ISHLT JOURNAL WATCH
September 2026 | Pediatrics

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Everolimus and Low-Dose Tacrolimus After Heart Transplant in Children: A Randomized Clinical Trial

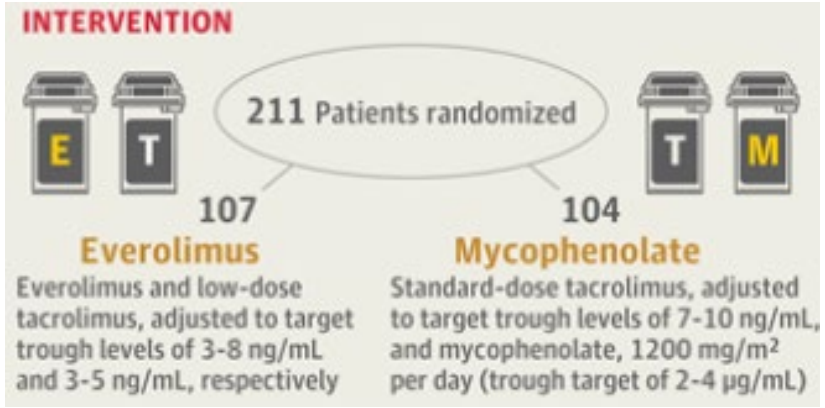
Raja KR, et al. *JTCVS Open,* 2026 April;30(101608)| DOI: 10.1016/j.xjon.2026.101608

Study Highlights

Objective:
To determine safety and efficacy of everolimus combined with low dose tacrolimus compared to standard dose tacrolimus and mycophenolate in preventing major adverse effects in transplant

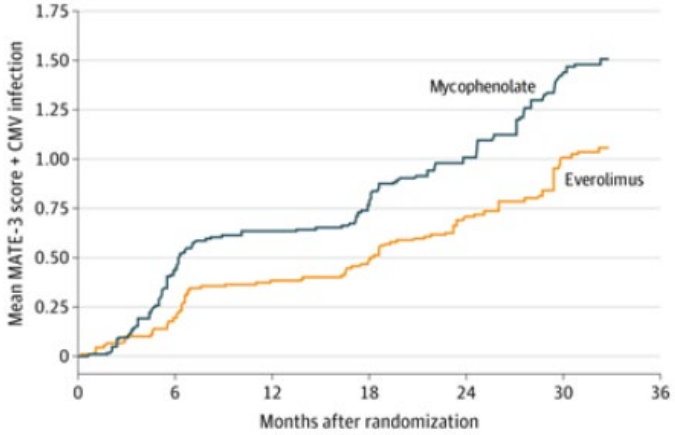
Methods:
- Multicentre, open-label clinical trial
- Randomised at 6 months post transplant (n= 211 patients)
- Follow up 30 months
- Primary efficacy end point: MATE-3 score (validated composite score comprising of Acute cellular rejection (ACR), Cardiac Allograft Vasculopathy (CAV) and Chronic Kidney Disease (CKD)
- Primary safety endpoint: MATE-6 score (MATE-3 score + events of Antibody Mediated Rejection (AMR), infection and Post Transplant Lymphoproliferative Disease (PTLD)

Results:
- At 30 months- no difference in the MATE-3 scores
- MATE- 6 score was not higher in the everolimus group
  →Everolimus and low dose tacrolimus regimen meets pre set trial safety criteria
- Everolimus associated with an improvement in eGFR at 12 months (but no difference between groups seen thereafter) and a lower incidence of CMV infection (see graph)
- 9 Graft loss events (6 deaths and 3 retransplants).
  - Everolimus group = 4
  - Mycophenolate group = 5
  - 1 death due to infection in each group



Cumulative MATE-3 score at 30 months plus CMV (mean diff, −0.45; 95% CI, −1.07 to −0.01; *P* = 0.03)

	Mean MATE-3 + CMV subscores at 30 mo			
	ACR	CAV	CKD	CMV
Everolimus	0.44	0.46	0.03	0.14
Mycophenolate	0.38	0.82	0.05	0.26



Reviewer's Comments

- FDA issued a black box warning against the use of everolimus in 2012 following increased early death related to infection post heart transplant in adults. However this trial has shown it is safe to initiate everolimus in children 6 months post-transplant. This data may be supportive of revision of the FDA guidance for heart transplant recipients.
- Whilst everolimus and low dose tacrolimus regimen did not differ from Mycophenolate and standard tacrolimus in preventing ACR, CAV and CKD, this new regimen may be associated with better kidney function and less CMV infection.
- Early improvement of renal function seen in the everolimus group is likely due to lower exposure to nephrotoxic tacrolimus (as difference in tacrolimus levels between groups is highest in the first 12 months). This regimen could be of clinical benefit in children at higher risk of renal complications early post transplant.

