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Turning 18 with congenital heart disease: prediction of infective endocarditis based on a large population

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Aims The risk of infective endocarditis (IE) in adults with congenital heart disease is known to be increased, yet empirical risk estimates are lacking. We sought to predict the occurrence of IE in patients with congenital heart disease at the transition from childhood into adulthood.

Methods and results We identified patients from the CONCOR national registry for adults with congenital heart disease. Potential predictors included patient characteristics, and complications and interventions in childhood. The outcome measure was the occurrence of IE up to the age of 40 and 60. A prediction model was derived using the Cox proportional hazards model and bootstrapping techniques. The model was transformed into a clinically applicable risk score. Of 10 210 patients, 233 (2.3%) developed adult-onset IE during 220 688 patient-years. Predictors of IE were gender, main congenital heart defect, multiple heart defects, and three types of complications in childhood. Up to the age of 40, patients with a low predicted risk (<3%) had an observed incidence of less than 1%; those with a high predicted risk (≥3%) had an observed incidence of 6%. The model also yielded accurate predictions up to the age of 60.

Conclusion Among young adult patients with congenital heart disease, the use of six simple clinical parameters can accurately predict patients at relatively low or high risk of IE. After confirmation in other cohorts, application of the prediction model may lead to individually tailored medical surveillance and educational counselling, thus averting IE or enabling timely detection in adult patients with congenital heart disease.

Keywords Heart defects • Congenital • Endocarditis • Epidemiology • Long-term • Prognosis

Introduction

Over the past decades, the number of adults with congenital heart disease in the population has markedly increased, and is currently estimated at more than 1 million in the USA,[1] and over 1.2 million in Europe.[2] Despite major advancements in medical care for these patients, a vast proportion experiences mild to life-threatening complications.[3–5] A clinically relevant subgroup among these patients are youngsters who have recently made the transition from the paediatric to the adult cardiologist. The paucity of evidence on long-term prognosis makes it difficult to establish an optimal medical management plan, where accurate information on future health perspectives is important to both the young adult patient and the cardiologist.[6,7]

One of the complications encountered in adult patients with congenital heart disease is infective endocarditis (IE), which carries a substantial risk of morbidity and mortality with a mortality rate up to 20%.[8,9] This stresses the importance of identifying

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patients who are at high risk for developing IE. Currently, risk estimates of individual patients are based on consensus of expert opinions rather than solid scientific evidence,[10,11] since the available literature largely concentrates on patients with acquired heart disease,[12–14] and accurate risk estimates of IE in young adults with congenital heart disease are lacking. Yet, timely identification may target patients who would maximally benefit from preventive measures or increased medical surveillance, aimed at lowering the risk of developing IE.

We used the Dutch national CONCOR registry for adults with congenital heart disease to predict in 18-year-old adult patients with congenital heart disease their risk of IE before the age of 40 and 60 years using simple clinical parameters.

Methods

CONCOR registry

The CONCOR (CONgenital CORvitia) Dutch national registry database has been described in detail.[15] Briefly, CONCOR aims to facilitate research into the aetiology of congenital heart disease and on its outcome. From November 2001, patients with congenital heart disease aged 18 years or older have been recruited and included by three independent, permanently employed research nurses through the treating cardiologist or via response to advertisements in local media. Clinical data such as diagnosis, clinical events, and procedures—classified using the European Paediatric Cardiac Code Short List coding scheme[16]—as well as patient and family history were obtained from medical records. In case of multiple diagnoses in one patient, a pre-specified hierarchical scheme founded on consensus-based classification of defect severity[17] was used, by means of which the diagnosis with the worst prognosis was established as main diagnosis. After entry, data on major cardiac events prior to entry and during follow-up were systematically recorded from the patients' medical letters written by their cardiologist. Quality control of data is performed by randomly verifying around 10% of data yearly; less than 1% of all data was erroneous. Currently, 102 Dutch hospitals are participating, including all 8 tertiary referral centres from which 70% of patients originate.

Predictors

In CONCOR, patients aged at least 18 years at the time of analysis (9 March 2009) were identified. Date of birth, gender, main diagnosis, the presence of other defects, and the occurrence and date of established IE, diagnosed according to the modified Duke criteria in all affiliated institutions alike,[18] were derived. Furthermore, a number of complications and interventions that had occurred prior to the age of 18 were included as predictors, because they either potentially increased the risk of IE or were considered clinically important events that, therefore, may have predictive ability:[19] cerebrovascular accident or transient ischaemic attack, supraventricular arrhythmias or conduction disturbances, ventricular arrhythmias, aortic complications (comprising aneurysm and dissection), myocardial infarction, systemic hypertension, pulmonary hypertension, and Eisenmenger syndrome. Pulmonary arterial hypertension was defined as a systolic pulmonary pressure above 40 mmHg and was estimated on the basis of echocardiographic evaluation (tricuspid regurgitation jet velocity measurements), as invasive data were generally not available. Pulmonary hypertension was considered to be Eisenmenger syndrome after shunt reversal of the original systemic-to-pulmonary shunt, accompanied by cyanosis. Death was also recorded. Finally, interventions prior to age 18 were recorded that may have increased the risk of IE by inducing high-velocity or turbulent flows, or by introducing foreign tissue into the heart: implantation of a pacemaker or implantable cardioverter defibrillator, stent placement, prosthetic valvar replacement, other interventions using prosthetic material, and palliative shunts or conduits including Fontan.[11]

