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Incidence, risk factors, and predictors of infective endocarditis in adult congenital heart disease: focus on the use of prosthetic material

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Aims Adult congenital heart disease (ACHD) predisposes to infective endocarditis (IE). Surgical advancements have changed the ACHD population, whereas associated prosthetic material may constitute additional IE targets. We aimed to prospectively determine contemporary incidence, risk factors, and predictors of IE in a nationwide ACHD cohort, focusing on the presence of prosthetics.

Methods and results We identified 14 224 patients prospectively followed in the CONCOR ACHD registry (50.5% female, median age 33.6years). IE incidence was determined using Poisson regression, risk factors and predictors using Cox regression. Overall incidence was 1.33 cases/1000 person-years (124 cases in 93 562 person-years). For risk-factor analysis, presence of prosthetics was forced—as separate time-updated variables for specific prosthetics—into a model with baseline characteristics univariably associated with IE. Valve-containing prosthetics were independently associated with greater risk both short- and long term after implantation [0–6 months: hazard ratio (HR) = 17.29; 7.34–40.70, 6–12 months: HR = 15.91; 6.76–37.45, beyond 12 months: HR = 5.26; 3.52–7.86], non-valve-containing prosthetics, including valve repair, only in the first 6 months after implantation (HR = 3.34; 1.33–8.41), not thereafter. A prediction model was derived and validated using bootstrapping techniques. Independent predictors of IE were baseline valve-containing prosthetics, main congenital heart defect, multiple defects, previous IE, and sex. The model had fair discriminative ability and provided accurate predictions up to 10 years.

Conclusions This study provides IE incidence estimates, and determinants of IE risk in a nationwide ACHD cohort. Our findings, essentially informing IE prevention guidelines, indicate valve-containing prosthetics as a main determinant of IE risk whereas other prosthetics, including valve-repair, are not associated with increased risk long term after implantation.

Keywords Congenital heart defect • Adult • Surgery • Prosthetic material • Epidemiology

Introduction

Congenital heart disease (CHD) predisposes to infective endocarditis (IE).[1,2] The adult CHD (ACHD) population at risk for IE has considerably changed in size and composition over the past decades, largely due to surgical advancements and consequent increased survival of especially those with severe defects.[3,4] Moreover, prosthetic material implanted during repair and palliation constitute additional

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IE targets that may be of increasing importance in the contemporary ACHD population. These changes are reflected in patterns of ACHD-associated IE over the past decades, showing a proportionate increase of patients with complex defects and/or previous surgery involving prosthetic material.[5–7] Yet, estimates of IE incidence in ACHD, and identification of high-risk defects and risk factors are based primarily on retrospective single-institution studies from specialized centres spanning several past decades,[5–9] hampering generalizability to the contemporary ACHD population. No prospective, population-based studies addressing these issues have been reported to date. Consequently, IE risk stratification is based mainly on expert consensus.[1,2] Identification of high-risk patients is important for developing IE prevention guidelines and appropriately targeting patient counselling and medical surveillance. We aimed to prospectively determine contemporary IE incidence, and determinants of IE risk in a nationwide cohort of ACHD patients, focusing on the presence of prosthetics.

Methods

The study was approved by the ethics boards of all participating centres,[10] and complies with the Declaration of Helsinki.

CONCOR registry

CONCOR was initiated in 2001.[10] CHD patients ≥18 years old are eligible for inclusion and recruited by research nurses through the treating cardiologist or a nationwide media campaign.[11] After written informed consent, data on diagnoses and occurrence and date of clinical events and procedures before inclusion and during follow-up—classified using the European Pediatric Cardiac Code Short List[12]—are obtained from medical records. In patients with multiple defects, the most severe defect according to a consensus-based classification of CHD severity is designated the main defect.[13]

Study population and data collection

The study cohort comprised all 14 224 clinically followed ≥18-year-old patients included in CONCOR per 1 October 2015, representing 90% of the registry [*N* = 15 727, 1478 (9%) no clinical follow-up data, 25 (0.2%) <18 years old]. Clinical follow-up data, collected at hospital-level, were available in 96% of patients with complex[13] and 87% of those with simple (atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA)] CHD. Proportionately more of the latter are included from the population at large,[11] and thus not followed in a participating hospital (complex: 0%, simple: 7%).

Date of birth, sex, inclusion date, main congenital heart defect, additional cardiac defects and the occurrence and date of cardiac procedures, cause and date of death and occurrence and corresponding date of incident IE, defined as hospitalization with a diagnosis of IE, were extracted. Clinical data from the index hospitalization were collected for 98 (79%) IE cases. In 88 (90%), sufficient data could be retrieved and related to the Duke criteria for validation of the outcome definition:[14] criteria for definite and possible IE were met in 64 (73%) and 24 (27%) cases, respectively (see Supplementary material online, *Table S1A* and *B*). No alternative diagnoses were established, all cases were treated as IE. All Duke-possible cases were diagnosed as IE on alternative imaging and/or clinical picture. Follow-up ended at the time of latest medical record review.