Limitations

- MATE-3 is a composite end point and surrogate score; cannot fully exclude the possibility of a false negative in the primary efficacy assessment.
- Study participant selection (excluded patients with severe kidney dysfunction and multiple early rejection episodes) limits application of these findings to all children post transplant.
- Higher proportion of Donor and Recipient negative for CMV in everolimus group may contribute to reduced incidence of CMV seen.

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Double bridge to heart transplantation: Outcomes of early versus delayed extracorporeal membrane oxygenation crossover in pediatric population

Raja KR, Farrukh SM, Kroslowitz B, O'Connor MJ, et al. *JTCVS Open,* 2026 April;30(101608)| DOI: 10.1016/j.xjon.2026.101608

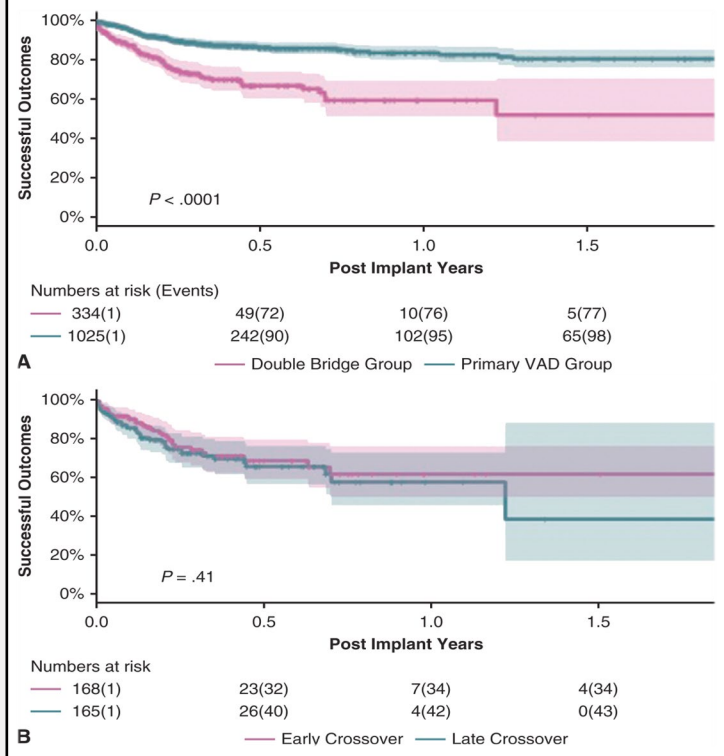
Study Highlights

Objective:
Compare outcomes between early vs late crossover in pediatric patients that were double-bridged (ECMO before VAD implantation) to heart transplantation.

Methods:
- Multicenter retrospective study using ACTION database
- Double-bridge (DB) to heart transplantation was subcategorized as early vs late ECMO to VAD crossover. Primary VAD group was used as reference for comparison.
- Univariate and multivariate Cox regression analysis performed to identify independent risk factors of outcomes. Survival assessed with Kaplan-Meier curves and competing risk analysis.

Results:
- Out of 1360 patients in the registry, 334 (24.6%) underwent DB strategy. At 1 year, DB group had a mortality of 23% compared with primary VAD group with a mortality of 9%. DB groups had an early (≤6 days) crossover mortality of 20% compared to 24.7% in the late (>6 days) crossover group.
- Within the entire cohort of patients, device intent of bridging to candidacy and ventilator support within 7 days of VAD implant were independent predictors of higher risk of mortality. A diagnosis of DCM/myocarditis and higher BSA led to lower risk of mortality.
- In DB group, device intent of bridging to candidacy was a predictor of increased mortality, whereas a diagnosis of DCM/myocarditis led to decreased mortality.
- Early crossover to VAD implantation was not an independent predictor of outcomes.

Conclusions:
- Timing of transition from ECMO to VAD as part of double bridge to transplant strategy was not independently associated with outcomes.