Prediction model

Our aim is to construct a risk model for 18-year-old patients who recently transferred from the paediatric to the adult cardiologist. The components should, in daily clinical setting, be easily obtained from medical history taking. The outcome was IE up to 40 and 60 years of age; we chose these cut-off points as they form large yet recognizable time spans to both patients and clinicians and because they allowed for a stable fixed-age model. We considered it the best approximation to clinical setting to include all candidate predictors (*Table 1*) in a Cox proportional hazards model, with adult-onset IE or death from IE (yes vs. no) as the time-dependent outcome variable and sets of predictors as independent variables; elapsed time between 18th birthday and censoring was calculated. In case of multiple episodes of adult-onset IE in a single patient, the first episode was used for the analysis. Congenital heart defect was entered as a dummy variable with atrial septal defect as the reference category; patent arterial duct (84% ligated) was added to this category, having no cases of IE. Candidate predictors were entered into the model and subsequently excluded in a backward stepwise fashion using the likelihood ratio test with a *P*-value according to Akaike's Information Criterion.[20,21] We specified the total follow-up experience for IE to a fixed 22- and 42-year follow-up from the age of 18 years (thus up to the age of 40 and 60, respectively) using the linear predictor from the final model and the set baseline hazard of the CONCOR patients who had exactly 22 years ($n = 205$) and 42 years ($n = 95$) of follow-up from the age of 18.[22,23]

To study the performance of the final prediction model, we assessed its discrimination and calibration. Discrimination is the ability of the model to distinguish between patients with and without IE. Discrimination was quantified by the concordance-statistic (c-statistic), which is equal to the area under the receiver operating characteristic curve (AUC).[24] An AUC ranges from 0.5 (no discrimination; equal to flipping a coin) to 1.0 (perfect discrimination).[25] Calibration refers to the agreement between the predicted risk estimates and the observed probabilities. We introduced a cut-off value in the predicted risk estimates at 0.03, thus categorizing patients as having a low or high risk of developing IE up to the age of 40 and 60. This cut-off point was chosen both on the basis of the distribution of observed occurrence of IE and for reasons of practical applicability. Then we calculated the observed cumulative incidences (Kaplan–Meier estimates) after 22- and 42-year follow-up for each predicted risk category and compared them graphically (*Figure 2*).

Prediction models derived using multivariable regression analysis may overestimate regression coefficients, resulting in overvalued predictions when applied in new patients.[26,27] Therefore, we internally validated our model with bootstrapping techniques, resulting in a shrinkage factor for the regression coefficients and the c-statistic.[26,28] The corrected c-statistic may be considered an estimate of discriminative ability that is expected in future adult patients with congenital heart disease.

To facilitate the practical application of the model in clinical practice, the regression coefficients of the predictors in the model were converted into a score chart; the total points (sum scores) were divided by 10, rounded to the nearest integer, and subsequently linked to the risk of developing IE up to the age of 40 and 60.

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Table 1 Candidate predictors in all CONCOR patients and by status of adult-onset infective endocarditis

	All (n = 10 210)		IE (n = 233)		No IE (n = 9977)	
Patient characteristics	***n***	**%**	***n***	**%**	***n***	**%**
Female gender	5186	51	70	30	5116	51
Multiple congenital heart defects	5159	51	149	64	5010	50
Main congenital heart defect						
Ventricular septal defect	1726	17	62	27	1664	17
Atrial septal defect	1535	15	9	4	1526	15
Aortic coarctation	1002	10	14	6	988	10
Tetralogy of Fallot	940	9	21	9	919	9
Aortic stenosis	922	9	26	11	896	9
Pulmonary stenosis	778	8	3	1	775	8
Bicuspid aortic valve	551	5	31	13	520	5
Atrioventricular septal defect	476	5	10	4	466	5
Marfan syndrome	458	4	12	5	446	4
Transposition of the great arteries	449	4	6	3	443	4
Patent arterial duct	159	2	0	0	159	2
Ebstein malformation	154	2	3	1	151	2
Pulmonary atresia with ventricular septal defect	118	1	8	3	110	1
Congenitally corrected transposition of the great arteries	117	1	6	3	111	1
Univentricular heart/double inlet left ventricle	107	1	4	2	103	1
Other congenital heart defects (n < 100)	718	7	18	8	700	7
Complications in childhood[a]						
Infective endocarditis	89	1	14	6	75	<1
Cerebrovascular accident/transient ischaemic attack	23	<1	2	<1	21	<1
Supraventricular arrhythmia/conduction disturbances	585	6	5	2	580	6
Ventricular arrhythmia	41	<1	0	0	41	<1
Aortic complications	17	<1	0	0	17	<1
Systemic hypertension	56	1	0	0	56	<1
Pulmonary hypertension	71	1	2	<1	69	<1
Eisenmenger syndrome	16	<1	0	0	16	<1
Interventions in childhood[a]						
Pacemaker implantation	142	1	2	<1	140	1
Intracardiac cardioverter defibrillator implantation	8	<1	0	0	8	<1
Stent placement	35	<1	0	0	35	<1
Prosthetic valvar replacement	154	2	5	2	149	1
Other interventions using prosthetic material	777	8	15	6	762	8
Palliative shunt/conduit or Fontan operation	713	7	23	10	690	7

[a]Subjects may appear in more than one row. IE, infective endocarditis.