We defined the following prosthetic material categories: (i) valve-containing prosthetics (prosthetic valves, valve-containing conduits) and (ii) non-valve-containing prosthetics, comprising valve repair (considered *in situ* if the valve was not replaced after repair), patches/septal closure devices, baffles/Fontan conduits, pacemakers or implantable cardioverter defibrillators and extracardiac prosthetics (implanted into the major vessels connected to the heart). Prosthetics were coded 'Possibly' present if procedures were performed which may include its implantation, without specification of implantation: intracardiac patches/septal closure devices (unspecified septal defect closure/ventricular aneurysm repair) and extracardiac prosthetics (unspecified aortic coarctation repair). Supplementary material online, *Table S2* shows constituent procedures per prosthetic material category.

Statistical analysis

Analyses were performed using *R* version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 22 (IBM Corp., Armonk, NY, USA).

Incidence rates were calculated using Poisson regression. Incidence rates in the first and later years after inclusion, compared to assess the possibility of inclusion conditional on greater instantaneous baseline risk, were equal (see Supplementary material online, *Table S3*).

Candidate risk factors/predictors were selected on clinical relevance: presence of prosthetics, history of non-prosthetic procedures to the heart/major vessels, main congenital heart defect, multiple cardiac defects, previous IE, sex, and age. Presence of prosthetics and history of non-prosthetic procedures were included as time-dependent covariates in risk-factor analysis (full model, *see below*); baseline status of these characteristics was included in the prediction model (*see below*). Main defect was categorized on clinical/anatomical distinction: pulmonary atresia with VSD, double-outlet right ventricle, univentricular heart, tetralogy of Fallot, left-sided defects, and all other CHD (reference group). There was no evidence of within-category heterogeneity in IE risk (see Supplementary material online, *Table S4*).

Cox regression analysis with time to first follow-up IE as the outcome was performed to investigate the relationship between candidate risk factors/predictors and IE risk. Proportionality of hazards was evaluated by examining the Schoenfeld residuals. Risk-factor analysis was performed, forcing all prosthetics into a multivariable model with all univariably significant ($P < 0.05$) baseline characteristics (full model). Intracardiac patches/closure devices and extracardiac prosthetics were entered as categorical variables (separate levels for definite and possible presence). Assuming the respective prosthetics to be either present or absent after possible implantations did not affect the association of these prosthetics with IE risk (see Supplementary material online, *Table S5*). To investigate the temporal impact of prosthetics on IE risk, time since implantation was segmented into 0–6, 6–12, and >12 months after index implantation. Time-updated binary covariates for each time interval were entered into a multivariable model, including all other covariates in the full model.[15] Results are presented as hazard ratios (HRs) with 95% confidence intervals (95% CIs); 95% CIs not including 1.0 ($P < 0.05$) were considered statistically significant.

A prediction model was derived using backward model selection, based on Akaike's Information Criterion, in 100 bootstrap samples. Entry criterion was $P < 0.250$ in univariable analysis. Variables selected in >60% of bootstrap samples were included in the prediction model (see Supplementary material online, *Figure S1*).[16] Full follow-up experience was used (maximum follow-up: 13.7 years). Discriminative ability of the model was assessed using the concordance-statistic (*c*-statistic). Internal validation was performed using bootstrapping techniques, calculating the optimism-corrected *c*-statistic penalized for overfitting (detailed procedure: see Supplementary material online, Supplementary methods).[17] A clinically applicable risk-score was developed, converting the predictors' regression coefficient into points and calculating score as the sum of points. Scores were linked to 5- and 10 year risk of developing IE.

