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Infective endocarditis in adult patients with congenital heart disease☆

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ABSTRACT

Background: Congenital Heart Disease (CHD) predisposes to Infective Endocarditis (IE), but data about characterization and prognosis of IE in CHD patients is scarce.
Methods: The ESC-EORP-EURO-ENDO study is a prospective international study in IE patients ($n = 3111$). In this pre-specified analysis, adult CHD patients ($n = 365$, 11.7%) are described and compared with patients without CHD ($n = 2746$) in terms of baseline characteristics and mortality.
Results: CHD patients (73% men, age 44.8 ± 16.6 years) were younger and had fewer comorbidities. Of the CHD patients, 14% had a dental procedure before hospitalization versus 7% in non-CHD patients ($p < 0.001$) and more often had positive blood cultures for Streptococcus viridans (16.4% vs 8.8%, $p < 0.001$). As in non-CHD patients, IE most often affected the left-sided valves. For CHD patients, in-hospital mortality was 9.0% vs 18.1% in non-CHD patients ($p < 0.001$), and also, during the entire follow-up of 700 days, survival was more favorable (log-rank $p < 0.0001$), even after adjustment for age, gender and major comorbidities (Hazard Ratio (HR) 0.68; 95% CI 0.50–0.92). Within the CHD population, multivariable Cox regression revealed the following effects (HR and [95% CI]) on mortality: fistula (HR 6.97 [3.36–14.47]), cerebral embolus (HR 4.64 [2.08–10.35]), renal insufficiency (HR 3.44 [1.48–8.02]), *Staphylococcus aureus* as causative agent (HR 2.06 [1.11–3.81]) and failure to undertake surgery when indicated (HR 5.93 [3.15–11.18]).

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Conclusions: CHD patients with IE have a better outcome in terms of all-cause mortality. The observed high incidence of dental procedures prior to IE warrants further studies about the current use, need and efficacy of antibiotic prophylaxis in CHD patients.

1. Introduction

The population of adults with congenital heart disease (CHD) is rapidly growing since advances in catheter- and surgery-based cardiac interventions have rendered almost all types of CHD amenable for correction or palliation. Currently, >95% of newborns with CHD survive to adulthood [1]. In 2010, 1.4 million adults were living with CHD in the United States, which outnumbered the number of children with CHD [2]. However, most of these adult patients encounter residual problems (e.g. valvular disease, heart failure, arrhythmia) which emphasizes that these patients are not "cured". As a result, it is not an exception that multiple cardiac interventions are performed within the same CHD patient [3].

One of the most serious late complications in CHD patients is infective endocarditis (IE). IE is a life-threatening disease which portends a poor outcome [4]. Despite improvements in health care during past decades, mortality from IE remains high [5]. Patients with CHD are at increased risk for developing IE. It is estimated that CHD patients have an IE risk in excess of 100 times that of the general population [6]. This higher risk is probably related to the high prevalence of residual shunts, cyanosis, prosthetic valves, pacemaker leads, and other implanted materials. Also risk behavior, like body piercing and tattoos, is a reason for concern in young adults. In the past, most CHD patients were instructed to use endocarditis prophylaxis prior to a dental procedure and therefore the possible impact of changing this policy [7] in 2007 might be visible especially in this patient population.

Despite this important healthcare problem there is a paucity of data concerning IE in CHD patients. Available data is often retrospective, single-center and spanning several decades. We therefore sought to characterize a large contemporary cohort of CHD patients included in a prospective international study (European Infective Endocarditis Registry, EURO-ENDO [8]), in order to better describe their presentation, compare them with IE patients without CHD, and to determine their prognosis.

