EVITA

EValuation of cardiac magnetic resonance **I**maging (MRI) in follow up assessmen**T** of patients with pulmonary **A**rterial hypertension (PAH)

Prospective cohort study *of cardiac MRI in PAH*

STATISTICAL ANALYSIS PLAN

N GIRERD / K DUARTE

15th of December 2020

Sponsor: Centre Hospitalier Régional Universitaire de Nancy

Identifiers: NCT02845518 **Unique Protocol ID:** PHRC-15-0210

Principal Coordinator / Central Contact Person: Professor Ari CHAOUAT

Methodologists and statisticians: Nicolas GIRERD & Kévin DUARTE

I/ General considerations:

The 2-tailed significance level will set to $p<0.05$.

II/ Descriptive analysis

Continuous variables will be expressed as mean±SD or as median (25-75 percentile) as appropriate. Categorical variables will be expressed as frequencies (percentages).

III/ Analyses to respond to main objective:

The aim of the trial is to assess the sensitivity and specificity cardiac magnetic resonance imaging (cMRI) regarding the diagnosis of hemodynamic criteria for intermediate risk or high-risk status determined from right heart catheterization (RHC) measurements. There will be 3 time-points: baseline, between 3 and 6 months and 24 months.

The outcome variable will consequently be hemodynamic criteria for intermediate risk or high-risk status defined as a cardiac index (CI)< 2.5 l/min/m2 or right atrial pressure > or = to 8 mm Hg. This definition is in line with the last ESC/ERS guidelines for diagnosis and treatment of pulmonary hypertension (1).

The cMRI exposition variable will be defined as a cMRI CI < 2.5 l/min/m^2 or a right ventricle ejection fraction (RVEF) < 35% or an absolute decrease of 10% of RVEF at a follow-up evaluation (for the second and third time-point).

Sensitivity, specificity and their exact 95% confidence intervals will be computed using the binomial distribution.

However, by nature, 3 tests will be performed for each subject unless they experience death or are unable to perform one (or more) test during the follow-up. The repeated nature of the data will be considered including a random effect in the analyses. We will construct a logistic regression model with hemodynamic criteria for intermediate risk or high-risk status as outcome and cMRI dichotomous variable as exposure using a random effect at the patient level (2). The glmer command from the lme4 package will be used (R package, CRAN). Sensitivity and specificity and their confidence interval will then be extracted from the logistic model.

This analysis will consequently provide the overall (i.e. across the 3 time-points) sensitivity and specificity of cMRI integrated aforementioned exposition variable for the integrated aforementioned RHC definition taking into account the repeated nature of the data.

In addition, the following secondary analyses will be performed:

- sensitivity and specificity evaluation of cMRI integrated exposition variable for the integrated RHC at each time points (i.e. at baseline, 3-6 months and 24 months),
- sensitivity and specificity evaluation for each component of the RHC definition (i.e. considering only cardiac index< 2.5 l/min/m^2 or only right atrial pressure > or = to 8 mm Hg) and cMRI definition (i.e. considering only cMRI CI < 2.5 l/min/m^2 or only RVEF < 35% or only absolute decrease of 10% of RVEF at a follow-up evaluation) overall and at each time-points.

In addition, parametric or non-parametric correlation analyses (depending on variable distributions) will also be performed for cMRI CI and RHC CI.

IV/ Analyses of Secondary objectives

Secondary objectives 1 and 2:

1) To assess the predictive value of the first occurrence of morbimortality events in 2 different analyses derived from RHC criteria (cardiac index (CI)< 2.5 l/min/m^2 or a right atrial pressure = or > 8 mm Hg) and from cMRI criteria (CI < 2.5 l/min/m^2 or RVEF < 35% or an absolute decrease of 10% of RVEF at a follow-up evaluation).

2) To assess the univariable association between first morbimortality events occurrence and NYHA functional class, 6-minute walk distance, plasma level of BNP/NT-proBNP, and continuous hemodynamic variables from cMRI, RHC and echocardiography data collected at baseline and after 3-6 months of follow-up.

The morbimortality event will be defined as the composite endpoint of

- 1 Death from any cause
- 2 Lung transplantation
- 3 Atrial septostomy
- 4 Worsening of PAH defined by all three following criteria: a decrease in the 6-minute walk distance of at least 15 % from baseline (or unable to perform the test), a worsening of PAH symptoms and an unscheduled hospitalization (or an increase in the length of stay in the hospital) due to PAH

The following exposition variables will be used:

- RHC and cMRI definition used in the primary analysis
- Components of the RHC and cMRI definitions
- Additional RHC variables: stroke volume index, mean pulmonary arterial pressure, pulmonary vascular resistance, SvO_2, pulmonary arterial compliance (stroke volume divided by pulse pressure)
- Additional cMRI variables: stroke volume index, right ventricular end-systolic volume index, right ventricular end-diastolic index, right ventricular end-systolic volume divided by stroke volume as an estimate of right ventriculo-arterial coupling
- Echocardiography variables: pericardial effusion, TAPSE < 18 mm, right atrium area = or > 18 cm^2.