Risk factors for mortality after double-bridge to transplant-multivariable Cox regression model

Variable	Hazard ratio	Lower 95% CI	Upper 95% CI	*P* value
All patients (double-bridged and primary VAD implants)				
ECMO ever–yes	1.420	0.998	2.021	.051
Dilated cardiomyopathy/myocarditis	0.346	0.239	0.501	<.001 *
Bridge to candidacy	2.172	1.589	2.968	<.001 *
BSA	0.747	0.566	0.987	.040
Mechanical ventilation–yes	1.951	1.305	2.917	.001 *
Double-bridge group				
Crossover–early	0.881	0.557	1.392	.587
Dilated cardiomyopathy/myocarditis	0.367	0.204	0.658	<.001 *
Bridge to candidacy	2.122	1.342	3.353	.001 *

Reviewer's Comments

- This is the first study evaluating the duration of ECMO in double bridging to heart transplantation and its effect on patient outcomes in pediatric patients.
- Data supports that ECMO as a bridge to VAD leads to worse overall outcome, however timing of transition from ECMO to VAD was not independently associated with increased mortality.
- Increased mortality in the DB strategy is most likely a reflection of greater risk profile including younger age, small size, diagnosis other than DCM/myocarditis, higher proportion of CHD diagnosis and an INTERMACS 1 profile at time of implant compared to primary VAD group.
- Physiologic recovery, mitigation of risk factors and end organ function in DB group might play a role in the difference in outcome and not ECMO support/duration independently.

Limitations

- This was a retrospective voluntary registry analysis and hence design was chosen clinically (not randomized), so strategy and patient risk are inseparably confounded.
- There is a lack of accountability for variables that could add a risk for the double bridge group which are not accounted for like ECPR status, peripheral vs central ECMO and post cardiotomy status.
- Longitudinal data is not available to assess physiologic derangements or mitigation of risk with ECMO or VAD therapies.

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The United Kingdom National Programme of DCD heart transplantation: Timings, techniques, feasibility, and outcomes with abdominal normothermic regional perfusion

Morcos K, Simmonds L, Rushton S, Hogg R, et al. *J Heart Lung Transplant*. 2026;45:1581-1598. | DOI: 10.1016/j.healun.2026.04.027

Study Highlights

Objective:
A comparison of outcomes of heart transplants in the UK following donation after circulatory death (DCD) and donation after brain death (DBD). Primary outcomes were severe primary graft dysfunction (PGD) and survival.

Methods:
The study cohort comprised first-time, heart-only transplants at seven UK centres (2020-2024): 188 DCD and 523 DBD.
DBD hearts were retrieved and transported in ice. DCD hearts underwent direct procurement and ex-situ organ care system (OCS) perfusion, with or without Abdominal Normothermic Regional Perfusion (A-NRP). Primary outcomes were severe PGD and survival.

Results:
DCD transplants increased total activity by 7% versus the preceding four years. One-year survival was 87% vs 88% (P = 0.81). Severe PGD was 28% DCD vs 24% DBD unadjusted (P = 0.26), but adjusted odds (for pre-transplant mechanical circularity support, diagnosis, previous open-heart surgery, and recipient and donor age) were higher after DCD (OR 1.54, 95% CI 1.04-2.28; P = 0.03).
Longer OCS perfusion and implant times were associated with severe PGD/death at 1 year.

Conclusions:
Overall survival did not differ, but adjusted severe-PGD odds were higher after DCD. Longer OCS and implant times are potentially modifiable associations. A-NRP was feasible, but outcomes remain uncertain because the subgroup was small.

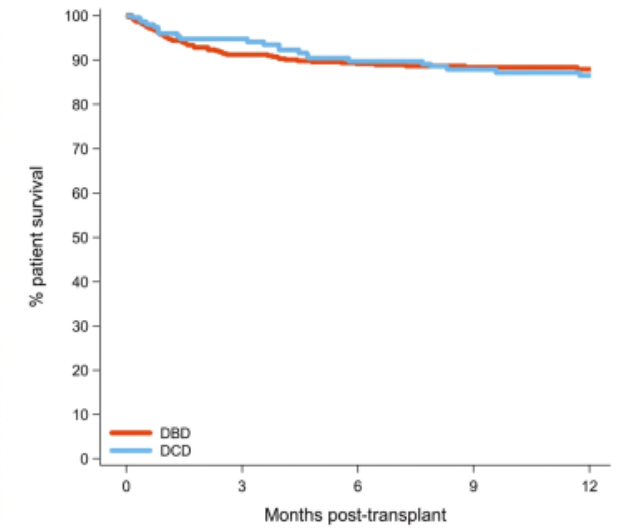

Figure 1. No 1-year survival difference was detected.