2. Methods

2.1. Patient selection and inclusion

The rationale and design of the ESC EURObservational Research Programme (EORP) EURO-ENDO study have been described previously [8,9]. Briefly, any patient aged ≥18 years and hospitalized between 1 January 2016 to 31 March 2018 with definite IE (or possible IE, considered and treated as IE) based on the European Society of Cardiology 2015 diagnostic criteria [10] was eligible for EURO-ENDO inclusion. Patients were asked to participate in the EURO-ENDO study during the index event (i.e. during hospitalization for IE). All participants (or their legally authorized representative) received written information concerning the study and provided signed informed consent. These patients were prospectively followed for the outcome of interest (all-cause mortality, both in-hospital and during follow up). Individual patient data were collected across 156 centres in 40 countries. These centres were accepted on a voluntary basis through national coordinators. For the current study, we analyzed all IE patients born with a congenital heart defect (CHD-group) and compared them with the patients without CHD (non-CHD group). The registry was approved by local ethical review boards according to the regulations of each participating centre and country. National coördinators, in conjunction with participating centres managed the approvals of national or regional ethics committees or Institutional Review Boards, according to local regulations. The study complies with the Declaration of Helsinki.

2.2. Data collection

Patient demographics, CHD diagnosis, patient history (including non-cardiac invasive interventions within the last 6 months (e.g. colonoscopy, dental procedure), clinical data at admission, routine serum analysis, microbiological and imaging results were collected using an electronic case report form. In addition, antibiotic treatment, surgical interventions and outcome at follow up were registered. Follow-up lasted until April 2019. The inclusion of patients in the registry had no impact on the clinical management by the treating physicians.

2.3. Statistical analysis

Continuous variables are reported as mean ± standard deviation if normally distributed and as median with interquartile range (IQR) if skewed. Categorical data are presented by count and percentages. Statistical tests were performed to compare baseline and IE characteristics in patients with and without CHD in order to highlight the difference between the two groups. For quantitative variables, a comparison was performed using Mann-Whitney U test (CHD versus non-CHD). For categorical variables, among-group comparisons were made using a χ^2 test or Fisher's exact test. For time-to-event analyses, the Kaplan-Meier method was used. The log-rank test was used for comparison of survival curves between IE patients with and without CHD. A multivariable analysis was performed with age, gender, CHD and co-morbidities to see, if after adjustment, CHD was an important factor of survival in this younger population without co-morbidities.

Univariable analysis of mortality in CHD patients was performed with a Cox proportional hazards model. Variables with $p < 0.05$ were entered in a multivariable Cox proportional hazards model with a backward selection procedure and a significance level of $p = 0.05$. Before performing multivariable Cox model, multicollinearity was verified among the significant parameters found in the univariable analysis. Some measures of model fit were considered: concordance and the Goodness of fit test proposed by May and Hosmer. In addition, Schoenfeld residual test was calculated to verify the assumptions. A propensity analysis was also performed to account for the imbalance of age between CHD and non-CHD patients. The propensity score was fitted using exact age. In-hospital mortality rates and during the study were compared using McNemar's test and Cox proportional hazard model using the matching pairs information.

All tests were two-sided. All statistical analyses were conducted using SAS statistical software version 9.4 (NC, USA).

3. Results

A total of 3111 (mean age 59.3 ± 18.0 years, 68.9% male) IE patients were included. Of these patients, 365 (11.7%) had CHD. Congenital cardiac diagnoses are presented in Fig. 1. The majority of patients had an aortic valve related problem ($n = 206$, 56.4%), including bicuspid valves, but also subvalvular aortic membranes ($n = 5$) or monocuspid aortic valves ($n = 3$). Important other congenital anomalies were ventricular septum defects (VSD; $n = 38$) and atrioventricular septum defects ($n = 8$) and Right Ventricular Outflow Tract (RVOT) disorders ($n = 35$; e.g. Tetralogy of Fallot). Marfan's syndrome was classified among the connective tissue disorders.