Data summaries

Frequencies of complications and interventions up to the age of 18 years were calculated. The incidence rate of IE was calculated by dividing the number of patients with IE by patient-years (i.e. number of all patients multiplied by duration between 18th birthday and censoring) for each defect ($n \geq 100$). Results were expressed as hazard ratios (HR) with 95% confidence intervals (CI); 95% CI not including 1.0, corresponding to two-sided P-values of less than 0.05, were considered statistically significant. Analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) and R (version 2.8.1, http://www.r-project.org).

Results

Of 10 210 patients, 5186 (51%) were female and the median age was 37.3 years (range 18.1–93.5) at the time of analysis. Median follow-up duration was 18.9 years (range 0.1–75.5). Adult-onset IE occurred in 233 patients (2.3%) during 220 688 patient-years; among these patients, 28 subjects (12%) experienced IE twice throughout life, and 6 patients (3%) encountered three or more episodes of IE. Median age at IE was 31.3 years (range 18.1–76.2), and 163 (70%) were male. Women had a 60% lower

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risk of IE than men ($P < 0.001$) after adjustment for underlying defect.

Among all patients, there was no significant difference in IE risk between patients who had undergone an intervention in childhood ($n = 4864$, 48%) and patients who had not (HR 0.9, 95% CI 0.6–1.2, $P = 0.37$). The incidence of adult-onset IE was 2.6% in patients who had undergone a palliative intervention in childhood, and 1.3% in patients who had undergone a corrective intervention. The risk of IE did not differ significantly between these groups after adjustment for gender and underlying defect (HR 1.6, 95% CI 0.9–3.0, $P = 0.10$).

During follow-up in CONCOR, 13 patients died from IE; their most frequently underlying defects were aortic stenosis ($n = 4$), Tetralogy of Fallot ($n = 2$), and ventricular septal defect ($n = 2$). Separately, patients with IE had a 90% higher risk of all-cause death than patients without IE ($P = 0.02$) after adjustment for gender and defect.

Figure 1 shows the incidence of IE per 1000 patient-years by defect. The overall incidence rate of IE at adult age was 1.1 (95% CI 0.9–1.2) case per 1000 patient-years. Patients with pulmonary atresia and congenitally corrected transposition of the great arteries had the highest incidence rate of IE with 5.8 (95% CI 1.8–9.8) and 2.3 (95% CI 0.5–4.1) cases per 1000 patient-years, respectively. Among patients with patent arterial duct, of whom the vast majority (84%) had undergone ligation, there were no cases of IE. Of nine patients with atrial septal defect and IE, eight patients had concomitant lesions, being either valvular (particularly of the mitral valve) or a small ventricular septal defect.

Table 2 shows the predictors of the final model, including gender, multiple defects, main congenital heart defect, and three types of complications in childhood: IE, cerebrovascular accident or transient ischaemic attack, and supraventricular arrhythmia or conduction disturbances. The mean predicted risk up to the age of 40 was 2.4%, and up to the age of 60 was 4.7%. The model discriminated fairly well between patients who developed IE and patients who did not, as the c-statistic was 0.75. For reasons of possible model instability, patients with pulmonary stenosis were added to the reference group in a separate analysis, but that did not materially influence the results (data not shown).

Figure 2 shows the cumulative risk of IE over time after 18 years of age in all CONCOR patients. The risk of IE increased with age in a linear fashion; the cumulative observed risk of IE at the age of 40 was 2.4%, and at the age of 60 was 4.4%. In addition, this figure shows the agreement between the risk of IE as observed in CONCOR patients and the subgroups of patients who, according to the prediction model, are at low or at high risk for IE up to 40 and 60 years of age. In patients with a low predicted risk up to the age of 40 (risk $<3\%$; $n = 7710$, 76% of the population), the observed incidence of IE was less than 1%. Among patients with a high predicted risk ($\geq 3\%$ or higher; $n = 2500$, 24%), the observed incidence of IE was 6%. Additionally, the risk of IE up to 60 years of age was calculated. Patients with a low predicted risk ($n = 4176$, 41%) had an observed incidence of 1%; those with a high predicted risk ($n = 6034$, 59%) had an observed incidence of 7%.

Table 3 shows the score chart for practical application of the prediction model on the individual 18-year-old patient with

