Study design and rationale of the pAtients pResenTing with cONGenital heatRt diseaseAse Register (ARTORIA-R)

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Abstract

Aim Due to improved therapy in childhood, many patients with congenital heart disease reach adulthood and are termed adults with congenital heart disease (ACHD). ACHD often develop heart failure (HF) as a consequence of initial palliative surgery or complex anatomy and subsequently require advanced HF therapy. ACHD are usually excluded from trials evaluating heart failure therapies, and in this context, more data about heart failure trajectories in ACHD are needed to guide the management of ACHD suffering from HF.

Methods and results The pAtients pResenTing with cOngenital heaRt disEase Register (ARTORIA-R) will collect data from ACHD evaluated or listed for heart or heart–combined organ transplantation from 16 countries in Europe and the Asia/Pacific region. We plan retrospective collection of data from 1989–2020 and will include patients prospectively. Additional organizations and hospitals in charge of transplantation of ACHD will be asked in the future to contribute data to the register. The primary outcome is the combined endpoint of delisting due to clinical worsening or death on the waiting list. The secondary outcome is delisting due to clinical improvement while on the waiting list. All-cause mortality following transplantation will also be assessed. The data will be entered into an electronic database with access to the investigators participating in the register. All variables of the register reflect key components important for listing of the patients or assessing current HF treatment.

Conclusion The ARTORIA-R will provide robust information on current management and outcomes of adults with congenital heart disease suffering from advanced heart failure.

Keywords Adults with congenital heart disease; Heart transplantation; Heart failure; Ventricular assist device; Arrhythmia; Lung transplantation

Introduction

Advances in medical and surgical treatment continue to improve outcome of children with congenital heart disease. Consequently, these children are surviving to adulthood, resulting in a growing population of adults with congenital heart disease (ACHD). ACHD now account for about two thirds of all patients with congenital heart disease. ACHD often develop severe cardiovascular problems due to residual disease or due to complications developing in the surgically-operated heart. ACHD with complex cardiac anatomy have a 20–50% risk of developing heart failure (HF) during their lifetime. Heart failure is responsible for approximately 20% of mortality in ACHD, often during early adulthood. The relatively small number of ACHD and their unique anatomy exclude them from heart failure trials. Consequently, there is a shortage of data to inform the optimal management of ACHD with HF. As HF often develops at young age in otherwise relatively healthy patients, heart transplantation is one of the most established options to treat ACHD with advanced HF. Problems listing these patients are well recognized as ACHD are commonly regarded to be in the lowest risk category and when reaching conventional criteria for urgent transplantation are often delisted due to...
clinical deterioration or die on the waiting list. An international registry comprising unselected ACHD waiting for cardiac transplantation could provide information on the current management and outcomes in ACHD with advanced heart failure.

**Methods**

**Study design**

The ARTORIA-R is an international, observational project collecting retrospective data from 16 countries in the time period 1989 to 2020 and will thereafter include data prospectively (Figure 1). These data include patient demographics at evaluation for listing, waiting list details, post-transplant data and basic donor data. Future data will be updated annually in July each year, and each institution willing to contribute anonymized data to the register is invited to participate. The study is registered at ClinicalTrials.gov (https://www.clinicaltrials.gov/) of the United States Library of Medicine with the identifier: NCT04848844.

The study has been reviewed, in individual countries, in line with national requirements for ethical approval and followed according to local protocols for data management. Inclusion and exclusion criteria are shown in Figure 2. The complete variable manual of the ARTORIA-R is available in the Supporting Information, Data S3.

**Study population**

ACHD are included in the register if

a) they are listed as an adult transplant candidate (≥18 years) for heart-only or heart-combined with other organs;

b) they have a congenital heart defect;

c) data are available from the initial evaluation for listing or the first listing on the waiting list;

d) data of patients with advanced HF evaluated for listing but being in a too poor condition to be listed are entered as well;

e) transferred data are anonymized; and

f) the institution/organization agrees to the data management and scientific cooperation plan (Supporting Information, Data S1).

ACHD are excluded if

a) if they are listed for a second heart transplantation (retransplantation).