3.1. Baseline characteristics

Of the 365 CHD patients, the mean age at diagnosis of IE was 44.8 ± 16.6 year and 73.2% were males (Table 1). CHD patients were significantly younger than non-CHD patients ($p < 0.001$) and had significantly less concomitant cardiovascular co-morbidities (hypertension, atrial fibrillation, coronary artery disease, heart failure, TIA/stroke) (all p-values<0.004). Additionally, non-cardiac comorbidities were also significantly less prevalent among the CHD group reflected by the lower Charlson Co-morbidity Score (1.5 vs 3.8, p < 0.001). However, the percentage of prior endocarditis between both groups was not different. CHD patients had significantly more previous valve interventions than non-CHD patients (38.6% vs 32.1%, respectively; $p = 0.01$). Of note, in the CHD group, these were mostly mechanical aortic valves ($n = 55$, 15.1%) and pulmonary bioprostheses ($n = 29$, 7.9%, including 7 homografts), while the non-CHD group had more surgical biological aortic valves ($n = 457$, 16.6%), transcatheter aortic valve implantation (TAVI) procedures ($n = 68$, 2.5%) and mitral valve prostheses ($n = 283$, 10.3%).

3.2. Clinical presentation

The clinical symptomatology of IE in CHD did not differ from non-CHD patients: fever was the most prevalent symptom (81.3%), followed by general non-wellbeing (52.1%), shortness of breath (34.4%), cough (16.3%), dizziness (10.7%), chest pain (7.7%), cerebrovascular symptoms (5.8%) and syncope (3.6%). However, CHD patients had a longer time between the start of symptoms and hospital admission than non-CHD patients (35.6 vs 28.7 days, $p = 0.004$). At admission, 14.0% of the CHD patients reported a dental procedure in the last 6 months (versus 7.0% in the non-CHD group, $p < 0.001$).

3.3. Diagnosis

The diagnosis was established based on clinical manifestations, blood cultures (or other microbiological data), and imaging (echocardiography, Computed Tomographic (CT) scan or ^{18}F-FluoroDeoxyGlucose Positron Emission (FDG-PET)/CT scan. After hospital admission, the diagnosis of IE was made faster in the CHD group (5.1 vs 9.8 days in the non-CHD group, $p < 0.001$). Positive diagnostic (modified Duke) criteria differed between the two groups: first, blood cultures were less often positive in CHD patients (71% vs 80%, $p < 0.001$). Also, when blood cultures were positive, the causative agents in CHD patients differed from non-CHD patients (see Fig. 2): more Streptococcus viridans and *Coxiella Burnetii*, but less *Streptococcus bovis*, *Staphylococcus aureus*, or Enterococcus spp. Overall, IE with Streptococcus viridans was more found in patients with a dental procedure (22.2%) than in patients without dental procedure (8.7%; p < 0.001). However, in patients with CHD the difference was much smaller and not significant (with dental procedure 18.8% versus without dental procedure 15.9%; $p = 0.62$).

Of the 365 IE cases in CHD patients, 76.9% were community-acquired cases, 11.4% were nosocomial infections and 11.7% were non-nosocomial infections ($p = 0.05$ vs non-CHD).

Second, the location of endocarditis was different for CHD patients (Table 2). Although in both non-CHD and CHD-patients, the left-sided valves were affected most often, the CHD patients more commonly had involvement of their aortic or pulmonary valve apparatus, while in non-CHD patients, mitral valve and tricuspid valves were affected more commonly. In more than half of the patients, in both CHD as well as non-CHD groups, the infection involved native tissue, resulting in native endocarditis (57.1% vs 58.8%, respectively, p = ns). Intracardiac device-related IE (CDRIE, defined as related to pacemaker or implanted cardioverter defibrillator) was less often diagnosed in CHD patients (6.4 vs 11.5%, $p = 0.003$).

Third, for those CHD patients diagnosed with aortic valve endocarditis, its manifestation appeared to be very advanced at admission: many had an aortic root abscess (20.2%), aortic pseudo-aneurysm (8.4%), aortic fistula (6.2%), aortic valve perforation (8.4%) and/or

Table 1
Baseline characteristics.

