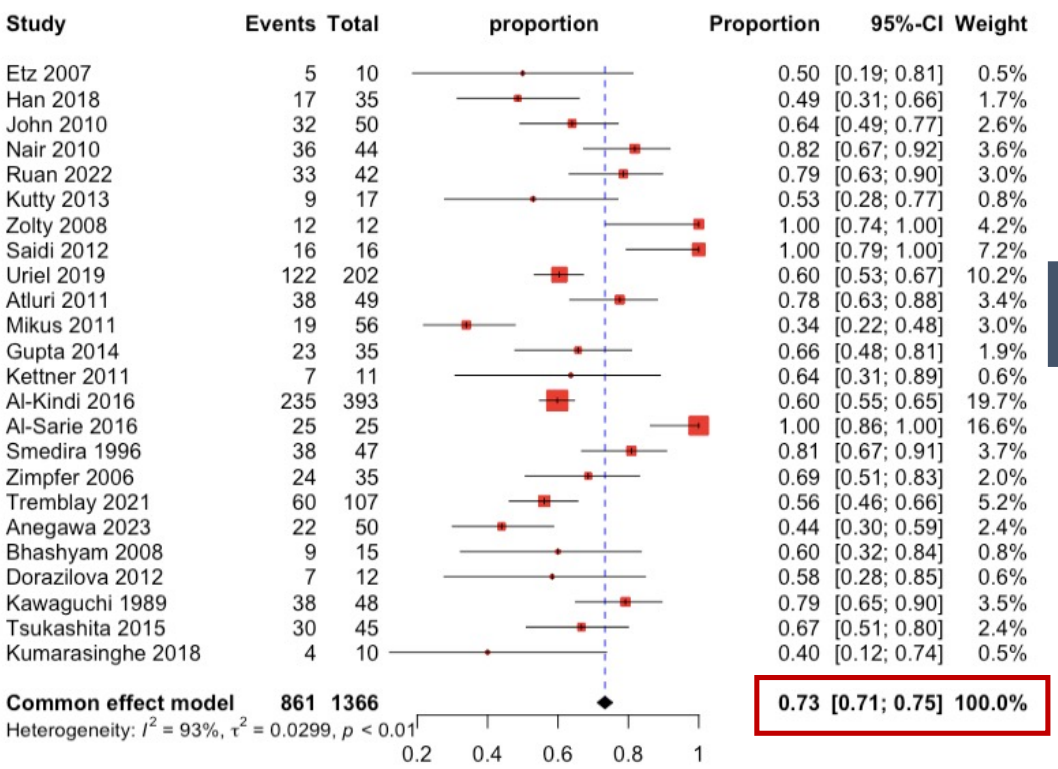
PH WITH LVAD VS NO LVAD

Forest Plot	RR	95% CI	P-Value	I^2 (%)
PH reversal	1.7	1.55 – 1.85	<0.00001	91
Short-term mortality post HTx	0.55	0.32 – 0.93	0.03	0
Survival Post HTx	1.11	1.05 – 1.17	0.0001	35

Forest plot Risk Ratio with fixed effect models of outcomes PH patients with LVAD vs No LVAD.

Outcomes Bridging PH patients with LVAD

(A)