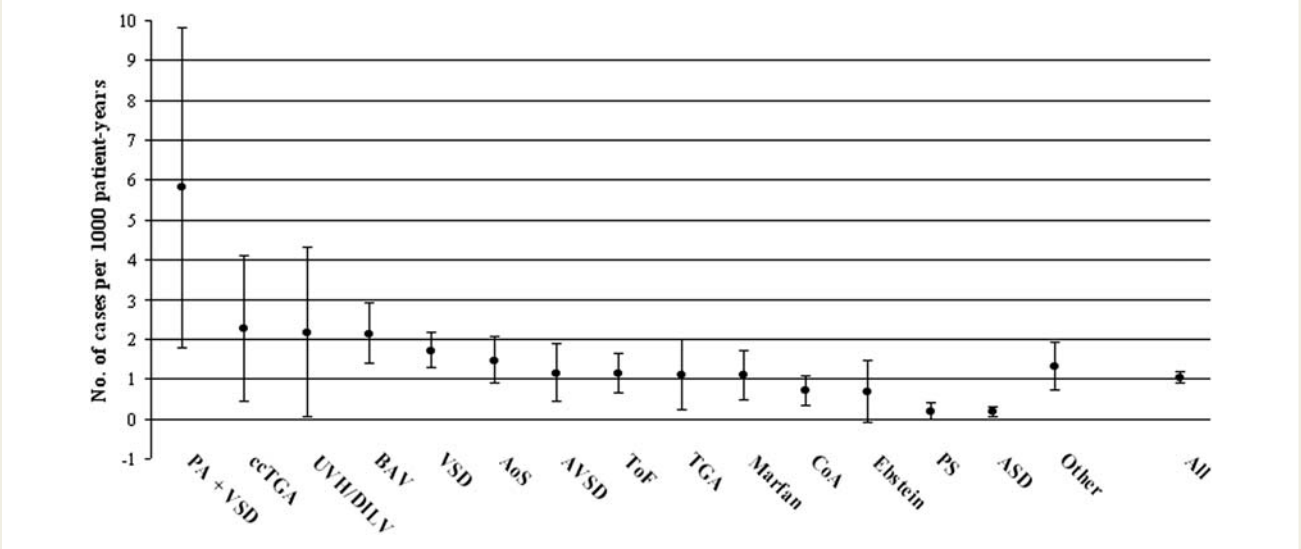

Figure 1 Incidence rate of infective endocarditis by defect per 1000 patient-years. Bars represent 95% confidence intervals for the incidences rates found (± 1.96*standard error). Rates are shown in descending order of frequency. PA + VSD, pulmonary atresia with ventricular septal defect; ccTGA, congenitally corrected transposition of the great arteries; UVH/DILV, univentricular heart/double inlet left ventricle; BAV, bicuspid aortic valve; VSD, ventricular septal defect; AoS, aortic stenosis; AVSD, atrioventricular septal defect (including atrial septal defect, primum type), ToF, Tetralogy of Fallot; TGA, transposition of the great arteries; Marfan, Marfan syndrome; CoA, aortic coarctation; Ebstein, Ebstein malformation; PS, pulmonary stenosis; ASD, atrial septal defect; Other, congenital heart defects with $n < 100$ [defects $n > 50$: mitral valvar prolapse ($n = 79$), aortic regurgitation ($n = 74$), double outlet right ventricle ($n = 73$), and tricuspid atresia ($n = 73$)]; All, all defects taken together.

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Table 2 Prediction model for developing infective endocarditis in adulthood up to the age of 40 and 60

Predictor	Regression coefficient[a]	HR	95% CI
Patient characteristics			
Female gender	−0.73	0.5	0.4–0.6
Multiple congenital heart defects	0.40	1.5	1.1–2.0
Main congenital heart defect			
Atrial septal defect/patent arterial duct	–	–	–
Ventricular septal defect	1.92	6.8	3.4–13.8
Aortic coarctation	0.92	2.5	1.1–5.9
Tetralogy of Fallot	1.46	4.3	1.9–9.5
Aortic stenosis	1.58	4.9	2.2–10.5
Pulmonary stenosis	0.07	1.1	0.3–4.0
Bicuspid aortic valve	1.84	6.3	3.0–13.4
Atrioventricular septal defect	1.54	4.7	1.9–11.6
Marfan syndrome	1.42	4.2	1.7–9.9
Transposition of the great arteries	1.51	4.5	1.6–13.0
Ebstein malformation	0.92	2.5	0.7–9.3
Pulmonary atresia with ventricular septal defect	2.82	16.7	6.3–44.3
Congenitally corrected transposition of the great arteries	1.96	7.1	2.5–20.1
Univentricular heart/ double inlet left ventricle	1.81	6.1	1.8–20.2
Other congenital heart defect	1.62	5.1	2.3–11.3
Complications in childhood			
Infective endocarditis	1.67	5.3	3.0–9.2
Cerebrovascular accident/ transient ischaemic attack	1.25	3.5	0.8–14.4
Supraventricular arrhythmia/conduction disturbances	−0.77	0.5	0.2–1.1
C-statistic[b]	0.75		0.72–0.78

HR, hazard ratio; 95% CI, 95% confidence interval.
[a]After adjustment for overfitting by shrinkage (shrinkage factor = 0.88).
[b]Adjusted for optimism using bootstrapping techniques.

congenital heart disease. As an example of how to use this chart, we consider a young man with a ventricular septal defect and a pulmonary valvar stenosis with a history of IE, who recently transferred from the paediatric to the adult cardiologist. His gender accounts for 0 points, whereas the presence of more than one defect yields 5 points. Ventricular septal defect is considered more severe than pulmonary valvar stenosis,[17] and is therefore regarded as the main diagnosis. Since only the main defect contributes to the score, ventricular septal defect accounts for 26 points. His childhood history mentions IE (23 points). Thus, this young man would have a total score of 0 + 5 + 26 + 23 = 54 points, which, divided by 10 and rounded to the nearest integer, corresponds to a risk of IE of 21% up to the age of 40, and a risk of 37% up to 60 years of age.

Discussion

We developed a prediction model to identify patients with congenital heart disease in transition from childhood to young adulthood who are at increased risk of IE. To our knowledge, this is the first study to provide absolute risk estimates of IE for individual patients who recently made the transition from the paediatric to the adult cardiologist based on a large body of long-term follow-up data.