The registry aims to achieve detailed information regarding the underlying congenital heart defect and the previous treatment of the patient. With this information, different cohorts [systemic left ventricle, systemic right ventricle, single ventricle (either anatomic left or right ventricle)] can be interrogated. Data will be collected about

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**Figure 1** Countries currently participating in the ARTORIA-R.
medical treatment, the haemodynamic evaluation of the patient, laboratory testing to assess additional organ function of the kidney or liver, and treatment in the intermediate care or intensive care unit. As it is of special relevance in ACHD, treatment of arrhythmia, antiarrhythmic medication, and the use of intracardiac defibrillator (ICD) or cardiac resynchronization therapy (CRT) will be evaluated. Where available, data at the time of listing regarding ejection fraction of the systemic ventricle obtained by echocardiography or cardiac magnetic resonance imaging will be collected.

Inherited cardiomyopathies such as hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, or non-compaction cardiomyopathy are increasingly recognized as causes of cardiovascular diseases in children and young adults. The disease-causing mutations mainly alter cardiomyocyte function, and thus, the clinical presentation and the reasons for heart transplantation differ from those of patients with complex congenital heart disease. Comparing patient characteristics and outcomes between patients with inherited cardiomyopathies requiring heart transplantation with those of patients with congenital heart disease will strengthen the planned analyses. Separate analyses of these patient groups and comparisons between groups are planned. In addition, these patients are sometimes listed in the category of ACHD and thus reflect real-world practice. Thus, patient data with these specific diseases will be collected for comparison with the ACHD cohort but not included in the original register.

During the study, additional institutions and organizations will be asked to include their data as well. Although the initial data are retrospective, additional data into the register will be entered prospectively.

**Study objectives**

The primary objective is to describe outcomes of ACHD evaluated for or listed on the waiting list for heart-only transplantation and heart-combined organ transplantation. Factors influencing outcomes, for example, underlying heart defect and type of anatomical correction, and medical therapy while on the waiting list, haemodynamic data, cardiopulmonary performance, and laboratory tests will be included in the analysis. We plan to calculate an ARTORIA-R score to estimate risk of adverse outcomes, defined as delisting due to clinical worsening or death while on the waiting list. In addition to ACHD listed on the waiting list, patients evaluated for listing but deemed to be in a too poor status for listing are entered as well.

Secondary objectives are related to additional important treatment factors in ACHD with advanced HF. These include ICD, CRT and arrhythmic events, for example, treatment of ventricular tachycardia or atrial fibrillation, in ACHD on the
waiting list. Further studies will focus on the impact and use of ventricular assist device (VAD) in ACHD on the waiting list. Comparison of the same anatomic defect with and without VAD treatment is foreseen. An additional aspect is the treatment of patients with univentricular heart and palliative surgery leading to a Fontan circulation. An important secondary objective is to analyse the effect of HF medication on the outcome. A specific analysis will assess the outcome of ACHD with increased pulmonary hypertension (PAH) requiring the need of combined heart and lung transplantation. In this context, ACHD with shunt lesions which were uncorrected and presenting with irreversible Eisenmenger syndrome represent an advanced PAH disease, which will be as well investigated. As the registry progresses, more outcome studies will be formulated. A current overview of the planned studies is shown in Figure 3.

**Statistical considerations**

Summary statistics will be reported for continuous variables as medians (25th percentile and 75th percentile) and for binary variables as absolute counts (frequencies). Categorization of ACHD in cohorts based on the year of evaluation or entering transplantation list is planned to assess time-dependent effects on patient characteristics and outcomes. A non-parametric Spearman test will be used to examine a potential trend over the time intervals. The null hypothesis of no trend in data will be tested for every group.

Cumulative incidence analyses will be estimated wherein heart transplantation is considered as competing risk of the primary composite endpoint death on waiting list or delisting within 5 and 10 years and will be calculated by the Aalen–Johansen estimator for the 5/10 year follow-up period. Additional endpoints will as well be evaluated with the secondary endpoint of delisting due to improvement or all-cause mortality following transplantation.

To evaluate predictors of 5-/10-year death/delisting, univariable and multivariable Cox regression models will be fitted. For the multivariable Cox regression model, variables with less clinical relevance and with missing values in >20% of the sample are not used in the models. The Cox regression models will then be weighted by the Fine and Gray estimator, which accounts for the competing risk (transplantation or death/delisting).

For all regression models, change in continuous variables will be modelled as change per standard deviation to enable the comparability of variables. A two-sided P-value of <0.05 will be considered statistically significant. Statistical calculations will be fitted to the projects as planned and adapted if needed.