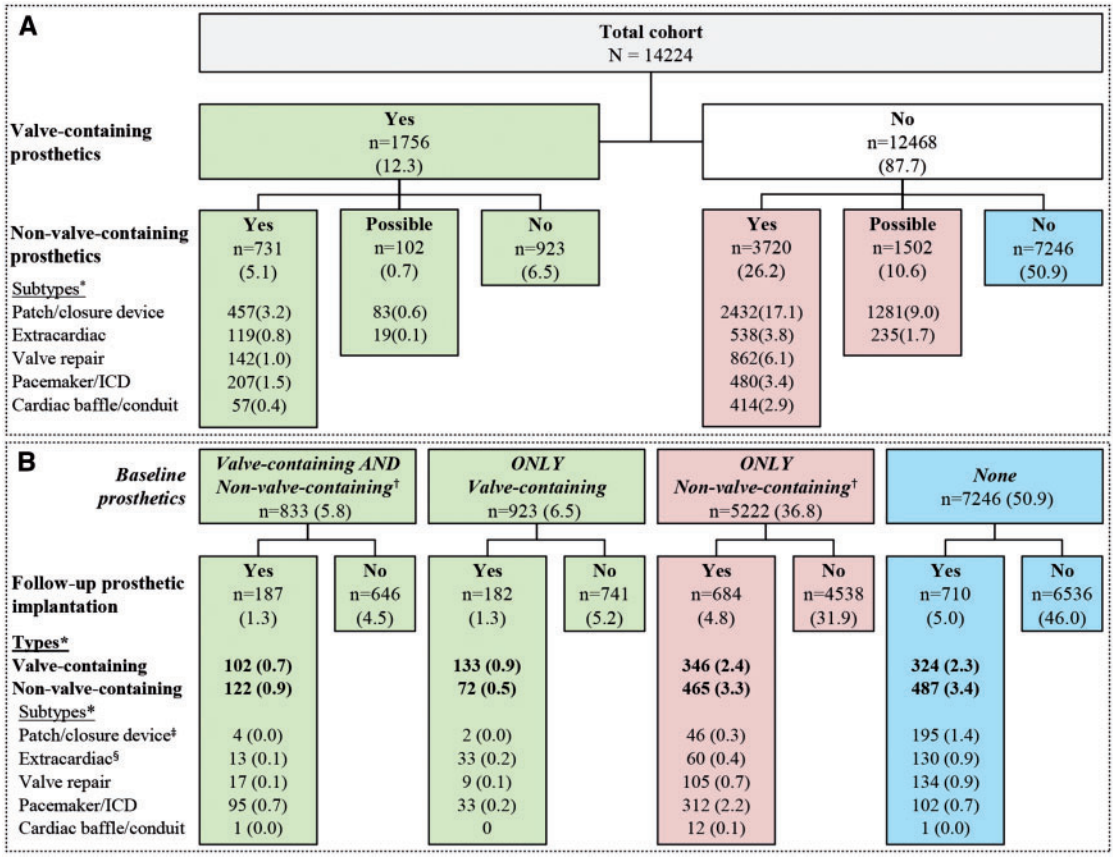

Figure 1 Baseline presence (*A*) and follow-up implantations (*B*) of specific prosthetics in study subjects. Counts represent numbers of patients (% of total cohort). Colours represent stratification of the cohort for cumulative incidence analysis (*Figure 3A and B*): valve-containing prosthetics (green), *only* non-valve-containing prosthetics (red), no prosthetics (blue). ICD, implantable cardioverter defibrillator. *Patients with >1 subtype are counted in > 1 row; †Including definite and possible presence; ‡Including 60 possible implantations; §Including two possible implantations.

Cumulative incidence of IE during follow-up was calculated, using the cumulative incidence function, stratified by baseline presence of prosthetic material: (i) valve-containing prosthetics (regardless of non-valve-containing prosthetics), (ii) *only* non-valve-containing prosthetics and (iii) no prosthetics (grouping visualized in *Figure 1*), both accounting and not accounting for the competing risk of prosthetic implantations during follow-up [which modifies subsequent risk (*Table 3*)]. Second, it was calculated stratified by predicted risk-category.

Results

Baseline characteristics and prosthetic material

Table 1 shows the baseline characteristics of the 14 224 patients. Median age at inclusion was 33.6 years, 49.5% was male, 42.6% had multiple cardiac defects, and 2.5% a history of IE. Mean follow-up was 6.6 years.

Figure 1A shows the numbers of patients with specific prosthetics present at baseline. *Figure 1B* shows implantations of prosthetics in study subjects during follow-up, by the baseline presence of prosthetics. Supplementary material online, *Table S6* shows baseline prosthetics by main CHD.

Incidence

Figure 2 shows IE incidence rates by defect. Overall incidence was 1.33 (95% CI, 1.11–1.57) cases/1000 person-years (py): 124 cases in 93 562 py in 120 (0.8%) patients. Median age at first follow-up IE was 37.8 years (range: 19.3–81.9). All eight ASD-associated cases occurred in patients with a closed defect, of whom six had concomitant valvular defects. In 9 of 13 VSD-associated cases, the defect was open. No PDA-associated cases occurred (83.5% closed).

Risk factors

Table 2 shows the results of multivariable Cox regression analysis, including presence of prosthetics as time-dependent variables, and all baseline characteristics significantly associated with IE in univariable analysis (full model). *Table 2* further shows IE incidence rates in the presence and absence of each prosthetic and baseline characteristic (univariable analysis, numbers of cases, and total person-time: see Supplementary material online, *Table S7A*). Valve-containing prosthetics were the only prosthetic type independently associated with greater IE risk (in stratified analyses, this was the case for both patients with left-sided and those with non-left-sided CHD). Interventions without prosthetics, and age were excluded

Table 1 Baseline characteristics

	Value	%
N	14 224	
Female, *n*	7187	50.5
Age, years	33.6 (22.8–47.2)	
Follow-up time		
Mean, years	6.6±4.0	
Total, person-years	93 562	
Main defect, *n*		
Left-sided	4606	32.4
Aortic coarctation	1410	9.9
Bicuspid aortic valve	1324	9.3
Left-ventricular outflow tract obstruction	999	7.0
Marfan syndrome	556	3.9
Other left-ventricular outflow tract defects	165	1.2
Mitral valve defect	152	1.1
Complex/conotruncal	2517	17.7
Tetralogy of Fallot	1136	8.0
Transposition of the great arteries	586	4.1
Pulmonary atresia with ventricular septal defect	159	1.1
Congenitally corrected transposition of the great arteries	149	1.0
Double outlet right ventricle	128	0.9
Univentricular heart	284	2.0
Other conotruncal defects	75	0.5
Ventricular septal defect	2462	17.3
Atrial septal defect	2178	15.3
Right-sided	1302	9.1
Right-ventricular outflow tract obstruction	1054	7.4
Ebstein's anomaly	222	1.6
Other right-sided defects	26	0.2
Atrioventricular septal defect	674	4.7
Partial atrioventricular septal defect	450	3.2
Complete atrioventricular septal defect	224	1.6
Patent ductus arteriosus	249	1.7
Other simple	236	1.7
Multiple defects, *n*	6061	42.6
History of IE, *n*	353	2.5