Variable	CHD ($n = 365$) Frequency (%) or Mean ± SD	Non-CHD ($n = 2746$) Frequency (%) or Mean ± SD	P-value
Male gender, n	267 (73.2%)	1875 (68.3%)	0.059
Age, years	44.8 ± 16.6	61.2 ± 17.3	<0.001
Prior endocarditis	33 (9.0%)	241 (8.8%)	0.87
Hypertension	94 (25.8%)	1405 (51.2%)	<0.001
Smoking	81 (23.0%)	674 (26.1%)	0.212
Congestive Heart Failure	59 (17.1%)	602 (24.2%)	0.004
Coronary artery disease	18 (5.2%)	601 (23.6%)	<0.001
Atrial fibrillation	40 (11.5%)	725 (28.2%)	<0.001
Stroke/TIA	25 (7.2%)	315 (12.5%)	0.004
ICD/PM	45 (12.3%)	490 (17.8%)	0.11
COPD/asthma	23 (6.3%)	294 (10.7%)	0.009
Chronic renal failure	22 (6.0%)	529 (19.3%)	<0.001
Dialysis	4 (1.1%)	159 (5.8%)	<0.001
Diabetes mellitus	31 (8.5%)	673 (24.5%)	<0.001
Cancer	11 (3.0%)	348 (12.8%)	<0.001
Charlson comorbidity index	1.5 ± 2.0	3.8 ± 2.9	<0.001
Valvular intervention (prosthesis/repair/TAVI)	141 (38.6%)	881 (32.1%)	0.012
Non-cardiac surgery	10 (2.7%)	243 (8.8%)	<0.001
Gastro-intestinal interventions/surgery	6 (1.7%)	98 (3.6%)	0.053

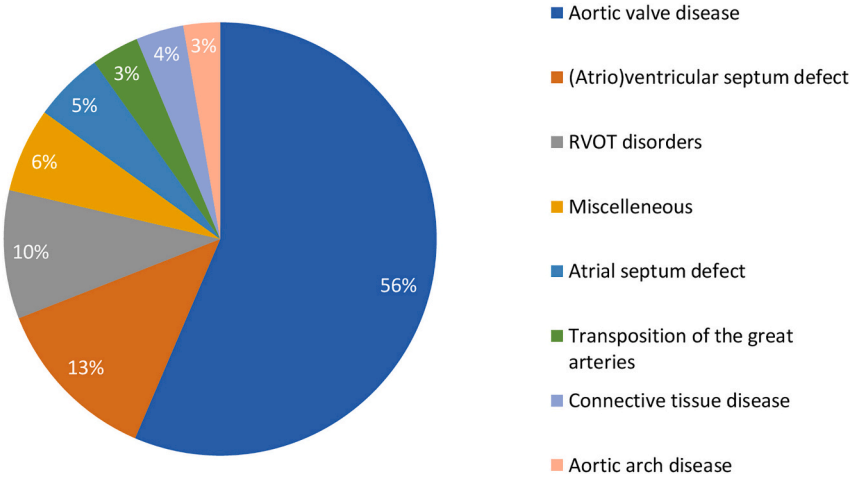

Fig. 1. Distribution of congenital heart disease anomalies in 365 patients. More than one anomaly can be present in one patient (e.g. bicuspid aortic valve and aortic coarctation). The most important diagnosis (in the setting of IE) was recorded. The subgroup with 'miscelleneous' comprises a miscellaneous group of low frequency diagnoses (e.g. Ebstein's disease, truncus arteriosus, etc). Within the group of Connective Tissue Disease mitral valve anomalies, Marfan's disease and Barlow valves were classified. Tetralogy of Fallot patients were classified among the RVOT disorders.