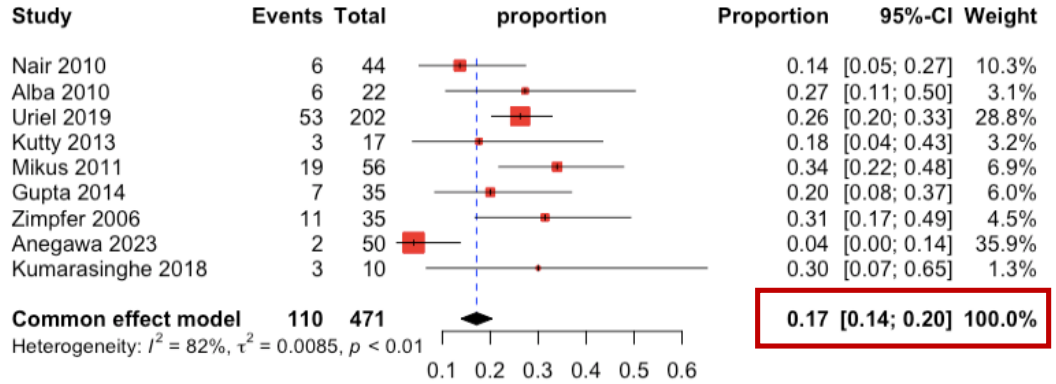


PH patients bridging with LVAD had **73% transplant success rate** [proportion 0.73; 95% CI 0.71 – 0.75; $p < 0.01$, $I^2 = 93\%$]

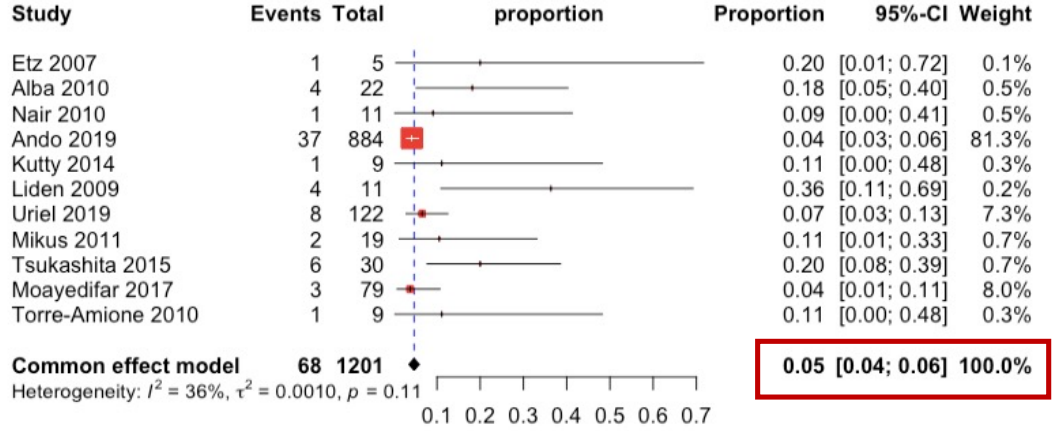
Forest plot proportion (%) with fixed effect models of outcomes bridging PH patients with LVAD. **(A)** Transplant success rate.

Outcomes Bridging PH patients with LVAD

(B)



(C)