DCD timings associated with severe PGD/death at 1 year			
Median, min	PGD/death	No PGD/alive	p value
Bypass	219	168	<0.0001
OCS perfusion	269	238	0.020
Implant	60	53	0.030

Table 1. Within DCD, severe PGD/death was associated with longer bypass, OCS perfusion and implant times.

Reviewer's Comments

- DCD activity rose by 7% versus the prior four years.
- Severe PGD decreased from 40% in a previous pilot study (Messer et al. 2023) to 28% in this work.
- Higher adjusted severe-PGD odds in the DCD group suggest this was a comparatively healthier group.
- Paediatric applicability is chiefly to adolescents/larger recipients.
- Of the DCD patients, those with OGD had longer OCS perfusion times, longer implant times and prolonged cardiopulmonary bypass times.

Limitations

- Observational registry across seven centres; case mix and practice varied, leaving residual confounding.
- DCD-specific analyses were unadjusted; the A-NRP subgroup was small (n=22), limiting power.
- No paediatric subgroup outcomes were reported; small-donor hearts (≤50 kg) were excluded.
- Rejection data were missing for some recipients and treatment was empirical; biopsy and CAV data were unavailable.

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Explantation of durable ventricular assist device for myocardial functional recovery in children: A report from the ACTION registry

Langanecha B, Jeewa A, Adachi I, Mavroudis CD, et al. *JHLT* 2026 Jun 15:S1053-2498(26)01952-2. | DOI: 10.1016/j.healun.2026.06.007

Study Highlights

Objective:
To characterize the outcomes of durable ventricular assist device (VAD) removal for myocardial functional recovery (MFR) in children using a large North American multicenter cohort—a scenario that remains poorly defined in pediatrics compared with adults.

Methods:
Retrospective analysis of the Advanced Cardiac Therapies Improving Outcomes Network (ACTION) registry. Durable VADs were defined as intracorporeal continuous-flow (ICF) and paracorporeal pulsatile-flow (PPF) devices; temporary and paracorporeal continuous-flow devices were excluded. Explantations for MFR from March 2012 through August 2023 were identified. The primary outcome was VAD- and transplant-free survival after explantation.

Results:

- 31 of 938 patients (3.3%) supported with a durable VAD underwent explantation for MFR, representing patients from only 15 of 47 centers.
- Median duration of VAD support before explantation was 111 days (IQR, 59–183 days); median age was 1.17 years, and median weight was 8.4 kg.
- The leading etiology was dilated cardiomyopathy/myocarditis (64.5%), followed by CHD (10.0%) and other diagnoses (25.8%).
- Compared with the non-explant cohort, the explant cohort was **younger, smaller, and sicker** at implantation, with higher INTERMACS profiles and greater use of pre-implant ECMO and mechanical ventilation, at the time of implantation.
- Independent factors associated with explantation included a bridge-to-recovery strategy (HR, 10.37), pre-implant ECMO (HR, 2.37), and non-CHD diagnosis (CHD vs. non-CHD: HR, 0.19).
- Of 29 patients with follow-up, 72% (21/29) were alive without VAD reimplantation or transplantation at a median follow-up of 2 years; 14% underwent transplantation, 10% underwent VAD reimplantation, and 3.4% died. Among surviving patients without transplantation, LV systolic function was normal or only mildly reduced, and mitral regurgitation was no more than mild.

Conclusions:
Durable VAD explantation for MFR is rare in children (~3%) but is associated with favorable medium-term outcomes, supporting careful candidate selection. Dedicated pediatric weaning and explantation protocols and improved predictors of myocardial recovery are needed.