Relation to current literature

We found an overall incidence rate of IE of 1.1 per 1000 patient-years, which is clearly increased compared with the rate of 1.7–6.2 per 100 000 patient-years in the general population.[12] Confined to congenital heart disease, Gersony *et al.*[29] reported the incidence rates of congenital aortic stenosis and ventricular septal defect of 2.7 and 1.4 per 1000 patient-years, respectively. Morris *et al.*[30] described the incidence of IE 30 years after childhood surgery for 12 congenital heart defects, yielding incidence rates of up to 11.5 cases per 1000 patient-years for pulmonary atresia with ventricular septal defect. However, these comparisons ought to be viewed with caution, since these studies comprise children with congenital heart disease. Hence, the findings cannot evidently be extrapolated to adults with congenital heart disease.

We found no cases of IE in patients with patent arterial duct, of whom the vast majority (84%) had undergone ligation. Similarly, a previous study reported no case of IE 30 years after repair of patent arterial duct.[30] Furthermore, the incidence rate of IE in patients with atrial septal defect was higher than expected. These patients had concomitant lesions that rendered them vulnerable to IE, being either valvular (particularly concerning the mitral valve) or a small ventricular septal defect. Moreover, we found a high incidence of IE in patients with congenitally corrected transposition of the great arteries, who represent a mere 1% of our study population, since this defect is both rare at birth and in many infants with congenitally corrected transposition of the great arteries too severe to reach adulthood. We believe that these adult patients have a relatively high incidence of IE as they, on average, have more complex congenital heart defects that are often accompanied by many residua. This makes them more vulnerable in general and in particular if they have residua from an accompanied ventricular septal defect. Furthermore, we found no difference in risk of IE between patients with corrective and palliative interventions. Apart from numbers that may have been too small to reach statistical significance, this may be partially due to the presence of residua in many defects.

We found a mortality rate by IE of almost 6% in our study population, which is comparable with other studies assessing mortality by IE in adults with congenital heart disease.[31,32] Various studies have described the clinical characteristics and outcomes of adult patients with congenital heart defects who developed IE.[31–33] Yet these studies are restricted to patients with congenital heart

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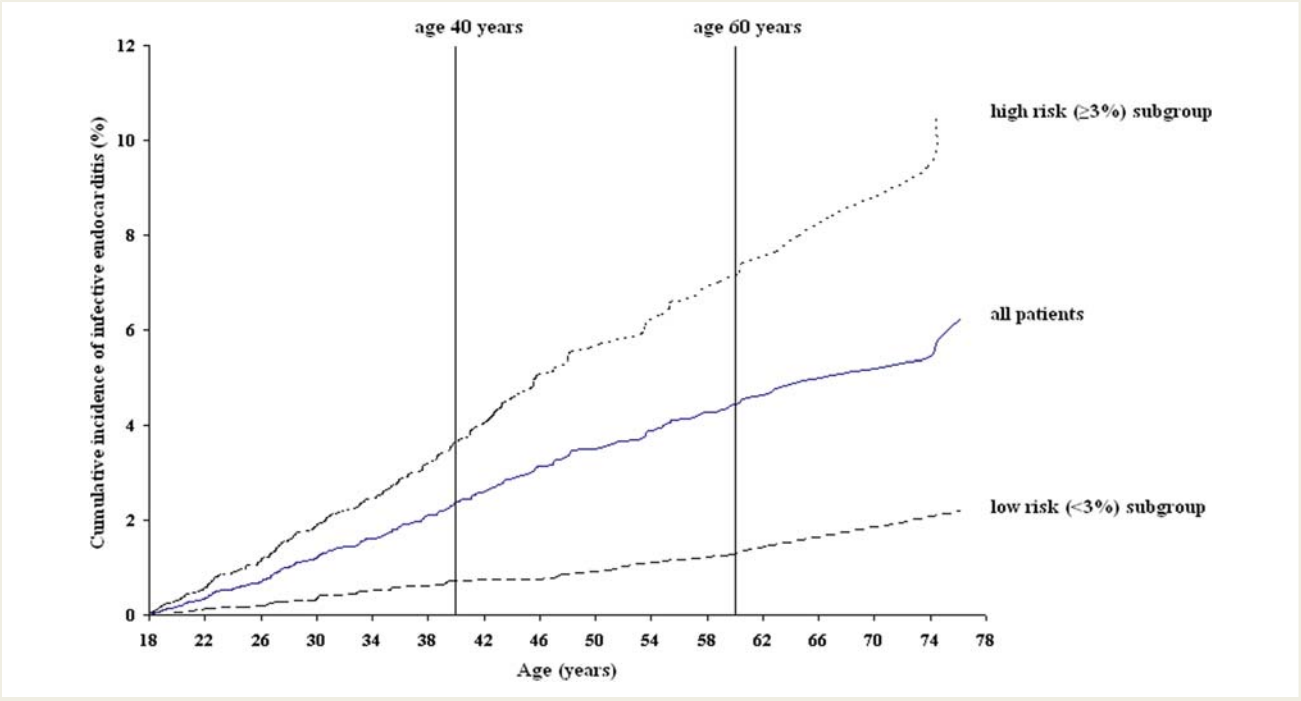