**Figure 3** Currently planned study projects with the outlook of additional projects in the future.

**Primary objectives:**

- Evaluation process/ waiting list outcomes of ACHD
- Characterisation of ACHD regarding device and arrhythmia management

**Secondary objectives:**

- Heart failure medication in ACHD
- Impact of use of ventricular assist devices and characterisation of patients with VAD treatment
- Frailty assessment and outcome of ACHD evaluated or listed for heart or heart/combined organ transplantation
- Calculation of a risk score to identify ACHD with the highest urgency for listing
- Outcome of patients with Eisenmenger syndrome as most severe form of PAH in ACHD
- Clinical characteristics of cohorts of ACHD with univentricular physiology, systemic right ventricle or patients without surgical correction in childhood
- Future projects are open for discussion and can be submitted in the future
Ethic committee approval and data management/security

The current concept of the register was approved by the ethic committee of the federal county Hamburg in Germany on 2 September 2020 (file reference WF163-20). The study has been reviewed, in individual countries, in line with national requirements for ethical approval and followed according to local protocols for data management. All data will be combined in anonymized fashion at the data custodian institution (University Heart & Vascular Center Hamburg, Hamburg, Germany). For data management, each patient will be submitted with listing identification number or with a unique identification code for the institution that contributes data of the patient to the data custodian institution. After transmitting the data to this data custodian institution, the patient receives a new identification number, and thus, even the institution providing the data cannot identify the patient according to this new identification code. The data are centrally stored on secure servers. Each organization or institution contributing data to the registry names a representative who stores the copy of the password secured database on a safe data storage (additional points are outlined in the Supporting Information, Data S2). The study complies with the current General Data Protection Regulation in Europe enacted on 23 May 2018.

Discussion

Rationale

Treatment of ACHD with advanced HF is still uncommon, and these patients should be referred to specialized centres as these patients often need to be evaluated and listed for heart or heart and combined organs transplantation, most commonly the lung.\textsuperscript{1,14,15} In general, HF is more frequent in those with more complex heart defects: 22% of adults with transposition of the great arteries following an atrial switch (Senning or Mustard operation), 32% of adults with congenitally corrected transposition of the great arteries, and 40% of adults following Fontan completion. Given the increasing complexity and numbers of ACHD, advanced HF will be common in the future, and more patients will need evaluation for heart or heart and combined organ transplantation globally.\textsuperscript{16}

What is currently known regarding heart transplantation in ACHD?

Previous reports could show that heart transplantation or even heart and lung transplantation is an effective treatment for ACHD\textsuperscript{10,14,17,18}; however, a commonly encountered problem in listing ACHD is the issue of urgency as these patients often have a low priority while on the waiting list.\textsuperscript{10,14} On the other hand, multiple organ involvement with renal dysfunction, liver failure, complex anatomy, and pulmonary arterial hypertension (PAH) contributes to deterioration, which can result in delisting or death while being on the waiting list.\textsuperscript{10,17–19} In ACHD, 1 year mortality after transplantation is high due to procedure related risk factors and advanced HF at the time of transplantation, but survival rates at 10 years are comparable or even better than those of patients with acquired heart disease.\textsuperscript{17–19} The reason for the better long-term survival is often attributed to the younger age at transplantation and the lower infection and malignancy rates following transplantation.\textsuperscript{19} In general, predictors of a poor outcome on the waiting list are comparable between ACHD and non-ACHD with the exception that previous cardiac surgery was more often related to a poor outcome in non-ACHD.\textsuperscript{10} In addition, non-ACHD have more established advanced HF therapies to extend the time on the waiting list such as VAD therapy or use of inotrope medication.\textsuperscript{10}

The ARTORIA-R will collect data on a global scale to identify these factors and highlight the risks for ACHD with advanced HF evaluated or listed for heart transplantation. In addition, besides these general considerations, other important factors have to be considered as well in ACHD, these are the following.

Anatomic complexity/previous cardiac surgery

The most common problem complicating ACHD transplantation is related to the variability of the underlying cardiac anatomy and physiology.\textsuperscript{17,18} Although recent studies evaluate this in more detail,\textsuperscript{17,18} the management of these complex anatomic variants is still not fully established, and additional evidence is needed. Transplantation is complicated by scarring caused by previous surgery, collateral vessels, and bleeding issues.\textsuperscript{1,14,18} There is the need of more data regarding the exact anatomic diagnosis of the underlying heart defects, lacking in these recent studies\textsuperscript{17,18}, or only mentioned as a general congenital heart defect\textsuperscript{10,19}; thus, a register specifically obtaining this granular data will significantly contribute to this debate.