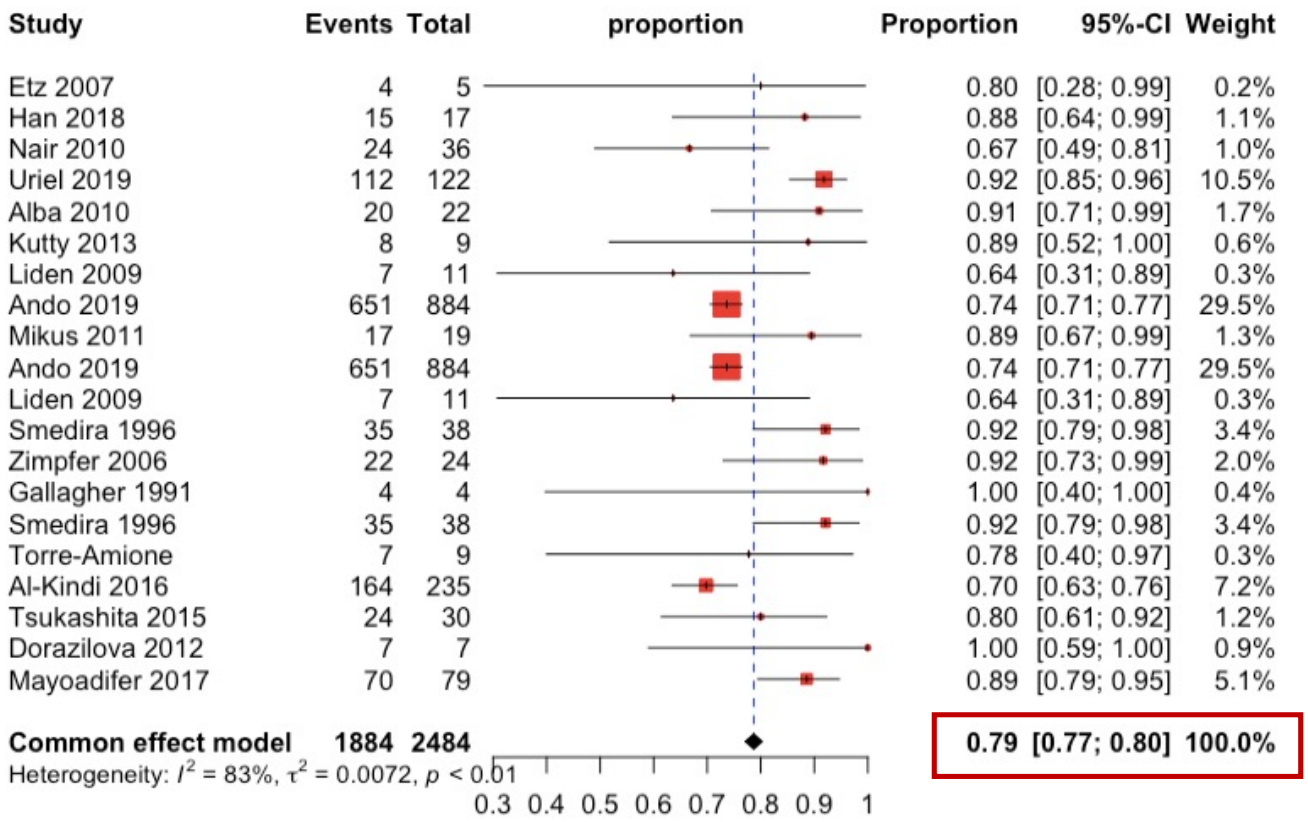


PH patients bridging with LVAD had **17% mortality rate on waiting HTx** [proportion 0.17; 95% CI 0.14 – 0.20; p < 0.01, I^2 = 82%] and **5% post transplant mortality** (30-days) [proportion 0.05; 95% CI 0.04 – 0.06; p = 0.11, I^2 = 36%]

Forest plot proportion (%) with fixed effect models of outcomes bridging PH patients with LVAD. **(B)** Mortality awaiting HTx. **(C)** 30-days Mortality Post HTx.

Outcomes Bridging PH patients with LVAD

(D)