Data are presented as number with percentage, mean ± SD or median (IQR).
IE, infective endocarditis; IQR, inter-quartile range; SD, standard deviation.

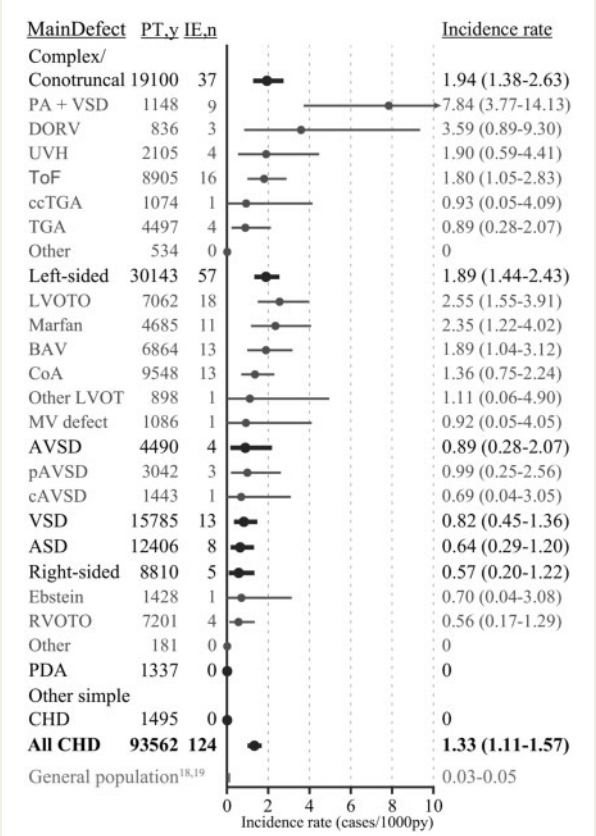

Figure 2 Incidence rate of infective endocarditis (IE) by main congenital cardiac defect. ASD, atrial septal defect; BAV, bicuspid aortic valve; cAVSD, complete atrioventricular septal defect; ccTGA, congenitally corrected TGA; CHD, congenital heart disease; CI, confidence interval; CoA, aortic coarctation; DORV, double-outlet right ventricle; LVOT(O), left-ventricular outflow tract (obstruction); MV, mitral valve; PA, pulmonary atresia; pAVSD, partial atrioventricular septal defect; PDA, patent ductus arteriosus; PS, pulmonary stenosis; py, person-years; RVOTO, right-ventricular outflow tract obstruction; TGA, transposition of the great arteries; ToF, Tetralogy of Fallot; UVH, univentricular heart; VSD, ventricular septal defect.

(non-significant in univariable analyses); adding them into the model marginally affected the HRs of included covariates.

Table 3 shows the temporal impact of prosthetic implantation. Adjusted for all other covariates in the full model (*Table 2*), valve-containing prosthetics were associated with significantly increased IE risk in the short- (0–6 months), medium- (6–12 months), and long term (>12 months) after implantation, non-valve-containing prosthetics only in the short term.

In patients with left-ventricular outflow tract (LVOT) lesions, IE incidence was lower in patients without than in those with prosthetic aortic valves (0.98 vs. 4.55 cases/1000 py, respectively, $P < 0.001$; see Supplementary material online, *Table S8*).

Predictors

Table 4 shows the prediction model. Independent baseline predictors of IE were presence of valve-containing prosthetics, main defect, multiple defects, previous IE, and sex (univariable analysis of baseline prosthetics: see Supplementary material online, *Table S7B*). With an optimism-corrected *c*-statistic of 0.73, this model had fair ability to discriminate between subjects who did and did not develop IE. *Table 4* further shows the score chart for predicted 5- and 10 year IE risk.

