Unique study approval ID (Sweden): 2019-05490

Official title: Improving care for children with congenital heart disease by cardiovascular biomarker profiling and advanced non-invasive cardiac imaging techniques.

Statistical analysis plan (date): 25th of Oct. 2020

Study protocol summary:

Study type & outcome measure for cases:

- Case-control study to evaluate diagnostic usefulness of non-invasive cardiac imaging measures and cardiovascular biomarkers in children.

- Need for open heart surgery or cardiac catheter intervention to treat predefined congenital heart disease lesions leading to pulmonary over-circulation (as below).

Enrolment:

After local advertisement and written informed consent (dedicated healthcare regions in Sweden).

Controls (0-17 years) without history or presence of cardiovascular disease at enrolment:

Number of assessments: 1 (at enrolment)

Type of assessments in local paediatric cardiology ambulatory / out-patient clinic settings:

1. Clinical evaluation cardiovascular examination by paediatric cardiologist

2. Standard 12 lead ECG recording

3. Transthoracic echocardiography examination (predefined standard paediatric protocol including but not limited to 2D, Doppler, TDI)

4. Cardiac magnetic resonance (CMR) evaluation of the heart using predefined sequence protocol (including 4D flow assessments) for comparison to cases reaching outcomes (matched subgroup)

5. Peripheral blood sampling for cardiovascular biomarker batch analysis (O-link proximity extension assay of 96 markers and quantitative analysis of selected biomarkers, e.g. NT-pro-BNP)

6. Optional saliva sampling at enrolment and/or retrieval of dried blood samples from neonatal screening laboratory if available for batch analysis and comparison to standard blood sample cardiovascular biomarkers (O-link proximity extension assay of 96 markers and quantitative analysis of selected biomarkers, e.g. NT-pro-BNP)

Cases (0-17 years) without treated congenital heart disease by open heart surgery or cardiac catheter intervention at enrolment:

Included lesions of congenital heart disease leading to pulmonary over-circulation:

- Atrial septal defect (ASD)

- Ventricular septal defect (VSD)

- Patent ductus arteriosus (PDA)

- Partial anomalous pulmonary venous drainage (PAPVD)

- Aorto-pulmonary window (APW)

Number of assessments:

- Minimum 2 (at enrolment and 6-12 months after outcome is reached)

- Maximum 4 (at enrolment and annually to a max. follow-up of 3 years if not reaching outcome)

Type of assessments in local paediatric cardiology hospital / out-patient clinic settings:

1. Clinical evaluation cardiovascular examination by paediatric cardiologist

2. Standard 12 lead ECG recording

3. Transthoracic echocardiography examination (predefined standard paediatric protocol including but not limited to 2D, Doppler, TDI)

4. Cardiac magnetic resonance (CMR) evaluation of the heart using predefined sequence protocol (including 4D flow assessments) for subjects reaching outcome (undergoing open heart surgery / cardiac catheter intervention) on hospital admission before treatment and 6-12 months after intervention in ambulatory setting.

5. Peripheral blood sampling for later cardiovascular biomarker batch analysis (proximity extension assay and quantitative analysis for selected biomarkers, e.g. NT-pro-BNP)

6. Optional saliva sampling at enrolment and/or retrieval of dried blood samples from neonatal screening laboratory if available as well as optional cardiovascular tissue sampling at time of open heart surgery for batch analysis and comparison to standard blood sample cardiovascular biomarkers (O-link proximity extension assay of 96 markers and quantitative analysis of selected biomarkers, e.g. NT-pro-BNP)

Table summarizing study protocol:

Type of assessment	**Subjects**	**Enrolment**	**1 year**	**2 years**	**3 years**
Clinical evaluation	Controls Cases	X X	- X	- X	- X
12-lead ECG	Controls Cases	X X	- X	- X	- X
Transthoracic echocardiography	Controls Cases	X X	- X	- X	- X
Cardiac magnetic resonance *	Controls Cases	X = 1 assessment for controls at enrolment X = 2 assessments for cases reaching outcome (1st on admission for intervention & 2nd 6-12 months post intervention)			
Peripheral blood sampling	Controls Cases	X X	- X	- X	- X

Optional saliva / dried blood sampling	Controls Cases	X X	- X	- X	- X
Optional cardiovascular tissue sampling	Controls Cases	- X (1 sample for subgroup of cases undergoing open heart surgery)			

*) Subgroup of cases reaching outcome during study and subgroup of matched controls.