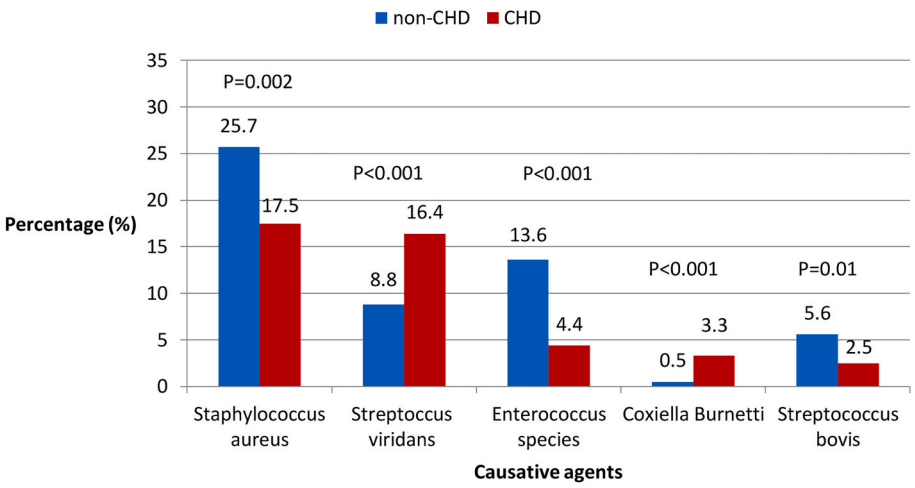

Fig. 2. Blood culture results and comparison between CHD patients and non-CHD patients. For Coxiella Burnettii: either positive blood culture or positive IgG antibody titre. Data are presented as percentage.

Table 2
Location of endocarditis.

Variable	CHD (n = 365) Frequency (%)	Non-CHD (n = 2746) Frequency (%)	P-value
Location			
Aortic valve	236 (65.6%)	1276 (47.4%)	<0.001
Pulmonary valve	46 (12.8%)	28 (1.0%)	<0.001
Mitral valve	74 (20.6%)	1210 (44.9%)	<0.001
Tricuspid valve	29 (8.1%)	320 (11.9%)	0.032
Type			<0.001
Native valve	197 (57.1%)	1565 (58.8%)	
Prosthesis, repair	130 (37.7%)	808 (30.4%)	
PM/ICD	18 (5.2%)	288 (10.8%)	

severe aortic regurgitation (32.5%). In addition, the CHD patients with a prosthetic valve often had paravalvular regurgitation (9.5%) or new prosthetic valve dehiscence (5.0%).

3.4. Treatment of IE

Treatment in all IE cases consisted of antimicrobial therapy, but additional surgery was more frequently performed in the CHD group as compared to the non-CHD group (81.1% vs 73.0%, $p = 0.005$). Non-CHD patients who were treated conservatively (i.e. not operated) were older and had more co-morbidities like diabetes, COPD, cancer, dialysis, coronary artery disease (all p-values ≤ 0.002).

Reasons for not performing a surgical intervention, despite having an indication for this, were patient refusal ($n = 5$), high surgical risk ($n = 24$), absence of surgical facilities ($n = 6$), neurological complications ($n = 4$) and death ($n = 11$). Hospital duration was equally long for both groups of patients (45.5 ± 36.0 days in CHD vs 48.8 ± 55.0 days in non-CHD patients, respectively, $p = 0.82$).

3.5. Follow-up

A total of 33 CHD patients died in the hospital (9.0%). This percentage was lower than in non-CHD patients, in whom in-hospital mortality occurred in 18.1% ($p < 0.001$). Another 18 CHD patients (5%) died after hospitalization for IE. The 1-year all-cause mortality was also lower in the CHD-group: 12.9% versus 24.5% in non-CHD patients ($p < 0.001$). Of the 51 IE patients with CHD who died, 33 patients died of cardiovascular causes. Among these deceased patients heart failure (75.8%) was the most prominent cause of death, followed by cerebral embolism in 15.2%.

In Fig. 3, the entire follow up of 700 days is for both groups depicted (log-rank for all-cause mortality $p < 0.0001$). Additionally, lower rates of cerebral complications during hospitalization were reported in the CHD group (6.3% vs 9.4%, respectively), which reached borderline significance ($p = 0.05$). Univariable Cox regression analysis showed that CHD had a hazard ratio of 0.49 (0.37–0.65, $p < 0.001$) for all-cause mortality during the entire follow up, which remained significant in multivariable analysis after adjustment for age, gender, hypertension, atrial fibrillation, coronary artery disease, COPD, Cancer, diabetes, stroke, and renal failure(HR 0.68; 95%CI 0.50–0.92; $p = 0.01$).