Table 2 Time-dependent Cox regression analysis of prosthetics as risk factors for IE, corrected for baseline characteristics univariably associated with IE

Characteristic	Incidence rate, cases/1000py(95% CI)[b]	Full model[a]	
		HR(95% CI)	*P*-value
Presence of prosthetic material[c]			
Valve-containing[d]			
No	0.63(0.47–0.82)	1	
Yes	4.85(3.84–6.04)	5.48(3.58–8.38)	*<0.001*
Valve repair[e]			
No	1.28(1.05–1.54)	1	
Yes	1.78(1.02–2.83)	1.03(0.58–1.83)	0.909
Pacemaker/ICD			
No	1.23(1.01–1.48)	1	
Yes	2.60(1.55–4.04)	1.21(0.70–2.08)	0.502
Baffle/Intracardiac Fontan conduit			
No	1.29(1.07–1.54)	1	
Yes	2.12(0.97–3.95)	1.51(0.65–3.54)	0.340
Intracardiac patch/septal closure device			
No	1.25(0.99–1.55)	1	
Yes	1.73(1.23–2.35)	1.31(0.70–2.44)	0.394
Possible	0.91(0.44–1.64)	0.96(0.45–2.04)	0.906
Extracardiac prosthetics			
No	1.24(1.02–1.49)	1	
Yes	2.59(1.46–4.20)	1.24(0.67–2.30)	0.485
Possible	1.47(0.24–4.55)	1.20(0.29–4.93)	0.806
Main defect[f]			
Pulmonary atresia with ventricular septal defect	7.84(3.77–14.13)	2.65(1.12–6.24)	*0.026*
Double-outlet right ventricle	3.59(0.89–9.30)	1.74(0.47–6.51)	0.408
Tetralogy of Fallot	1.80(1.05–2.83)	1.05(0.49–2.25)	0.895
Univentricular heart	1.90(0.59–4.41)	1.50(0.42–5.32)	0.533
Left-sided lesions	1.89(1.44–2.43)	1.43(0.84–2.44)	0.192
Other (reference)	0.69(0.49–0.95)	1	
Multiple defects			
No	0.89(0.65–1.18)	1	
Yes	1.83(1.46–2.27)	1.50(1.02–2.22)	*0.041*
History of IE			
No	1.21(1.00–1.45)	1	
Yes	5.52(3.11–8.94)	1.99(1.10–3.60)	*0.023*
Sex			
Female	0.81(0.58–1.09)	1	
Male	1.85(1.48–2.27)	1.80(1.21–2.67)	*0.004*

The italic numbers are *P*-values < 0.05, indicating statistical significance.
CI, confidence interval; HR, hazard ratio; ICD, implantable cardioverter defibrillator; IE, infective endocarditis; py, person-years.
[a]Multivariable Cox proportional hazards model including each prosthetic material type and all baseline characteristics significantly associated with the outcome in univariable analyses (*P* < 0.05, see Supplementary material online, *TableS7A*).
[b]Corresponding numbers of IE cases and total person-time: see Supplementary material online, *Table S7A*.
[c]Included as time-dependent variables.
[d]Valve replacement (HR = 4.83; 95% CI, 3.35–6.98) and valve-containing outflow tract conduits (HR = 7.59; 95% CI, 5.17–11.14) in separate univariable analyses.
[e]*In situ*: valve not replaced after repair.
[f]Composition of the defect categories, tests for within-category IE-risk heterogeneity: see Supplementary material online, *TableS4*.

Cumulative incidence

Figure 3 shows cumulative IE incidence curves stratified by baseline prosthetic material (panels *A*, *B*; stratification visualized in *Figure 1*) and predicted risk-category according to the prediction model (panel *C*), and includes estimates of observed cumulative risk at 5 and 10 years. Cumulative-incidence estimates by baseline prosthetics were

Table 3 Temporal impact of implantation of valve-containing and non-valve-containing prosthetics on subsequent IE risk

Time since event	First follow-up IE cases,*n*	Multivariable analysis[a]	
		HR(95% CI)	*P*-value
Valve-containing prosthetic implantation			
None	48	1	
0–6 months	6	17.29(7.34–40.70)	*<0.001*
6–12 months	6	15.91(6.76–37.45)	*<0.001*
>12 months	60	5.26(3.52–7.86)	*<0.001*
Non-valve-containing prosthetic implantation[b]			
None	58	1	
0–6 months	5	3.34(1.33–8.41)	*0.011*
6–12 months	1	0.66(0.09–4.80)	0.683
>12 months	56	0.90(0.62–1.32)	0.595

The italic numbers are *P*-values < 0.05, indicating statistical significance.
CI, confidence interval; FU, follow-up; HR, hazard ratio; IE, infective endocarditis.
[a]Cox proportional hazards model including all predictors in the full model (*Table 2*) and presence of the specified prosthetics, taking time since implantation into account.
[b]Including definite and possible implantation of intracardiac patches/closure devices and extracardiac prosthetics.

Table 4 Prediction model for developing IE, and score chart for the risk of developing IE up to 5 and 10 years

Predictor	HR(95% CI)	Points
Baseline valve-containing prosthetics	3.57(2.38–5.36)	3
Main defect[a]		
Pulmonary atresia with ventricular septal defect	4.05(1.85–8.86)	3
Double-outlet right ventricle	3.01(0.91–9.94)	2
Tetralogy of Fallot	1.81(0.99–3.33)	1
Univentricular heart	1.69(0.51–5.54)	1
Left-sided lesions	1.55(0.99–2.44)	1
Other	1	0
Multiple defects	1.68(1.15–2.46)	1
History of IE	2.21(1.22–4.01)	2
Male	1.89(1.28–2.81)	1

Score (sum points)