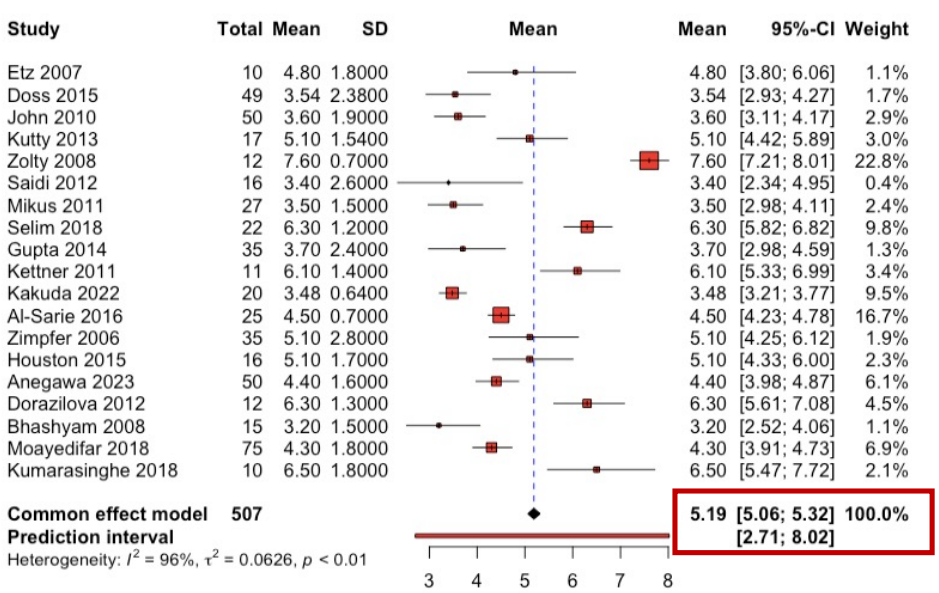


PH patients bridging with LVAD had **79% post transplant survival rate** [proportion 0.79; 95% CI 0.77 – 0.80; $p < 0.01$, I^2 = 83%]

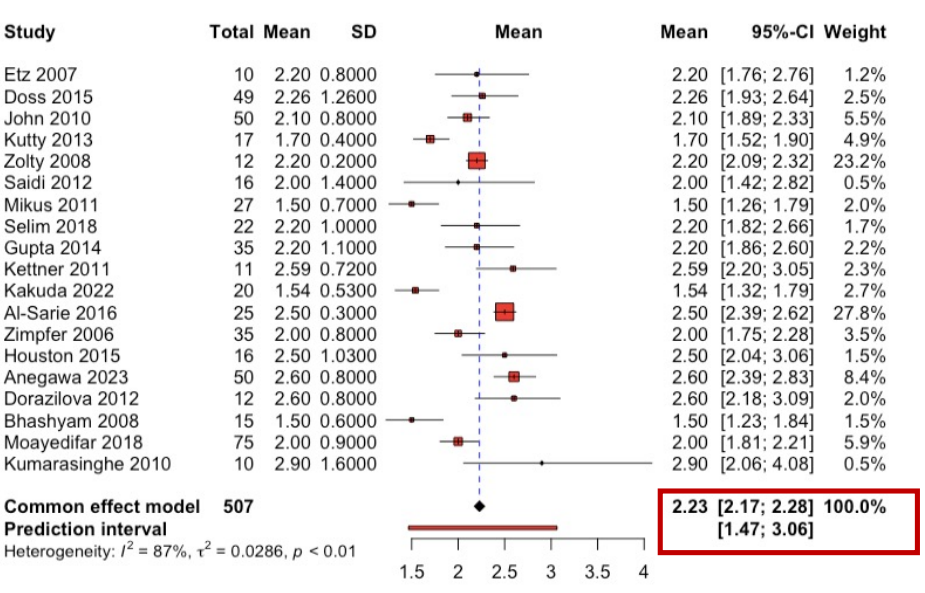
Forest plot proportion (%) with fixed effect models of outcomes bridging PH patients with LVAD. **(D)** Post transplant survival rate.

Outcomes Bridging PH patients with LVAD

(E)