Proportional hazard analysis

Association between factors and time to first occurrence of events will be assessed using Cox proportional hazard regression. Both univariable and multivariable analyses will be performed. The validity of the assumptions of the Cox models will be checked: proportional hazards, log-linearity, absence of interaction and collinearity.

The adjusted analyses will be adjusted for NYHA class, 6-minute walk distance and natriuretic peptides. Additional adjustment factors found significant will also be entered in a multivariable analysis after stepwise forward-backward selection using a 0.05 threshold.

Importantly, the aforementioned RHC and MRI definitions will be first used as exposition variables.

In addition, the components of each definition and additional cMRI variables will also be used as individual exposition variables.

Associations between echocardiography variables and outcome will also be evaluated.

Three sets of analyses will be provided. The first one will assess the association of baseline data with subsequent outcome, the second one will assess the association of 3-6 months data with subsequent and the last model will assess the association of baseline and 3-6 months data with outcome using a time-dependent Cox-model. In this time-dependant Cox model, association of baseline data will be considered until the 3-6 months data is acquired; association with outcome after the 3-6 months evaluation will be assessed using the 3-6 months data.

For each model, the predictive value will be assessed using C-index and NRI (3). In addition, changes in C-Index and NRI will also be evaluated comparing models including only covariates, including covariates and RHC data, including covariates and MRI data and including covariates, RHC and MRI data. This strategy has been used previously by our group (4).

Importantly, as sensitivity analyses,

- repeated events will be considering using a negative binomial model (5–7). This survival analysis will account for the occurrence of multiple events during the follow-up,
- the associations with the components of the composite endpoint will be assessed.

Secondary objective 3:

3) To assess the multivariable association between first morbimortality events occurrence and the above factors, identifying clinical and hemodynamic variables independently contributing to prognosis. Using the results of this analysis we plan to build a multiparameter prognostic score.

Two survival models will be used in this analysis, as mentioned above: Cox survival model (for first events) and negative binomial analysis as sensitivity analysis (accounting for repeated events).

Candidate variables for this analysis are the one mentioned for the analysis of secondary objective 1 and 2. A stepwise selection procedure will be used, retaining in the analysis only factor associated with a $p<0.05$ with the outcome.

Internal validation of the multivariable model and of the score which could be derived from it will be performed using the bootstrap method described by Harrell *et al* (8). Importantly, variables will be used both as dichotomized variables (using the cut-offs used in the primary objective) and as continuous variables. In case a continuous variable should be dichotomized for lack of log-linearity, the cutpoint will be validated in the same bootstrap resamples as for the model and score. In addition, optimal cutpoints will also be assessed on the continuous variables based on C-index maximization (9).

Secondary objectives 4:

4) To quantify complications due to cMRI and to RHC.

This will be mostly a descriptive analysis. The overall frequency of reported adverse events and severe adverse events will be compared between groups using the Chi-Square test (or Fisher's exact test where requested). In addition, to account for the paired nature of the data, a McNemar test will be performed.

Secondary objectives 5:

5) To determine the magnitude of better tolerability of cMRI over RHC for the patient.

Physical and psychological distress due to cMRI and RHC will be measured with questionnaires.

The comparison of the Likert-type scales of the questionnaires will be carried out using the Chi-Square test.

Secondary objective 6:

6) To create a biobank for diagnosis and prognosis purposes This study is a prospective cohort study. PAH patients will be recruited in 20 centers of the French network of severe pulmonary hypertension.

Blood samples to obtain DNA at one visit from circulating blood cells and plasma at all visits with MRI.

References

1. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 1 janv 2016;37(1):67-119.

2. Genders TSS, Spronk S, Stijnen T, Steyerberg EW, Lesaffre E, Hunink MGM. Methods for calculating sensitivity and specificity of clustered data: a tutorial. Radiology. déc 2012;265(3):910-6.

3. Uno H, Tian L, Cai T, Kohane IS, Wei LJ. A unified inference procedure for a class of measures to assess improvement in risk prediction systems with survival data. Stat Med. 30 juin 2013;32(14):2430-42.

4. Coiro S, Rossignol P, Ambrosio G, Carluccio E, Alunni G, Murrone A, et al. Prognostic value of residual pulmonary congestion at discharge assessed by lung ultrasound imaging in heart failure. Eur J Heart Fail. nov 2015;17(11):1172-81.

5. Claggett B, Pocock S, Wei LJ, Pfeffer MA, McMurray JJV, Solomon SD. Comparison of Time-to-First Event and Recurrent Event Methods in Randomized Clinical Trials. Circulation. 27 mars 2018;

6. Rogers JK, Pocock SJ, McMurray JJV, Granger CB, Michelson EL, Östergren J, et al. Analysing recurrent hospitalizations in heart failure: a review of statistical methodology, with application to CHARM-Preserved. Eur J Heart Fail. janv 2014;16(1):33-40.

7. Rogers JK, Yaroshinsky A, Pocock SJ, Stokar D, Pogoda J. Analysis of recurrent events with an associated informative dropout time: Application of the joint frailty model. Stat Med. 15 2016;35(13):2195-205.

8. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 28 févr 1996;15(4):361-87.

9. Sima CS, Gonen M. Optimal Cutpoint Estimation With Censored Data. Journal of Statistical Theory and Practice. 7(2):345-59.