Analysis Plan - Waiting List Outcomes in ACHD
ARTORIA-R investigators

Outcomes of adults with congenital heart disease on the waiting list for heart or heart and combined organ transplantation: Results of the ARTORIA-Registry

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Background

Heart failure represents a common end-stage syndrome for many adults with congenital heart disease (ACHD). These patients, however, have been excluded from most heart transplantation research. It is not known how current criteria, derived from non-ACHD populations and used to determine priority at the time of transplant listing, impact outcomes for ACHD patients listed for heart transplantation.

Heart failure occurs in approximately 25% of ACHD, even in patients in whom the congenital malformation has been corrected successfully in childhood. The time course and clinical presentation are heterogeneous due to variable congenital malformations, prior surgical or interventional repairs, and limitations of available treatment options. In particular, systemic right ventricular failure, single ventricle or Fontan physiology, pulmonary vascular disease, and residual lesions in biventricular circulation represent distinct pathophysiological substrates that may affect listing, waiting list outcome, and post-transplant survival.

The aim of this study is to provide comprehensive data on ACHD listed for heart or heart and combined organ transplantation using data from ARTORIA-R. A representative data set of ACHD patients evaluated for and listed for transplantation will be created and analyzed for: (a) underlying heart condition and repair; (b) clinical characteristics at evaluation or listing; (c) listing status and waiting list course; (d) factors associated with favorable and adverse outcomes in ACHD listed for transplantation; and (e) long-term outcomes after transplantation.

Analysis objectives

1. To describe the baseline characteristics of ACHD patients evaluated for and/or listed for heart or combined organ transplantation.
2. To determine event rates for transplantation, delisting due to recovery, death on the waiting list, and delisting due to deterioration or non-eligibility.
3. To compare outcomes across clinically meaningful pathophysiological disease groups.
4. To evaluate the association of listing status, transplantation type, ventricular assist device support, and clinical risk factors with favorable and adverse outcomes.
5. To describe long-term post-transplant survival and compare survival according to urgency status, type of transplantation, and disease group where sample size permits.

Study population

The primary analysis cohort will include adult patients with congenital heart disease aged 18 years or older who were listed for heart transplantation, heart-lung transplantation, or heart transplantation combined with another organ. Data from the first evaluation or first listing episode will be used. Patients listed for re-transplantation will be excluded from the primary analysis.

In addition to the listed cohort, ACHD patients who were evaluated for heart or combined organ transplantation but were not listed because they were not deemed eligible for transplantation will be described as a separate cohort. These patients are clinically important because they may represent a high-risk group that is not captured in classical waiting list studies. Baseline characteristics and reasons for non-listing will be analyzed descriptively. These patients will not be included in waiting list time-to-event analyses because no formal listing date is available.

Patients with missing essential baseline data or missing essential outcome information will be excluded from specific analyses. The number of patients excluded from each analysis and the reasons for exclusion will be reported transparently.

Patient groups

Event rates will be determined for the overall listed cohort and separately for predefined groups of ACHD patients. Instead of using only anatomical diagnoses, patients will be categorized according to the dominant pathophysiological mechanism of heart failure at the time of evaluation or listing. This approach is intended to reflect clinically relevant mechanisms that influence transplant candidacy, waiting list risk, and transplant outcome. If more than one mechanism is present, classification will be based on the clinically predominant mechanism as determined from the registry data.

Overall population

The overall population includes all listed ACHD patients fulfilling the inclusion criteria for the main analysis cohort.

Predefined pathophysiological disease groups

1. Systemic right ventricle

- Transposition of the great arteries after atrial switch operation (Mustard or Senning procedure).
- Congenitally corrected transposition of the great arteries.

This group is defined by systemic right ventricular physiology, which represents the hallmark mechanism of heart failure rather than by transposition of the great arteries alone.

2. Single ventricle physiology / Fontan circulation

- Fontan circulation.
- Hypoplastic left heart syndrome.
- Other univentricular hearts, including complex single ventricle anatomy.

This group includes patients in whom failure of the Fontan circulation, ventricular dysfunction, venous congestion, protein-losing enteropathy, hepatic congestion, or other Fontan-related complications contribute to transplant evaluation or listing.

3. Biventricular circulation with residual lesions or valvular disease

- Tetralogy of Fallot.
- Pulmonary valve stenosis or pulmonary valve disease.
- Repaired ventricular or atrial septal defects with residual lesions.
- Double outlet ventricle or other complex congenital heart defects after biventricular repair, where applicable.

This group captures ACHD patients with biventricular circulation in whom late residual lesions, valve disease, right or left ventricular dysfunction, arrhythmia burden, or sequelae of prior operations contribute to advanced heart failure.

4. Pulmonary vascular disease / Eisenmenger physiology

- Eisenmenger syndrome.
- Severe pulmonary arterial hypertension related to congenital heart disease.
- Patients listed for heart-lung transplantation due to irreversible pulmonary vascular disease where appropriate.

5. Cardiomyopathies associated with or recorded in congenital heart disease cohorts

- Hypertrophic cardiomyopathy.
- Dilated cardiomyopathy.
- Arrhythmogenic right ventricular cardiomyopathy.
- Non-compaction cardiomyopathy.
- Channelopathies

This group will be analyzed separately or in sensitivity analyses depending on the final scientific focus and sample size. If cardiomyopathies are considered outside the primary ACHD defect-based analysis, they may be excluded from the main analysis and reported separately.