Figure 2 Observed cumulative risk of infective endocarditis from 18th birthday up to the age of 40 and 60 in all ($n = 10\,210$) patients and by predicted risk group. Number of patients at risk at age 18: $n = 10\,210$, age 22: $n = 9446$, age 26: $n = 8110$, age 30: $n = 6871$, age 34: $n = 5806$, age 38: $n = 4831$, age 42: $n = 3873$, age 46: $n = 3036$, age 50: $n = 2360$, age 54: $n = 1819$, age 58: $n = 1375$, age 62: $n = 960$, age 66: $n = 659$, age 70: $n = 436$, age 74: $n = 265$, age 78: $n = 134$.

disease who have already had IE, and thus cannot assess the risk of IE in the whole population. It becomes clear that a gap exists in the current evidence on prognosis concerning the development of IE in adult congenital heart disease, which is reflected by current guidelines that lack accurate risk estimates of future IE in adults with congenital heart disease.[10,11] Notwithstanding the importance of expertise and clinical experience, it makes the call for an evidence-based risk assessment of IE even more compelling. The prediction model presented in this study is a first attempt to fill in this gap.

Our prediction model comprises several predictors that are known for predisposing to IE, such as gender,[34,35] increased age,[36] and a prior history of IE.[8,37] Factors attributing to the increased male risk of IE are sought in lifestyle such as inadequate dental hygiene[38] and intravenous drug use,[39] both of which are more common in men. Some of the associations may seem counterintuitive, such as prosthetic valves which did not predict IE, and rhythm or conduction disturbances that inversely predicted IE. These findings can be explained by the fact that these associations are found in a subset of patients of which the reference group consists of all other patients with congenital heart disease (and thus the morbidity associated with them), rather than a reference group of healthy counterparts without any history of disease or complications. Thus, it is important to recognize that a predictive association does not necessarily imply a causal relation, and therefore should not be interpreted as such. Our predictors merely reflect their ability to distinguish between patients who will and will not develop IE. Moreover, if childhood complications and interventions do not contribute to our model, this obviously does not exclude the possibility of a causal relationship with IE, it only means that their presence, for instance of prosthetic valves, does not have further discriminative ability in our patients.

Strengths and limitations

We used a large nationwide patient population that is representative of the adult patient population with congenital heart disease and outcomes of adult patients with congenital heart disease. Additionally, we were able to base the model on the wide spectrum of clinical characteristics of these patients, and a range of clinical variables were available to use as potential predictors. However, the relatively low number of patients with IE yields the danger of an unbalanced prediction model, although the shrinkage factor close to 1.00 and sufficient calibration suggest a fairly stable model. Our prediction model is conditional on the premise of both clinical and procedural characteristics changing over the years. Some predictors were more precisely estimated than others, as reflected by the confidence bands around the HR. Furthermore, some factors were not taken into account that might have influenced the risk of IE, such as knowledge of disease, medical centre, and social conditions. In the CONCOR registry, measurement of such factors is under consideration, but logistic implications and measurement validity are issues to be dealt with. Nevertheless, such factors may be aetiologically important and future research should reveal their added prognostic value. Our model fits the current clinical setting of the young adult with congenital heart disease who recently transferred from the paediatric

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Table 3 Score chart for the risk of developing adult-onset infective endocarditis up to the age of 40 and 60

Predictor	Score	Sum
Patient characteristics		...
Female gender	−10	
Multiple congenital heart defects	5	
Main congenital heart defect		...
Atrial septal defect	0	
Ventricular septal defect	26	
Aortic coarctation	12	
Tetralogy of Fallot	20	
Aortic stenosis	21	
Pulmonary stenosis	1	
Bicuspid aortic valve	25	
Atrioventricular septal defect	21	
Marfan syndrome	19	
Transposition of the great arteries	20	
Patent arterial duct	0	
Ebstein malformation	12	
Pulmonary atresia with ventricular septal defect	38	
Congenitally corrected transposition of the great arteries	26	
Univentricular heart/double inlet left ventricle	24	
Other congenital heart defect	22	
Complications in childhood		...
Infective endocarditis	23	
Cerebrovascular accident/transient ischaemic attack	17	
Supraventricular arrhythmia/conduction disturbances	−10	
		+
Total Sum Score		...
Score divided by 10 and rounded to the nearest integer		...

Score	0	1	2	3	4	5	6	7
Predicted risk up to age 40 (%)	<1	1	2	4	12	21	33	53
Predicted risk up to age 60 (%)	<1	3	5	9	22	37	56	79

to the adult cardiologist, in whom childhood and patient characteristics are to provide an estimate of IE risk. Preferably, the model needs to be validated in other cohorts to allow its use with confidence in clinical practice. Adult patients who died prior to enrolment in the CONCOR registry are not accounted for in this prediction model.