Using propensity analysis (with 364 CHD/non-CHD age-matched pairs) in-hospital mortality was higher in the non-CHD-group (12.9%) than in the CHD-group (8.8%). This difference was not significant ($p = 0.08$). However, using a Cox proportional hazard model, the in-hospital survival was less favorable in the non-CHD-group (HR 1.70 (95% CI 1.08–2.68; $p = 0.02$). Of those CHD patients who survived, New York Heart Association functional class at one year was class I in 65.1% and class II in 30.3%. Recurrence rates of IE were not significantly different between CHD and non-CHD patients (2.1% vs 4.6%, $p = 0.07$).

3.6. Factors associated with all-cause mortality

Within the CHD group, univariable Cox regression analysis revealed several significant factors associated with all-cause mortality during the entire follow-up (Table 3). After adjusting for these variables in a multivariable model, the following independent factors were identified: fistula (HR 6.97; 95%CI 3.36–14.47), cerebral complications (HR 4.64; 95%CI 2.08–10.35), renal insufficiency (i.e. Creatinine>2 mg/dl; HR 3.44; 95%CI 1.48–8.02), *staphylococcus aureus* as causative agent (HR 2.06; 95%CI 1.11–3.81) and not performing surgery in the presence of an indication (HR 5.93; 95%CI 3.15–11.18), see Fig. 4.

4. Discussion

This is the first study to prospectively investigate endocarditis in patients with CHD. In a contemporary cohort of 3111 adult patients with IE, we found that >10% had CHD. This population had unique features in terms of age, concomitant diseases, clinical presentation, site of infection and causative agents.

The main results of our study are that 1) CHD patients are younger and less often have comorbidities, 2) the majority of IE in CHD patients is left-sided, 3) CHD patients more often had a dental procedure in the 6 months before hospitalization and more frequent positive blood cultures for Streptococcus viridans, and finally, 4) both short-term and long-term prognosis are better in CHD patients than in non-CHD IE patients, which