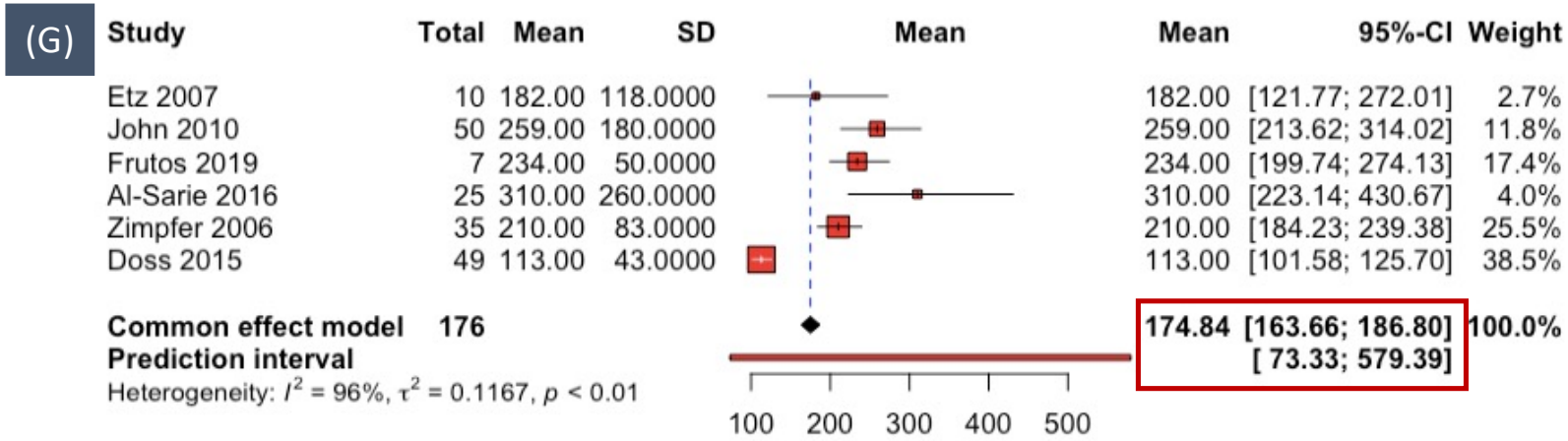
(F)



LVAD can reduce PVR from **5.19 WU** [mean 5.19; 95% CI 5.06 – 5.32; p < 0.01, I^2 = 96%] to **2.23 WU** [mean 2.23; 95% CI 2.17 – 2.28; p < 0.01, I^2 = 87%].

Forest plot mean with fixed effect models of outcomes bridging PH patients with LVAD.
(E) Baseline PVR. **(F)** Post LVAD implantation PVR

Outcomes Bridging PH patients with LVAD



Mean support time **174.84 days**
[mean 174.84; 95% CI 163.66 – 186.80; p < 0.01, I^2 = 96%]

Forest plot mean with fixed effect models of outcomes bridging PH patients with LVAD.
(G) Mean support time

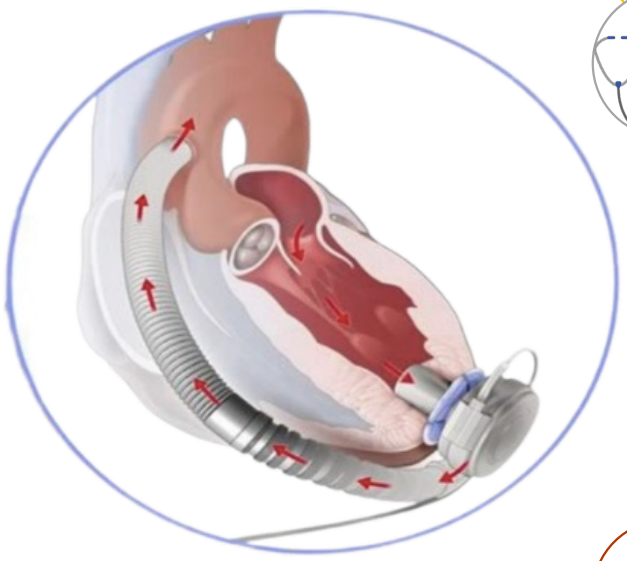
OUTCOMES BRIDGING WITH LVAD IN PH VS NO PH

Double arm forest plot of outcomes LVAD in PH vs No PH	RR	95% CI	P-Value	I^2 (%)
Transplanted	1.09	0.99 – 1.2	0.09	58
Mortality awaiting HTx	0.91	0.71 – 1.15	0.43	0
30-days mortality post HTx	1.69	0.99 – 2.89	0.06	14
Survival post HTx	1.02	0.95 – 1.10	0.37	8
RV Failure post HTx	1.03	0.75 – 1.41	0.85	0