Additional clinically relevant subgroups

Ventricular assist device support will not be treated as a disease group because VAD support can occur across all pathophysiological categories. Instead, patients receiving VAD support will be analyzed as a predefined treatment subgroup. VAD status at listing will be described separately and included as covariates in outcome models where appropriate.

Further predefined subgroups include listing status (high urgency versus transplantable), type of transplantation (heart only, heart-lung, or heart combined with other organs), era of listing, and geographical region where appropriate.

If sample sizes in individual disease groups are insufficient for robust statistical analysis, groups may be combined according to clinical plausibility. Any post hoc grouping decisions will be clearly reported.

Prespecified outcomes

The outcome structure distinguishes between favorable outcomes and adverse or safety outcomes during the waiting list period. Components of all composite outcomes will also be described separately as time-to-event analyses.

Primary outcome

The primary outcome will be time from first listing to cardiac transplantation, heart-lung transplantation, or heart transplantation combined with another organ, removal from the transplant list due to clinical recovery or treatment with a durable ventricular assist device. This outcome reflects a favorable course on the waiting list, either because transplantation was achieved or because clinical improvement made transplantation unnecessary.

Safety outcome

The safety outcome will be time from first listing to death on the waiting list or removal from the transplant list due to deterioration, worsening clinical status, or non-eligibility for transplantation. Delisting due to non-eligibility will include patients removed from the list because transplantation was no longer clinically feasible or appropriate.

Post-transplant survival

Post-transplant survival will be analyzed in all patients who undergo heart transplantation, heart-lung transplantation, or heart transplantation combined with another organ during follow-up. The endpoint will be defined as time from transplantation to all-cause mortality. Patients will be censored at last follow-up if alive.

Secondary Analyses

Secondary outcomes include analyses of the components of the composite endpoints as well as prespecified subgroup and disease-specific analyses.

Unless otherwise specified, the following analyses will be performed for:

- the primary (efficacy) outcome
- the safety outcome
- and, where applicable, post-transplant survival

The following secondary analyses are prespecified:

1. Outcomes and utilization of ventricular assist device support in adults with congenital heart disease on the waiting list for heart or heart/lung transplantation.
    - Analysis of the primary and safety outcome
    - Additional analysis of VAD as time-dependent covariate if feasible
2. Impact of guideline-adherent heart failure therapy on waiting list outcomes and post-transplant survival in adults with congenital heart disease.
    - Association with primary and safety outcome
    - Exploratory association with post-transplant survival
3. Outcomes associated with implantable cardioverter-defibrillator (ICD) therapy and or cardiac resynchronization therapy (CRT) including primary and secondary prophylactic implantation, in adults with congenital heart disease awaiting transplantation.

A two-sided p-value below 0.05 will be considered statistically significant. All analyses will be performed using validated statistical software such as R or equivalent software. The exact software version and packages used will be reported in the final manuscript or statistical report.

The final decision on multiple imputation versus complete-case analyses should be made together with the responsible statistician after assessment of data completeness. The exact handling of cardiomyopathy patients should be defined before final analysis. Disease group assignment should be reviewed centrally to ensure consistency across centers. The endpoint definitions for delisting due to recovery, delisting due to deterioration, and non-eligibility should be harmonized before database lock.

Planned display items

Figure 1 - PRISM diagram showing the study population and a world map with countries participating in the registry, number of hospitals, and number of patients included. Patients excluded from the main analysis, including patients listed for re-transplantation and patients assigned to separate descriptive cohorts, will be displayed.

Figure 2 - Time to transplantation or recovery as the primary outcome: (A) overall and (B) by disease group. Additional panels may show Kaplan-Meier or cumulative incidence curves for survival or favorable outcome according to disease group, depending on the final endpoint presentation.

Figure 3 - Time to delisting or death as the safety outcome: (A) overall and (B) by disease group. Competing risk curves will display the probability of adverse waiting list outcomes while accounting for transplantation as a competing event.

Figure 4 - Forest plot showing predictors of favorable outcome (transplantation or delisting due to recovery) and predictors of adverse outcome (death or removal from the transplant list due to deterioration or non-eligibility).

Table 1 - Baseline characteristics for the different outcome cohorts: still on waiting list, transplanted, deceased or delisted due to clinical worsening, and delisted due to clinical improvement.

Table 2 - Baseline characteristics and treatments by disease group, including medication, number of prior operations, VAD support, and functional status where available.

Table 3 - Number of patients with the primary outcome (transplantation or recovery) by disease group.

Table 4 - Number of patients with the safety outcome (death or delisting due to deterioration/non-eligibility) by disease group.

Table 5 - Univariable predictors of favorable and adverse outcomes.

Table 6 - Multivariable predictors of favorable and adverse outcomes.

Authorship and consortium contribution statement

All authors are part of the ARTORIA-R consortium and contributed to study conception, registry design, data acquisition, data interpretation, or manuscript development. The manuscript and analysis plan will be circulated to all co-authors for critical revision. All authors will be asked to approve the final version and to take responsibility for the integrity of the data and analysis. Authorship will be granted according to predefined consortium rules based on active participation in the study and manuscript preparation.

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