	Score									
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**>8**
Predicted 5 year risk (%)	<1	<1	1	1	1	2	3	4	7	9
Predicted 10 year risk (%)	<1	1	1	1	3	3	5	7	12	15

CI, confidence interval; HR, hazard ratio; IE, infective endocarditis.
[a]Only the main defect (i.e. most severe defect according to a classification of CHD severity[13]) contributes to score in case of multiple defects.

lower accounting for follow-up prosthetic implantation as a competing risk (*Figure 3A*), compared with not accounting for this competing risk (*Figure 3B*). *Figure 3C* shows the agreement between observed and predicted IE risk, demonstrating adequate calibration of the prediction model. In subjects with low (<1%, *n* = 10 551, 74%) and high (≥1%, *n* = 3673, 26%) predicted 10 year risk, observed 10 year cumulative incidence was 0.6% and 3.2%, respectively.

Location of infection and causative organisms

Of 92 cases with retrievable imaging and/or surgical data concerning IE location (see Supplementary material online, *Table S1A*), 31 had only valve-containing prosthetics, 19 only non-valve-containing prosthetics, and 27 had both (15 had none). Supplementary material online, *Table S1C* shows the distribution of infected sites by prosthetics present: infected sites in the 58 cases with valve-containing prosthetics: 47 (81%) valve-containing prosthetics, 2 (3%) native tissue, and 9 (16%) undetermined [31 cases with *only* valve-containing prosthetics: 26 (84%) valve-containing prosthetics, 1 (3%) native tissue, 4 (13%) undetermined]; infected sites in the 46 cases with non-valve-containing prosthetics present: 8 (17%) non-valve-containing prosthetics, 21 (46%) valve-containing prosthetics, 11 (24%) native tissue, and 6 (13%) undetermined [19 cases with *only* non-valve-containing prosthetics: 8 (42%) non-valve-containing prosthetics, 10 (53%) native tissue, 1 (5%) undetermined].

Supplementary material online, *Table 1D* shows the distribution of causative organisms by infected site in the 91 cases with retrievable microbiological diagnostic data. Overall distribution was 29% *Staphylococci*, 26% *Streptococci*, 34% other species, and 11% culture-negative. Distributions differed between prosthetic-material infections (36% *Staphylococci*, 13% *Streptococci*, 38% other, 13% culture negative) and native-tissue infections (17% *Staphylococci*, 58% *Streptococci*, 16% other, 8% culture negative; *P* = 0.001).

Outcome

Four (3.3%) patients experienced recurrent IE [after a median 1.2 years (range 1.0–2.8)]. Of 124 cases, 20 were lethal. Additionally, three patients died <1 year after IE (two heart failure, one postoperative sepsis): IE-