Forest plot Risk Ratio with fixed effect models of outcomes LVAD in PH vs No PH

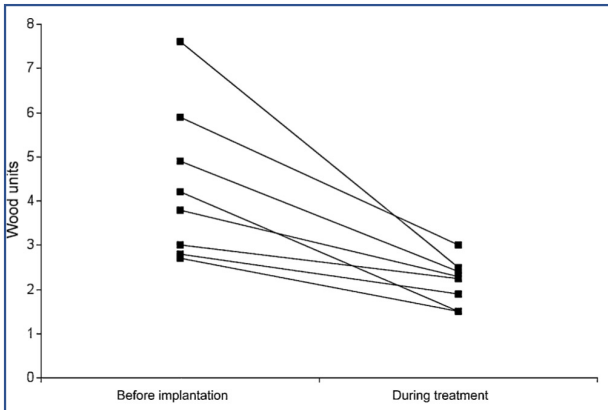
KEY FINDINGS

Using LVAD as bridge-to-transplant can normalize PVR

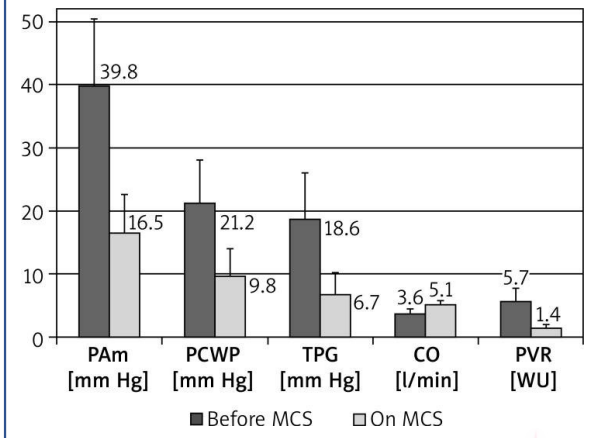


- LVAD give benefit on hemodynamic : Increase CO, overall reduction on TPG (marked by PVR reduction)
- Patients with non-reversible PH & not elegible to transplant → converted to transplant candidate
- The prognosis and survival post transplant are comparable with those normal PVR at baseline supported with LVAD
- Incidence of RV failure post HTx not significantly increase compare to those with normal PVR at baseline and supported with LVAD