Future research and implications

Several studies have shown that adult patients with congenital heart disease often have inadequate knowledge of the symptoms and risk factors of IE as well as hygienic measures despite educational counselling.[40–42] Yet IE is a serious condition, as confirmed by the two-fold increased mortality risk we found. We seek the explanation of this finding in the fact that patients with IE are more vulnerable in general, which makes them prone to both IE, other health issues, and death. Using our model, patients with an estimated IE risk up to 40 years of, for instance, at least 3% (which accounts for 24% of our study population) may be targeted for intensified education on proper daily dental and skin care, and signs or symptoms that should prompt them to consult their cardiologist immediately. Additionally, the physician may be more vigilant on both timely identification and prevention by assessing risk factors, aside from affirming the need for antibiotic prophylaxis in patients who have the highest risk of adverse outcome from IE.[10] High-risk patients who have an untreated or residual ventricular septal defect may also benefit from closure, although this remains a matter of debate.[43,44] By applying these measures, a decrease in the occurrence of IE and its sequelae might be expected. We believe that our model is a first step in this direction. Finally, further research on the effect of 22q11 deletion or other syndromes on the incidence or mortality of IE might be of interest.

In conclusion, the risk of IE can be accurately predicted in young adult patients with congenital heart disease using a few simple clinical parameters. Application of the prediction model, which should preferably be preceded by confirmation in other cohorts, may lead to individually tailored medical surveillance and educational counselling for IE, thus enabling early detection or averting IE in adult patients with congenital heart disease.

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Appendix

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References

1. Hoffman JI, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. *Am Heart J* 2004;**147**:425–439.
2. Moons P, Engelfriet P, Kaemmerer H, Meijboom FJ, Oechslin E, Mulder BJ. Delivery of care for adult patients with congenital heart disease in Europe: results from the Euro Heart Survey. *Eur Heart J* 2006;**27**:1324–1330.
3. Engelfriet P, Boersma E, Oechslin E, Tijssen J, Gatzoulis MA, Thilen U, Kaemmerer H, Moons P, Meijboom F, Popelova J, Laforest V, Hirsch R, Daliento L, Thaulow E, Mulder B. The spectrum of adult congenital heart disease in Europe: morbidity and mortality in a 5 year follow-up period. The Euro Heart Survey on adult congenital heart disease. *Eur Heart J* 2005;**26**:2325–2333.
4. Perloff JK. Congenital heart disease in adults. A new cardiovascular subspecialty. *Circulation* 1991;**84**:1881–1890.
5. Verheugt CL, Uiterwaal CS, Grobbee DE, Mulder BJ. Long-term prognosis of congenital heart defects: a systematic review. *Int J Cardiol* 2008;**131**:25–32.
6. Hilderson D, Saidi AS, Van Deyk K, Verstappen A, Kovacs AH, Fernandes SM, Canobbio MM, Fleck D, Meadows A, Linstead R, Moons P. Attitude toward and current practice of transfer and transition of adolescents with congenital heart disease in the United States of America and Europe. *Pediatr Cardiol* 2009;**30**:786–793.
7. Moons P, Pinxten S, Dedroog D, Van Deyk K, Gewillig M, Hilderson D, Budts W. Expectations and experiences of adolescents with congenital heart disease on being transferred from pediatric cardiology to an adult congenital heart disease program. *J Adolesc Health* 2009;**44**:316–322.
8. Castillo JC, Anguita MP, Ramirez A, Siles JR, Torres F, Mesa D, Franco M, Munoz I, Concha M, Valles F. Long term outcome of infective endocarditis in patients who were not drug addicts: a 10 year study. *Heart* 2000;**83**:525–530.
9. Karchmer AW. Infective endocarditis. In: Libby P, Bonow RO, Mann DL, Zipes DP (eds), *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 8 ed. Philadelphia: Saunders; 2007, p1713–1738.
10. Nishimura RA, Carabello BA, Faxon DP, Freed MD, Lytle BW, O'Gara PT, O'Rourke RA, Shah PM, Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr., Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Smith SC Jr., Jacobs AK, Buller CE, Creager MA, Ettinger SM, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Page RL, Tarkington LG, Yancy CW Jr. ACC/AHA 2008 guideline update on valvular heart disease: focused update on infective endocarditis: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2008;**118**:887–896.
11. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP Jr., Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD, Smith SC Jr., Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Page RL, Riegel B, Tarkington LG, Yancy CW. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2008;**52**:e1–e121.