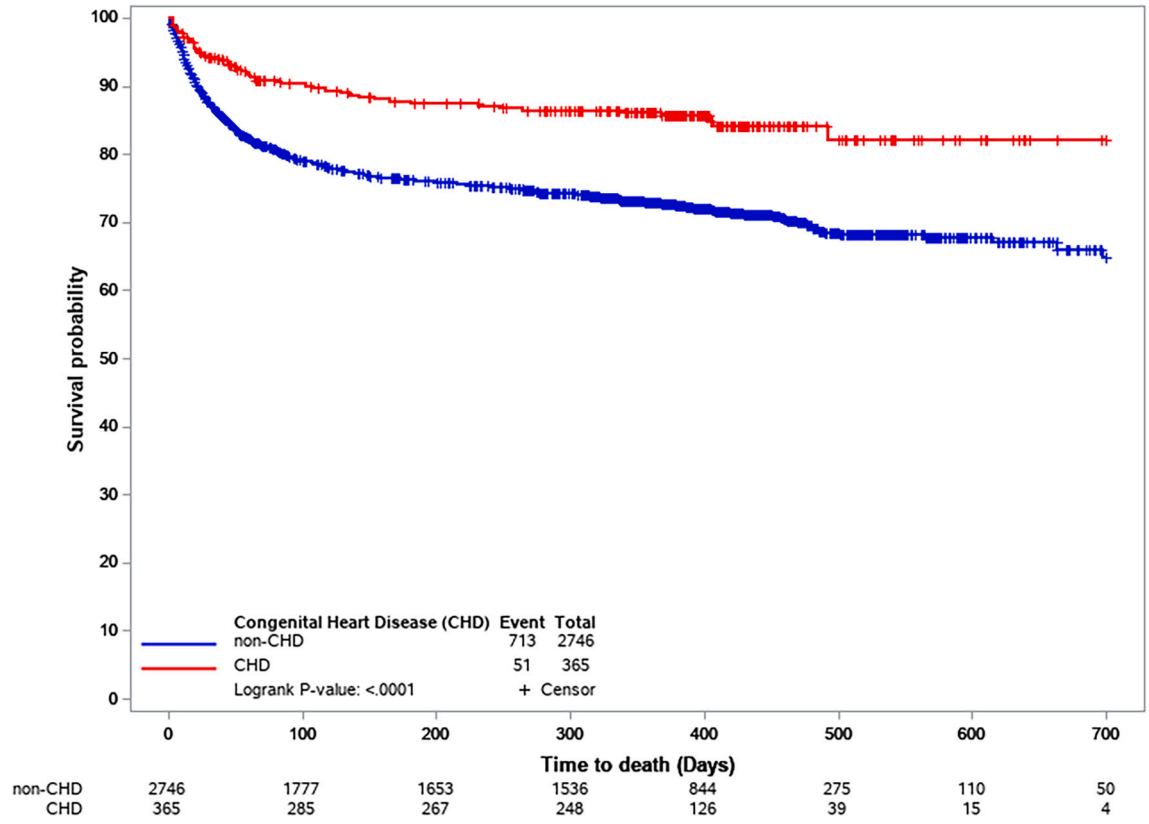

Fig. 3. Kaplan Meyer curve: freedom of all-cause mortality in IE congenital heart disease (CHD) patients compared to non-congenital heart disease (non-CHD) patients.

Table 3
Univariable Cox regression analysis for all-cause mortality within CHD patients (n = 365).

		Hazard ratio (95% CI)	p-value
Age		1.00 (0.99–1.02)	0.64
Gender	Male	0.81(0.45–1.46)	0.47
Charlson index		1.13 (1.01–1.27)	0.03
Creatinine>2 mg/dl		3.49 (1.57–7.79)	0.002
Staph aureus		2.52 (1.39–4.56)	0.002
Congestive Heart failure		2.60 (1.33–5.08)	0.005
Cerebral complications		3.18 (1.49–6.79)	0.003
Abscess		2.22 (1.22–4.06)	0.009
Fistula		6.44 (3.29–12.60)	<0.001
Indication- surgery not performed		6.31 (2.92–13.64)	<0.001
Indication – surgery performed vs No indication		0.97 (0.44–2.14)	0.93

is partly explained by their younger age.

For many decades CHD has been known as a predisposing factor for developing IE. The higher risk profile could be related to the high prevalence of residual shunts, cyanosis, prosthetic valves, pacemaker leads, besides other implanted materials. In a nationwide study in the Netherlands, Kuijpers et al [11] found an incidence of IE in CHD of 1.33 cases/1000 person-years which is 27–44 times higher than in the general population. Valve-containing prosthetics are particularly associated with IE. In our study, this was reflected by a high proportion of CHD patients with a previous valve prosthesis or repair (39%). We found that IE patients with CHD were younger (mean age 44.8 years) than those without CHD, which is in accordance with other studies. For example Ly et al [12] reported a mean age of 37 years in a cohort of 142 adult CHD patients. Hence, our new observation that the CHD patients had significantly fewer co-morbidities and lower Charlson Comorbidity Score could hardly be considered as a surprise. Conversely, the older non-CHD group was characterized by certain invasive interventions as a preamble to their hospitalization for IE, i.e. more non-cardiac surgery, gastrointestinal interventions and dialysis. CHD patients had a longer time between the start of symptoms and hospital admission than non-CHD patients (35.6 vs 28.7 days): CHD patients may have a higher threshold to see a doctor. Also, they could more often had sub-acute IE. Therefore, better patient education is warranted. As soon as CHD patients do present at the hospital, the time-to-diagnosis is shorter, probably because of the higher level of suspicion of IE by the treating physician.