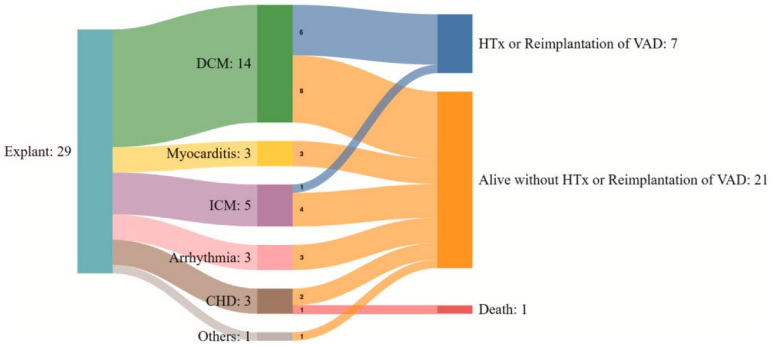

Figure 4 Sankey diagram of post explant outcomes for different underlying diagnoses. CHD, Congenital Heart Disease; ICM, Ischemic Cardiomyopathy; DCM, Dilated Cardiomyopathy; MCS, Mechanical Circulatory Support; HF, Heart Failure.

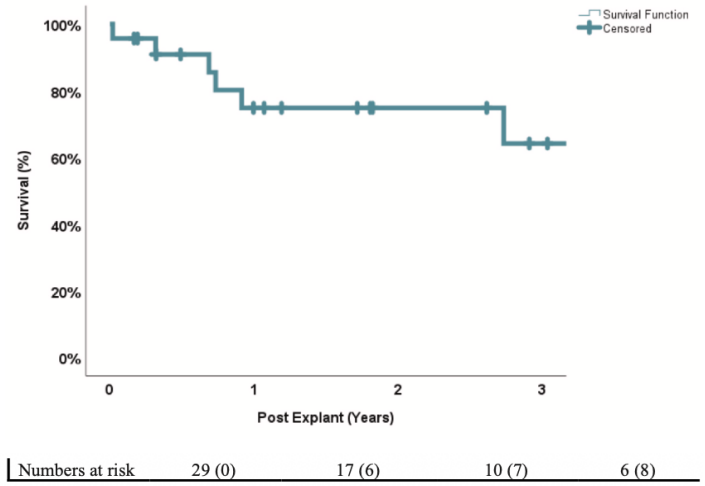

Figure 5 Post VAD explant transplant/VAD-free survival.

Reviewer's Comments

- First multicenter pediatric cohort dedicated to VAD explant for MFR.
- Reassuring outcomes: ~72% VAD-/transplant-free survival at ~2 years with preserved LV function.
- Only 3% of the bridge-to-transplant cohort were explanted, so recovery in this group is rare. That being said, nearly half of explanted children had been listed as bridge-to-transplant — suggesting MFR could be missed.
- Notably, recovery occurred across diverse etiologies including ALCAPA/ischemic and CHD, and in patients supported on continuous-flow devices.
- Actionable takeaway: supports building pediatric-specific surveillance, weaning, and guideline-directed medical therapy protocols on VAD support.

Limitations

- Retrospective registry design with potential selection and reporting bias; incomplete retrospective capture before 2018 may under- or over-estimate explant rates.
- Small explant cohort (n=31) limited multivariable modeling to three variables, risking residual confounding.
- Patients with partial MFR, or significant MFR who were not explanted, were not studied — so true recovery potential is likely underestimated.
- Paracorporeal continuous-flow durable devices were excluded.
- Deaths after explant may have been missed given retrospective ascertainment.
- No standardized weaning/echocardiographic explant protocol across centers, limiting generalizability of selection criteria.

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Macitentan in Pediatric Pulmonary Arterial Hypertension (TOMORROW): A Randomized Clinical Trial

Berger RMF, Ivy DD, Borissoff JI, Cerovic S, et al. J Pediatr. 2026;293:115057. | DOI: 10.1016/j.jpeds.2026.115057

Study Highlights

Macitentan, a dual endothelin receptor antagonist established in adult PAH, had previously been evaluated in children only through small, single-center observational cohorts. **TOMORROW** was designed to close this gap as a purpose-built pediatric trial conducted within a formal extrapolation framework.