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12. Mylonakis E, Calderwood SB. Infective endocarditis in adults. *N Engl J Med* 2001; **345**:1318–1330.
13. Hoen B, Alla F, Selton-Suty C, Beguinot I, Bouvet A, Briancon S, Casalta JP, Danchin N, Delahaye F, Etienne J, Le Moing V, Leport C, Mainardi JL, Ruimy R, Vandenesch F. Changing profile of infective endocarditis: results of a 1-year survey in France. *JAMA* 2002;**288**:75–81.
14. Wang A, Athan E, Pappas PA, Fowler VG Jr., Olaison L, Pare C, Almirante B, Munoz P, Rizzi M, Naber C, Logar M, Tattevin P, Iarussi DL, Selton-Suty C, Jones SB, Casabe J, Morris A, Corey GR, Cabell CH. Contemporary clinical profile and outcome of prosthetic valve endocarditis. *JAMA* 2007;**297**:1354–1361.
15. van der Velde ET, Vriend JW, Mannens MM, Uiterwaal CS, Brand R, Mulder BJ. CONCOR, an initiative towards a national registry and DNA-bank of patients with congenital heart disease in the Netherlands: rationale, design, and first results. *Eur J Epidemiol* 2005;**20**:549–557.
16. Franklin RC, Anderson RH, Daniels O, Elliott M, Gewillig MH, Ghisla R, Krogmann ON, Ulmer HE, Stocker FP. Report of the Coding Committee of the Association for European Paediatric Cardiology. *Cardiol Young* 2000; **10**(Suppl. 1):1–26.
17. Warnes CA, Liberthson R, Danielson GK, Dore A, Harris L, Hoffman JI, Somerville J, Williams RG, Webb GD. Task force 1: the changing profile of congenital heart disease in adult life. *J Am Coll Cardiol* 2001;**37**:1170–1175.
18. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. *Am J Med* 1994;**96**: 200–209.
19. Warnes CA. The adult with congenital heart disease: born to be bad? *J Am Coll Cardiol* 2005;**46**:1–8.
20. Steyerberg EW, Eijkemans MJ, Harrell FE Jr., Habbema JD. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. *Stat Med* 2000;**19**:1059–1079.
21. Harrell FE Jr. *Regression Modelling Strategies*. New York: Springer-Verlag, 2001.
22. Spijker J, de Graaf R, Ormel J, Nolen WA, Grobbee DE, Burger H. The persistence of depression score. *Acta Psychiatr Scand* 2006;**114**:411–416.
23. Grobbee DE, Burger H, Moons KGM. Prognostic research. In: Grobbee DE, Hoes AW (eds), *Clinical Epidemiology*. 1 ed. Sudbury: Jones and Bartlett; 2009, p127–128.
24. Harrell FE Jr., Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. *JAMA* 1982;**247**:2543–2546.
25. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;**143**:29–36.
26. Harrell FE Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;**15**:361–387.
27. Altman DG, Royston P. What do we mean by validating a prognostic model? *Stat Med* 2000;**19**:453–473.
28. Efron B. Censored data and the bootstrap. *J Am Stat Assoc* 1981;**76**:312–319.
29. Gersony WM, Hayes CJ, Driscoll DJ, Keane JF, Kidd L, O'Fallon WM, Pieroni DR, Wolfe RR, Weidman WH. Bacterial endocarditis in patients with aortic stenosis, pulmonary stenosis, or ventricular septal defect. *Circulation* 1993;**87**:I121–I126.
30. Morris CD, Reller MD, Menashe VD. Thirty-year incidence of infective endocarditis after surgery for congenital heart defect. *JAMA* 1998;**279**:599–603.
31. Li W, Somerville J. Infective endocarditis in the grown-up congenital heart (GUCH) population. *Eur Heart J* 1998;**19**:166–173.
32. Niwa K, Nakazawa M, Tateno S, Yoshinaga M, Terai M. Infective endocarditis in congenital heart disease: Japanese national collaboration study. *Heart* 2005;**91**: 795–800.
33. Di Filippo S, Delahaye F, Semiond B, Celard M, Henaine R, Ninet J, Sassolas F, Bozio A. Current patterns of infective endocarditis in congenital heart disease. *Heart* 2006;**92**:1490–1495.
34. Tleyjeh IM, Steckelberg JM, Murad HS, Anavekar NS, Ghomrawi HM, Mirzoyev Z, Moustafa SE, Hoskin TL, Mandrekar JN, Wilson WR, Baddour LM. Temporal trends in infective endocarditis: a population-based study in Olmsted County, Minnesota. *JAMA* 2005;**293**:3022–3028.
35. Verheugt CL, Uiterwaal CSPM, van der Velde ET, Meijboom FJ, Pieper PG, Vliegen HW, van Dijk APJ, Bouma BJ, Grobbee DE, Mulder BJM. Gender and outcome in adult congenital heart disease. *Circulation* 2008;**118**:26–32.
36. Moreillon P, Que YA. Infective endocarditis. *Lancet* 2004;**363**:139–149.
37. Mansur AJ, Dal Bo CM, Fukushima JT, Issa VS, Grinberg M, Pomerantzeff PM. Relapses, recurrences, valve replacements, and mortality during the long-term follow-up after infective endocarditis. *Am Heart J* 2001;**141**:78–86.
38. Peres MA, Peres KG, de Barros AJ, Victora CG. The relation between family socioeconomic trajectories from childhood to adolescence and dental caries and associated oral behaviours. *J Epidemiol Community Health* 2007;**61**:141–145.
39. Armstrong GL. Injection drug users in the United States, 1979–2002: an aging population. *Arch Intern Med* 2007;**167**:166–173.
40. Cetta F, Warnes CA. Adults with congenital heart disease: patient knowledge of endocarditis prophylaxis. *Mayo Clin Proc* 1995;**70**:50–54.
41. Moons P, De Volder E, Budts W, De Geest S, Elen J, Waeytens K, Gewillig M. What do adult patients with congenital heart disease know about their disease, treatment, and prevention of complications? A call for structured patient education. *Heart* 2001;**86**:74–80.
42. Dore A, de Guise P, Mercier LA. Transition of care to adult congenital heart centres: what do patients know about their heart condition? *Can J Cardiol* 2002; **18**:141–146.
43. Gabriel HM, Heger M, Innerhofer P, Zehetgruber M, Mundigler G, Wimmer M, Maurer G, Baumgartner H. Long-term outcome of patients with ventricular septal defect considered not to require surgical closure during childhood. *J Am Coll Cardiol* 2002;**39**:1066–1071.
44. Otterstad JE, Erikssen J, Michelsen S, Nitter-Hauge S. Long-term follow-up in isolated ventricular septal defect considered too small to warrant operation. *J Intern Med* 1990;**228**:305–309.

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