Ventricular assist devices

Due to organ shortage and the fact that the need for organ transplantation is increasing in both non-ACHD and ACHD,\textsuperscript{1,18} the use of VADs became a more established treatment option both for bridge to transplant and destination therapy.\textsuperscript{8} However, the use of VADs in ACHD is not straightforward as there are no clear recommendations for this cohort of patients. A recent large study suggested that ACHD may gain a benefit in terms of being able to wait longer for an organ transplantation before fatal deterioration occurs.\textsuperscript{20} However, again patients were only described as ACHD without classification of
the underlying anatomical disease.20 Due to the described heterogeneity of ACHD, more data are needed with a clear description of the underlying defect. Data from a recent study provided more details regarding the underlying anatomy of the ventricle needing support and showed that the survival of ACHD and non-ACHD was similar, but ACHD needing biventricular VAD had a poor outcome.21 Thus, the ARTORIA register as described could provide more background information on this important topic as VAD might be an option to stabilize ACHD and prolong the time on the waiting list comparable with non-ACHD.8

**Device treatment and arrhythmia management**

In ACHD, the entire spectrum of arrhythmias can be encountered where some are caused by advanced HF and some are due to the surgery for anatomical or palliative correction with scarring or a consequent remodelling of the heart.1,22,23 While some forms of arrhythmia are treatable,7,22,23 some types of arrhythmia worsen with advanced HF and indicate a poor prognosis emphasizing the need for urgent listing for organ transplantation.1,22,23 Recommendations which ACHD should receive an ICD while on the waiting list are less clear although a recent joint position paper provides a consensus opinion when ICD for ACHD on the waiting list may be considered.22 While its use is established in patients without congenital heart disease,24,25 its use is not generally comparable in ACHD due to the different anatomy and risk factors for implantation.22,23 The ARTORIA-R register includes variables detailing the use of ICD or CRT in ACHD in conjunction with antiarrhythmic medication and presence of previous events like atrial fibrillation ablation or ventricular tachycardia ablation. Thus, as pointed out in the current guidelines, study results will shed more light on characterizing ACHD and advanced HF. Again highlighting that more data on this topic are needed especially in the context of absence of randomized clinical trials in ACHD.

**Co-morbidities, particularly pulmonary arterial hypertension**

Co-morbidities are often present in ACHD listed for heart or heart/lung transplantation with PAH being very common.1,17,18,26 More data are needed to study how this co-morbidity affects the outcome of patients on the waiting list. Especially the most advanced form of PAH with Eisenmenger syndrome due to an uncorrected shunt lesion is reported to have a poor outcome.27,28 The timing when these patients should be evaluated or listed for organ transplantation is difficult, and there is the need to document organ function of the liver or renal function as well. Patients with too many co-morbidities with poor liver or renal function might not be candidates for transplantation listing. However, specific medical treatment of patients on the waiting list and numbers regarding combined heart/lung transplantation and long-term outcome of these patients is still scarce. This fact underlines the need of more data regarding patients with advanced forms of PAH in ACHD or even Eisenmenger syndrome as the most severe form of PAH.

In summary, ARTORIA-R is one of the largest registries collecting data of ACHD with advanced HF evaluated for transplantation or listed for heart-only or heart-combined organ transplantation from multiple countries and regions. This register aims to improve treatment of patients by investigating prognostic factors and thus allow for a better risk stratification. Furthermore, the register aims to promote research and awareness for ACHD with advanced heart failure.