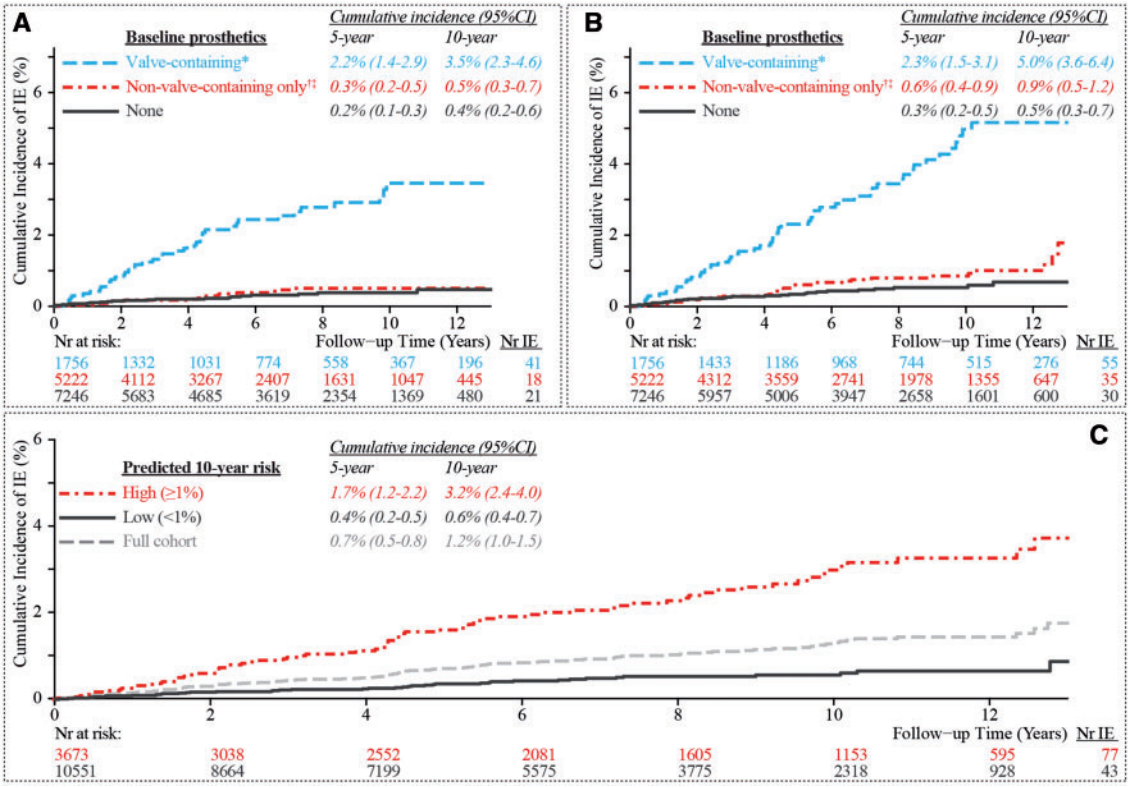

Figure 3 Cumulative incidence of infective endocarditis (IE) during follow-up by presence of prosthetic material at baseline (*A* and *B*) and predicted risk-category (*C*). Cumulative incidence by baseline prosthetics was calculated both accounting (*A*) and not accounting (*B*) for first follow-up prosthetic implantation as a competing risk. *Regardless of baseline non-valve-containing prosthetics; †*No* baseline valve-containing prosthetics; ‡Including patients with possible intracardiac patch/closure device or extracardiac prosthetics. Exclusion of these patients did not change the results.

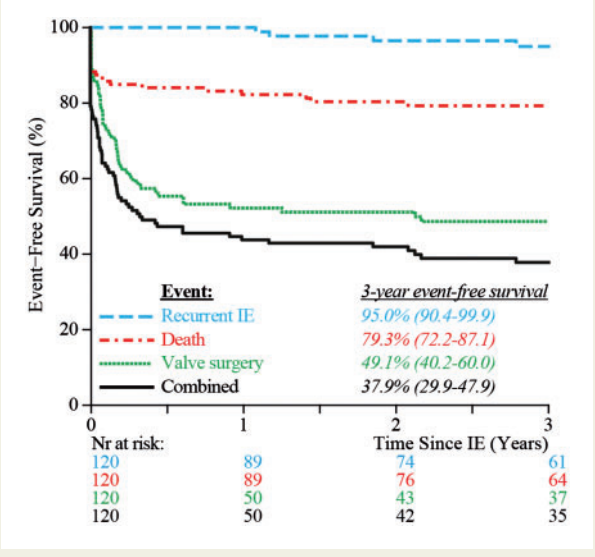

Figure 4 Adverse outcome-free survival after infective endocarditis (IE).

associated and 1 year mortality were 16% and 19%, respectively. *Figure 4* shows freedom from recurrence, death, valve surgery and these endpoints combined up to 3 years after first follow-up IE, and estimates of event-free survival at 3 years. Presence of prosthetics was not associated with risk of the combined endpoint (HR = 1.44; 95% CI, 0.77–2.67).

Discussion

Our results indicate valve-containing prosthetics as an important independent risk-factor for IE in ACHD patients, short- and long term after implantation, whereas non-valve-containing prosthetics are associated with greater risk only in the short term after implantation. A prediction model including valve-containing prosthetics and other readily obtained patient characteristics was developed to identify patients at increased risk of IE.

The overall IE incidence rate of 1.33 cases/1000 py for ACHD patients in the present cohort is ∼27–44 times that reported for contemporary adults in general (∼3–5 cases/100 000 py).[18,19] It is ∼3 times that reported for children in the Quebec CHD Database (0.41 cases/1000 py).[20] This overall difference may reflect generally greater incidence in adults,[18,19,21] although different defect distribution and prevalence of prosthetics between the cohorts may contribute. Incidence in left-sided CHD was greater here than in the paediatric

cohort, whereas incidence in complex[13] or conotruncal CHD, right-sided and atrioventricular septal defects were similar.[20]

Presence of valve-containing prosthetics—comprising prosthetic valves and valve-containing conduits, which had similar impact on IE risk (*Table 2*, footnote)—was an important risk factor for IE in this study. The majority (81%) of infections in patients with valve-containing prosthetics was located on these prosthetics. Although the impact of valve-containing prosthetics on IE risk is greatest in the first year after implantation, it is conserved thereafter (*Table 3*) and thus likely not attributable only to surgical factors associated with implantation,[1,20] but also to their long-term presence.

Non-valve-containing prosthetics were associated with increased IE risk only within the first half year after implantation, not thereafter. Moreover, in their presence, only a minority of infections were located on these prosthetics. These prosthetics may constitute susceptible surfaces only the first ∼6 months after implantation.[1,2,8] That valve repair was not associated with long-term increased IE risk could be relevant to treatment of valvular disease: when deemed equally effective and durable, repair may be preferable to replacement. Importantly, the reference group for patients with non-valve-containing prosthetics consisted of all other patients in the cohort, rather than 'healthy' subjects: present results cannot dismiss non-valve-containing prosthetics as potential IE targets.[5,6] Rather, their presence does not identify patients at greater IE risk *within* the ACHD population.

