Lifetime burden of morbidity in Ebstein anomaly patients: A two-country, population-based study including 823 patients

Eckerström F[1,2], Dellborg M[3], Hjortdal VE[1,2], Eriksson P[3,4], Mandalenakis Z[3,4]

[1]Department of Cardiothoracic Surgery, Rigshospitalet, Copenhagen University Hospital, Denmark; [2]Department of Clinical Medicine, Copenhagen University, Denmark; [3]Department of Molecular and Clinical Medicine, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden; [4]Adult Congenital Heart Disease Unit, Department of Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden
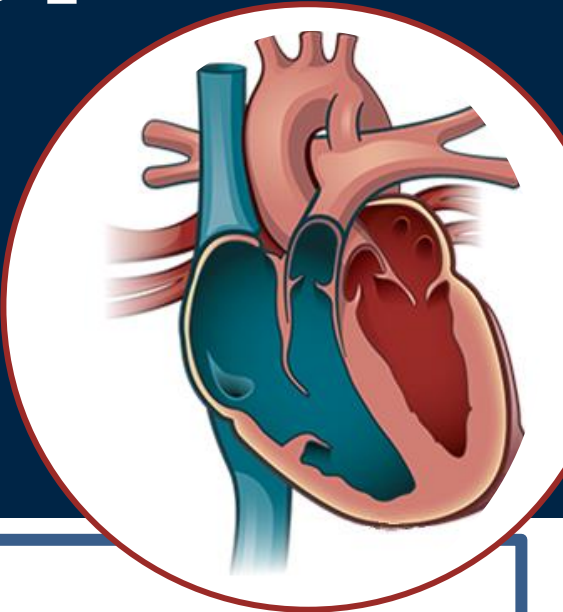
BACKGROUND

Ebstein anomaly (EA): Low birth prevalence and referral bias constitute significant obstacles to elucidate the natural history of EA.

Morbidity: EA is commonly associated with arrhythmias and heart failure but rates are almost exclusively limited to operated cases.

PURPOSE

Describe the burden of morbidity in patients with EA.

METHODS

Study population:
- Patients diagnosed with EA in Denmark or Sweden, born in the period 1930 to 2017.
- Operated and non-operated patients.
- Patients matched by age, sex, and country of residence with ten controls without congenital heart disease.

Study design:
- Two-country, population-based cohort study using nationwide medical registries from Denmark and Sweden.

Statistics:
- Medians with interquartile range for descriptive statistics.
- Cox proportional hazard regression model for hazard ratio estimates of morbidity.
- Follow-up started at birth and all estimates compared with matched controls.

BASELINE CHARACTERISTICS

TABLE 1	Patients (n=823)	Controls (n=8,230)
Female sex, numbers (%)	430 (52.2)	4,300 (52.2)
Median follow-up, years (IQR)	32.2 (15.5-55.5)	32.5 (19.5-56.5)
Median age at diagnosis, years (IQR)	17.2 (173 days-39.7)	-

MORBIDITY [TOTAL COHORT]

TABLE 2	No. events (% of total)		IR per 10,000 person-years		HR (95% CI)
	Patients	Controls	Patients	Controls	
Arrhythmia	293 (35.6)	233 (2.8)	118.4	7.6	20.8 (17.4-24.8)
Heart failure	131 (15.9)	124 (1.5)	46.3	4.0	13.1 (10.2-16.7)
Stroke	30 (3.6)	85 (1.0)	103.9	27.5	4.0 (2.6-6.0)

MORBIDITY [BY ASSOCIATED LESIONS]

TABLE 3		No. events (% of total)		IR per 10,000 person-years		HR (95% CI)
		Patients	Controls	Patients	Controls	
Isolated	Arrhythmia	145 (32.8)	172 (3.9)	90.5	9.4	13.1 (10.5-16.4)
Isolated	Heart failure	51 (11.5)	88 (2.0)	28.7	4.8	6.9 (4.9-9.8)
Isolated	Stroke	12 (2.7)	62 (1.4)	6.7	3.3	2.1 (1.1-3.9)
+ASD	Arrhythmia	50 (46.3)	26 (2.4)	147.2	5.7	46.6 (27.6-78.8)
+ASD	Heart failure	25 (23.1)	19 (1.8)	60.4	4.1	19.6 (10.5-36.8)
+ASD	Stroke	12 (11.1)	17 (1.6)	28.9	3.7	8.3 (4.0-17.4)
Complex	Arrhythmia	98 (35.9)	35 (1.3)	183.7	4.4	59.2 (39.1-89.4)
Complex	Heart failure	55 (20.1)	17 (0.6)	86.8	2.1	46.8 (26.8-81.8)
Complex	Stroke	6 (2.2)	6 (0.2)	8.8	0.8	12.1 (3.9-37.6)

'Isolated' defined as no congenital cardiac malformation other than EA, '+ASD' defined as EA with concomitant ASD only, and 'complex' defined as EA with any other congenital cardiac malformation. ASD, atrial septal defect; CI, confidence interval; EA, Ebstein anomaly; IQR, interquartile range; IR, incidence ratio; HR, hazard ratio.

RESULTS

Surgical data:
- Median age at surgery: 16 (1-42) years.
- Cardiac surgery: n=365 (44%)
- Cardiac transplant: n= 9 (2.5%)

Mortality data:
- EA: 165 (20%) deaths of which 78 (47%) were operated.
- Controls: 509 (6.2%) deaths.

MORBIDITY [ISOLATED, BY TREATMENT]

TABLE 4		No. events (% of total)		IR per 10,000 person-years		HR (95% CI)
		Patients	Controls	Patients	Controls	
NON-OP	Arrhythmia	70 (19.8)	109 (3.1)	55.6	8.0	9.4 (6.9-12.7)
NON-OP	Heart failure	24 (6.8)	58 (1.6)	18.0	4.2	5.2 (3.2-8.3)
NON-OP	Stroke	9 (2.5)	47 (1.3)	6.8	3.4	2.1 (1.0-4.3)
OP	Arrhythmia	75 (85.2)	63 (7.2)	218.1	13.5	25.0 (17.7-35.3)
OP	Heart failure	27 (30.7)	30 (3.4)	60.0	6.4	10.1 (6.0-16.9)
OP	Stroke	3 (3.4)	15 (1.7)	6.5	3.2	1.9 (0.5-6.5)

NON-OP, conservatively managed EA patients; OP, surgically managed EA patients. CI, confidence interval; HR, hazard ratio; IR, incidence ratio; EA, Ebstein anomaly.

CONCLUSION

Patients with EA carry a substantial burden of arrhythmias, heart failure, and stroke compared with matched controls, irrespective of treatment pathway

- **Non-operated isolated EA:** 9-fold increased HR of **arrhythmia** and a 5-fold increased HR of **heart failure** compared with matched controls.
- **Operated isolated EA:** 25-fold increased HR of **arrhythmia** and 10-fold increased HR of **heart failure** compared with matched controls.
- Isolated EA associated with a 2-fold increased HR of **stroke**, while EA and ASD associated with an 8-fold increased HR.

Filip Eckerström, MD
Dept. of Cardiothoracic Surgery
Rigshospitalet, Copenhagen University Hospital
Blegdamsvej 9, 2100 København Ø, Denmark
Email: filip.eckerstroem@regionh.dk
Phone: +45 2814 2077

UNIVERSITY OF GOTHENBURG · VÄSTRA GÖTALANDSREGIONEN SAHLGRENSKA UNIVERSITETSSJUKHUSET · REGION H · Rigshospitalet · UNIVERSITY OF COPENHAGEN