Study Design:

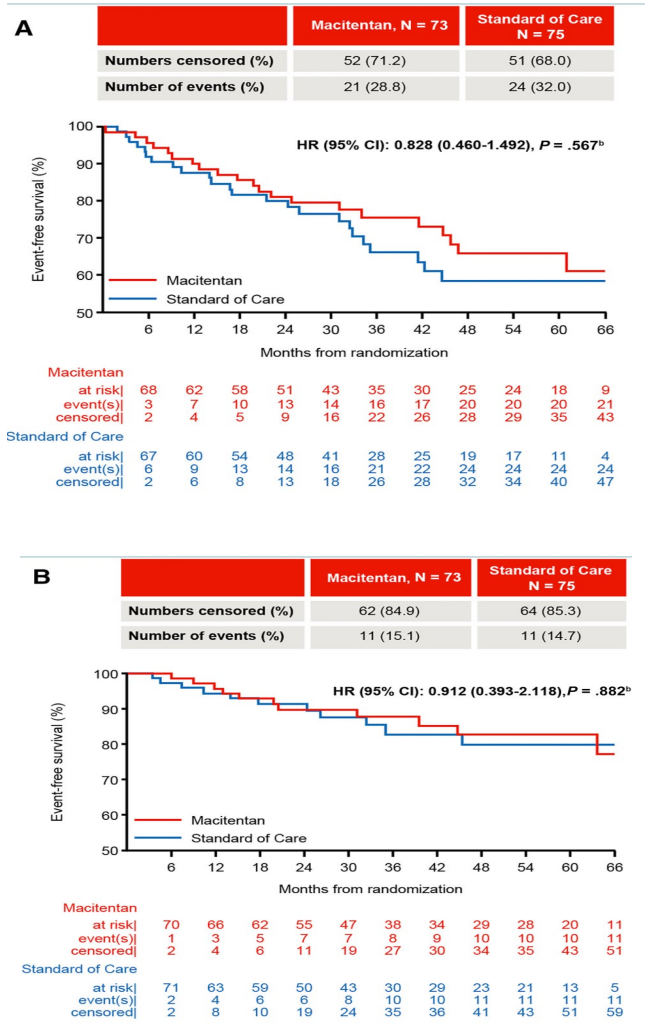
- Multicenter, open-label, phase 3 trial enrolling 148 children aged 2 to under 18 years with WHO Functional Class I–III PAH.
- Participants were randomized 1:1 to bodyweight-based macitentan (n=73) or standard of care, defined as up to two background PAH-specific therapies (n=75) i.e. ERA and/or PDE5 inhibitor.

The primary endpoint was steady-state trough plasma concentration of macitentan and its active metabolite, aprocitentan, at week 12, confirming pharmacokinetic adequacy of the pediatric dosing regimen.

Secondary endpoints included time to first clinical worsening event, safety and tolerability, change in NT-proBNP, and quality of life, assessed via the PedsQL instrument for both patients and parents.

Key findings: Steady-state drug exposure in children was consistent with adult PK data, supporting the proposed weight-based dosing.

- ***The trial was not statistically powered for its time-to-event secondary endpoints, and none reached significance***.
- Hazard ratios trended in favor of macitentan for disease progression (HR 0.83, 95% CI 0.46–1.49) and PAH-related hospitalization (HR 0.91, 95% CI 0.39–2.12), Kaplan-Meier curves A and B as shown.
- NT-proBNP was lower at week 12 (72% vs 101% of baseline; P = .086) but similar by week 24, while quality-of-life scores improved and safety remained consistent with adult data.



Kaplan-Meier Curves of time to A, first CEC-confirmed disease progression event, a B, first CEC-confirmed hospitalization for PAH.

Reviewer's Comments

TOMORROW's principal contribution is pharmacokinetic: it establishes that pediatric weight-based dosing achieves adult-equivalent exposure, the regulatory basis on which macitentan has since been approved for pediatric PAH in the EU, UK, and Australia.

The efficacy signals — favoring macitentan on functional class distribution, NT-proBNP trajectory, and quality of life — are directionally encouraging but underpowered, and the numerically worse mortality trend in the macitentan arm, while not statistically meaningful given the small sample, warrants transparent discussion rather than dismissal.

Limitations

- **Small sample size** — limits detection of rare adverse events and reduces power for subgroup analyses.
- **Short follow-up** — insufficient to assess long-term clinical outcomes or disease progression.
- **Strict inclusion criteria** — may not fully represent the broader paediatric PAH population.
- **Background therapy variability** — differences in concomitant PAH treatments may influence observed effects.
- **Efficacy not fully assessed** — study designed primarily for pharmacokinetics and safety, not powered for clinical endpoints.

Clinical relevance

For clinicians managing pediatric PAH, TOMORROW provides the pharmacokinetic and safety foundation needed to use macitentan confidently across the pediatric age and weight range. It should not, however, be read as demonstrating a clear survival or disease modification advantage over existing therapy — that question awaits an adequately powered trial or longer-term registry follow-up.