High IE incidence in complex[1,2,6,8,13] and left-sided CHD[9,20,22] and low incidence in right-sided CHD[9,20,22] are in line with previous studies. High risk among patients with LVOT defects is probably largely explained by prevalent prosthetic aortic valves (see Supplementary material online, *Table S8*).[1,2] While regarded of insignificant IE risk,[9] incidence in ASD patients exceeded that in the general population, possibly due to concomitant (valvular) defects.[20] In VSD patients, IE occurred predominantly in those with open defects.[9,22] As closure was not previously indicated, these were likely haemodynamically insignificant, underlining infectious risk of small open VSDs.[5] No IE occurred in PDA patients (closed in 84%). Closure of haemodynamically insignificant PDAs in adults for IE-risk reduction is probably not justified.[23] Increased risk associated with multiple CHDs emphasizes the contribution of concomitant defects to total risk.[1]

As found in general, male sex[18,19] was associated with increased risk, possibly attributable to sex-differences in risk-increasing lifestyle factors (e.g. dental health).[24] In contrast to the general adult population,[18,19] advancing age was not associated with IE risk. Factors generally determining risk-increase with age may not significantly influence risk in the ACHD population with prevalent risk-increasing defects throughout life. As generally found for ACHD-related IE, median age of occurrence (∼38 years) was low compared with general IE (60–70 years).[8,18,19] Prosthetic material did not presently influence outcome.[25] The 16% early mortality is within the 2–24% range in CHD-related IE case-series.[5–8] Rates of recurrence and valve surgery are similar to reports.[5–7]

Methodological issues

The prospective longitudinal data from a contemporary nationwide ACHD cohort constitute a major strength of this study. Previous studies[5–9,25] largely comprise retrospective case-series from specialized centres, spanning decades characterized by major changes in the ACHD population.[3,4] Moreover, limitations of a previous CONCOR study into IE using predominantly retrospective data[26] were overcome.

The present cohort represents ACHD patients followed in clinical practice, which may comprise those with more severe/complicated disease from the overall ACHD population. Selective inclusion from the clinically followed population, if related to IE risk, could induce bias. IE incidence did not differ between the first and later years after inclusion, mitigating risk of inclusion conditional on instantaneous risk (see Supplementary material online, *Table S3*). Inclusion conditional on long-term risk would affect validity of the incidence rates, but that of predictors only if dependent on factors associated with both predictor and outcome.

Infective endocarditis was defined as hospitalization with this diagnosis, as in previous population-based studies.[20,27] Case identification is deemed reliable: initiation of therapy and complication-risk necessitate hospitalization. Moreover, the study falls fully within the era of validated clinical criteria for IE diagnosis, used to validate the outcome definition (see Supplementary material online, *Table 1B*), and advanced diagnostics.[14] Misclassification of IE would cause over- or underestimation of incidence rates. In regression analyses, it would only cause bias away from the null value if differential with respect to predictors.

The prediction model, including readily determinable characteristics, fits the clinical setting. The internally validated discriminative ability, which may be considered a reliable estimate of the expected external predictive discrimination,[17] and adequate calibration suggest a valid model. Validation in other cohorts would ideally be performed before clinical implementation. The model performed well despite not accounting for the chance of future risk-altering events. Dependency of long-term IE risk on the chance of risk-altering events is demonstrated by greater IE incidence when not taking follow-up prosthetic implantations into account as a competing risk (*Figure 3A*). For reasons of model interpretability and clinical utility, competing risk of changing IE risk-score was not included in the prediction model. Naturally, IE risk should be re-evaluated after known risk-increasing events.

As clinical information was limited, factors that may be aetiologically important, including dental health/hygiene, non-cardiovascular procedures, comorbidities and lifestyle habits[1,2] could not be taken into account, nor could measures of disease severity,[22] residual defects[1] and antibiotic prophylaxis. CHD repair-status, known to affect IE risk, was not tested:[8,9] its effect differs between defects, and depends on implantation of prosthetics. Clinical data on IE cases were retrospectively collected, preventing complete retrieval of all relevant information. Statistical analyses were limited by the scarcity of events, precluding inclusion of interaction terms and all separate CHD types. Uncertainty in the presence of particular prosthetics (patches/septal occluders and extracardiac prosthetics), reflecting lacking detailed documentation of surgical techniques in medical records, is accounted for by including these prosthetics as categorical variables with separate levels for certain and possible presence. Neither definite nor possible presence was associated with IE risk (*Table 2*), and regarding these prosthetics as either present or absent

in uncertain cases did not affect their association with IE risk (see Supplementary material online, *Table S5*).

Implications

This study essentially informs IE prevention guidelines. Presented estimates of absolute IE risk, and risk factors and predictors for IE in a nationwide ACHD cohort identify high-risk patients, and provide data necessary for cost-effectiveness analysis of IE prophylaxis. Our results indicate valve-containing prosthetics as a main determinant of IE risk. Current European[1] and American[2] guidelines recommend IE prophylaxis in (i) patients with prosthetic material used for valve replacement or valve repair, and (ii) during the first 6 months after implantation of other prosthetics. Our results corroborate short- and long-term increased risk after valve-containing prosthetic implantation, and short-term increased risk after implantation of other prosthetics, including valve-repair. The latter indicates that, if reproducible in future (clinical) studies, valve-repair may be included in the second, rather than the first recommendation in future guidelines.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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