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**Conflict of interest**

Dr. Sinning (CS) is deputy editor of the *European Heart Journal – Case Reports*. Dr. Zengin (EZ) reports speaker fees from AstraZeneca unrelated to the submitted work. Dr. Magnussen (CM) reports speaker fees from AstraZeneca, Novartis, and Heinen & Loewenstein unrelated to the submitted work. Dr. Bernhardt (AB) reports speaker and consulting fees from Abbott, Abiomed, AstraZeneca, Berlin Heart, Medtronic, and Novartis unrelated to the submitted work. Dr. Schoenrath (FS) reports non-financial support from Medtronic, grants from Novartis and institutional fees from Cardiorentis AG, Abbott, AstraZeneca, and Orion Pharma unrelated to the submitted work. Dr. Ius (FI) has received speaker fees and congress fees from Biotest AG unrelated to the submitted work. Dr. Fabritz (LF) has received institutional research grants and non-financial support from European Union, British Heart Foundation, Medical Research Council (UK), several biomedical companies and DFG. The Institute of Cardiovascular Research, University of Birmingham, has received an Accelerator Award by the British Heart Foundation AA/18/2/34218. LF is listed as inventor of two patents held by University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783). Dr. Kirchhof (PK) receives research support for basic, translational, and clinical research projects from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council.
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20. Cedars A, Tecson KM, Zaidi AN, Lorts A, McCullough PA. Impact of durable ventricular assist device support on outcomes of patients with congenital heart disease waiting for heart transplant. *ASAIO J* 2020; 66: 513–519.

21. VanderPluym CJ, Cedars A, Eghtesady P, Maxwell BG, Gelow JM, Burchill LJ, Maltais S, Koehl DA, Cantor RS, Blume ED. Outcomes following implantation of mechanical circulatory support in adults with congenital heart disease: an analysis of the Intergency Registry for Mechanically Assisted Circulatory Support (INTERMACS). *J Heart Lung Transplant* 2018; 37: 89–99.

22. Hernandez-Madrid A, Paul T, Abrams D, Aziz PF, Blom NA, Chen J, Chessa M, Combes N, Dagres N, Diller G, Ernst S, Giamberti A, Hebe J, Janousek J, Kriebel T, Moltedo J, Moreno J, Peinado R, Pison I, Rosenthal E, Skinny JR, Zeppenfeld K, Group ESCSD. Arrhythmias in congenital heart disease: a position paper of the European Heart Rhythm Association (EHRA), the European Society of Cardiology (ESC) Working Group on Grown-up Congenital Heart Disease, endorsed by: Association for European Paediatric Cardiology (AEPC), and the European Society of Cardiology (ESC) and Congenital Cardiology (AEPC). *Eur Heart J* 2018; 40: 1719–1753.

23. Khairy P, Van Hare GF, Balaji S, Berul CI, Cecchin F, Cohen MI, Daniels CJ, Deal BJ, Dearani JA, Groot N, Dubin AM, Harris L, Janousek J, Kanter RJ, Karpawich PP, Perry JC, Seslar SP, Shah MJ, Silka MJ, Triedman JK, Walsh EP, Warnes CA. PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRS), and the International Society for Adult Congenital Heart Disease (ISACHD). *Heart Rhythm* 2014; 11: e102–65.

24. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggreve M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015; 36: 2793–2867.

25. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cledan J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE, Guidelines ESC/SC, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knust J, Kohl P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tomarago JL, Tendera M, Torbicki A, Wijns W, Windecker S, Document R, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bansch D, Baumgartner H, Bsata W, Buser P, Charron P, Dabbert JC, Doreano D, Faerestrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC, Wilson CM. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J* 2013; 34: 2281–2329.

26. Menachem JN, Schleendof KH, Mazurek JA, Bichell DP, Brinkley DM, Frischhertz BP, Mettler BA, Shah AS, Zalawadiya S, Book W, Lindenfeld J. advanced heart failure in adults with congenital heart disease. *JACC Heart Fail* 2020; 8: 87–99.

27. Hjortshoj CMS, Kempny A, Jensen AS, Sorensen K, Nagy E, Dellborg M, Johansson B, Rudiene V, Hong G, Opotowsky AR, Budt W, Mulder BJ, Tomkiewicz-Pajak L, D’Alto M, Prokselj K, Diller GP, Dimopoulos K, Estensen ME, Holmstrom H, Turanlati M, Thilen U, Gatzoulis MA, Sondagaurd L. Past and current cause-specific mortality in Eisenmenger syndrome. *Eur Heart J* 2017; 38: 2060–2067.

28. Diller GP, Korten MA, Bauer UM, Miera O, Tutarel O, Kaeimmerer H, Berger F, Baumgartner H. German Competence Network for Congenital Heart Defects I. Current therapy and outcome of Eisenmenger syndrome: data of the German National Register for congenital heart defects. *Eur Heart J* 2016; 37: 1449–1455.