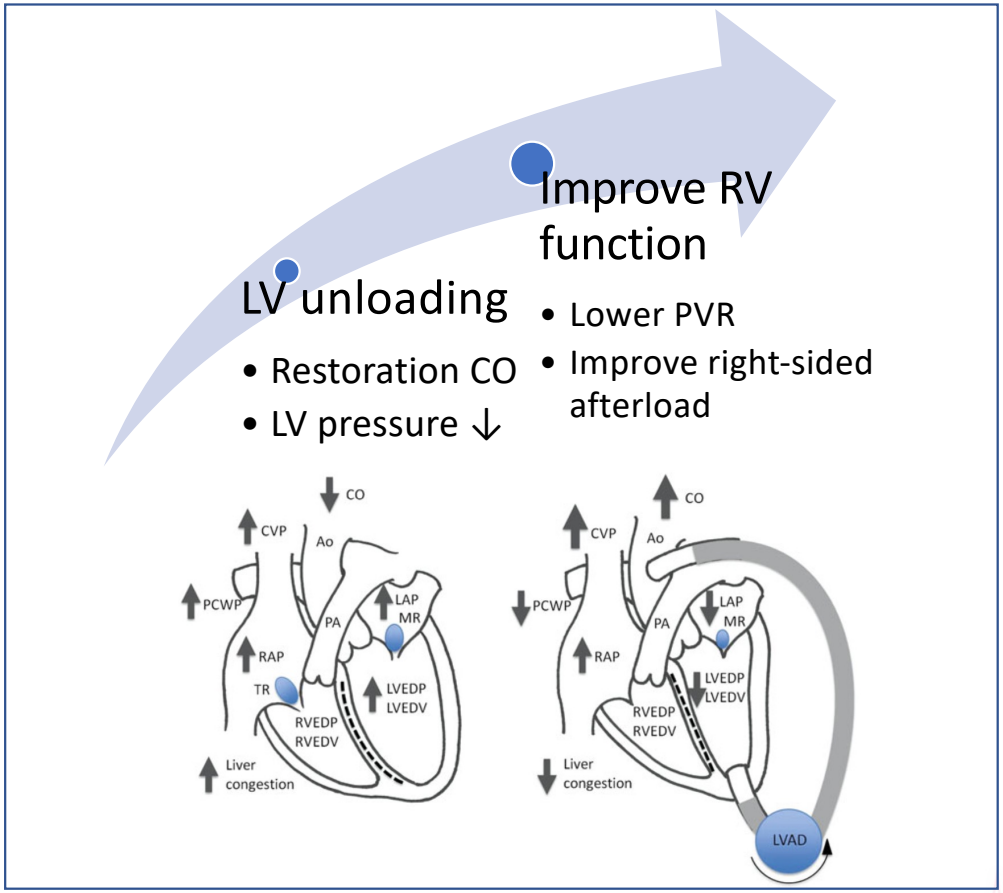
Normalization PVR using LVAD



PVR before and during support, $p < 0.01$

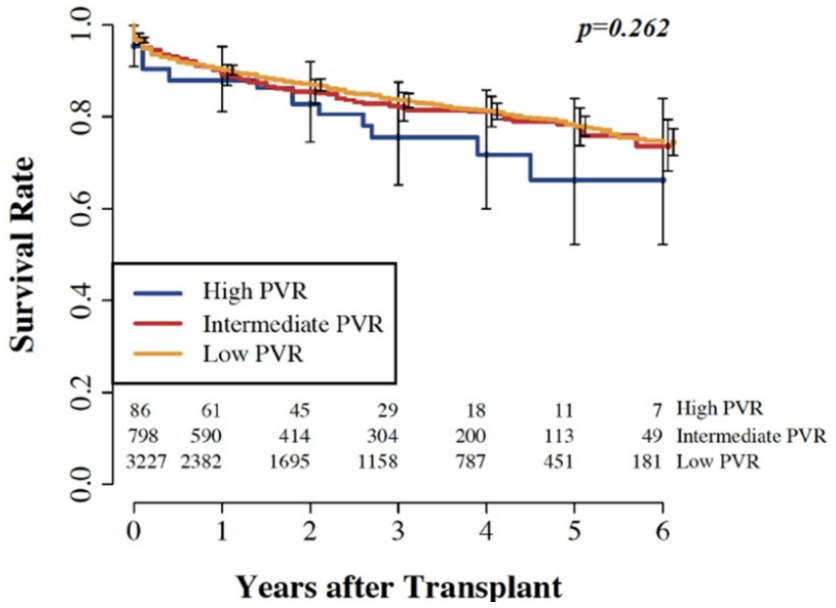


RHC before and during MCS therapy

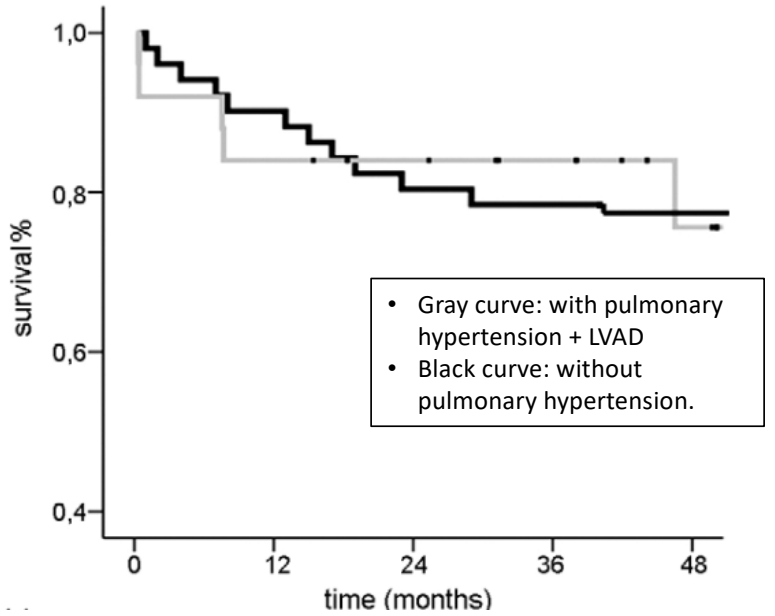


Eur J Cardio-thoracic Surg 2009; **35**: 1029–1035
Polish J Cardio-Thoracic Surg 2018; **15**: 23. 1
Springer Japan: Tokyo, 2014, pp 113–129

Survival Post Transplant



Kaplan-Meier curves showing no significant differences between the PVR in LVAD groups P=0.262

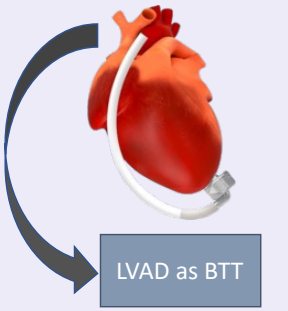


Kaplan-Meier curve displaying long-term post-transplant survival. Log-rank (p =0.124)

Ann Thorac Surg 2020; **110**: 158–164.
Eur J Cardio-thoracic Surg 2007; **31**: 698–702.

CONCLUSION

CONCLUSION



LVAD as BTT

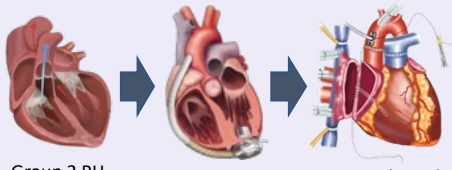
Fixed and Non-fixed PH undergo LVAD implantation (n=4511)

Double arm forest plot of outcomes PH with LVAD vs No LVAD	RR	95% CI	P-Value	I^2 (%)
PH reversal	1.7	1.55 – 1.85	<0.00001	91
Short-term mortality post HTx	0.55	0.32 – 0.93	0.03	0
Survival Post HTx	1.11	1.05 – 1.17	0.0001	35

0 1 2 3 4

Double arm forest plot of outcomes LVAD in PH vs No PH	RR	95% CI	P-Value	I^2 (%)
Transplanted	1.09	0.99 – 1.2	0.09	58
Mortality awaiting HTx	0.91	0.71 – 1.15	0.43	0
Mortality Post HTx	1.69	0.99 – 2.89	0.06	14
Survival Post HTx	1.27	1.15 – 1.4	<0.00001	87
RV Failure post HTx	1.03	0.75 – 1.41	0.85	0

0 1 2 3 4 5



Group 2 PH

PVR baseline 5.19 WU [mean 5.19; 95% CI 5.06 – 5.32; p < 0.01]

LVAD as BTT

17% mortality on waiting HTx [proportion – 0.17; 95% CI 0.14 – 0.20; p < 0.01]

PVR 2.23 WU [mean 2.23; 95% CI 2.17 – 2.28; p < 0.01]

Transplanted

73% transplant success rate

Proportion =0.73
95% CI 0.71 – 0.75; p < 0.01

5% short-term mortality post HTx

Proportion =0.05
95% CI 0.04 – 0.06; p = 0.11

79% post HTx survival rate

Proportion =0.79
95% CI 0.77 – 0.80; p < 0.01

Pre-transplant LVAD bridges patients with PH, especially non-reversible PH to eligible transplant candidate by normalize PVR. The prognosis and survival post heart transplant are comparable with those normal PVR at baseline and supported with LVAD.

Scan me!

Supplementary Material

THANK YOU

FEBRY KRISNA, MD

Udayana University, Bali, Indonesia