In general, the heterogeneity of congenital anomalies is large, especially in referral hospitals for CHD [13]. In the current study, data were collected from 156 participating hospitals in 40 countries, which were not all tertiary or quaternary CHD referral hospitals. This inclusion may have led to an overrepresentation of less complex left-sided anomalies such as aortic valve pathology (56%). For comparison, of the CHD patients who were treated for IE in a quaternary referral hospital in Sydney, only 48% had simple lesions according to the Bethesda level of complexity for underlying CHD [14]. Similarly, Cahill et al. reported a high percentage of right-sided lesions but this study had enrolled 41% pediatric patients with often complex anomalies treated in tertiary referral hospitals for CHD. Right-sided IE is more frequently seen in CHD compared to non-CHD patients. When located on the right side of the heart, pulmonary valve endocarditis [15] is important because many CHD patients have right-sided congenital anomalies (e.g. Tetralogy of Fallot) for which they received either a homograft, transcatheter pulmonary valve or other conduit. In our study the number of right-sided IE was not very high, since the starting point for the EURO-ENDO registry was endocarditis and not particular CHD, thus reflecting a more general population. Despite differences in complexity of CHD, the site of infection was generally the left side of the heart, with a high

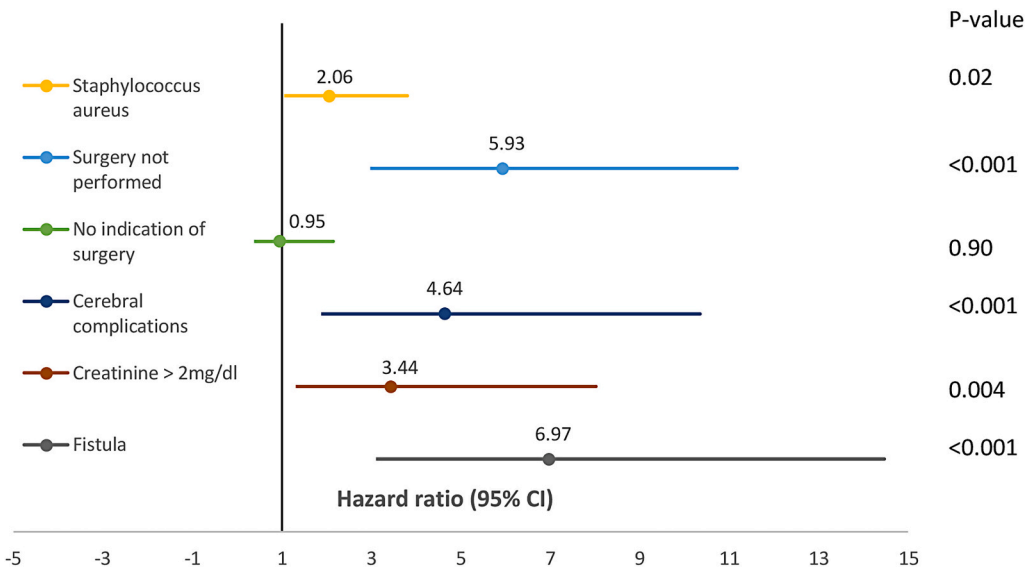

Fig. 4. Forest plot of Hazard Ratio's (bullets) and associated 95% Confidence Intervals (horizontal lines) of variables that are significant factors associated with all-cause mortality during the entire follow up after multivariable analysis. Significant univariable factors ($p < 0.05$, see Table 3) were proposed into the multivariable model after multicollinearity validation (Spearman correlation, VIF and tolerance).

preference for (bicuspid) aortic valves (which is in accordance with previous literature [16]).

The difference in microbiological profile of IE episodes between the CHD- and non-CHD-group may be an age-related phenomenon. Advanced age is associated with immune impairment, malignancy, and the need for prolonged medical and nursing care, all of which increase the likelihood of acquiring IE [17]. The higher incidence of enterococcus species may be related to an increase in the prevalence of health care-related interventional procedures in that group (indwelling venous lines, hemodialysis, etc). The high prevalence of *Streptococcus bovis* IE in the elder non-CHD relates to the increasing incidence of predisposing bowel lesions with advancing age (ulcers, diverticular disease and malignancy).

In our study, 14% of the CHD patients had a dental procedure before hospitalization. which is clearly higher than the 7% in the non-CHD patients. This may reflect a greater awareness of the need of good dental hygiene in this population. This is in line with a study by Cahill et al [13] who reported that dental procedures preceded 11% of the IE cases, but considerably lower than Tutarel et al. [18] (27.9%). Unfortunately, in our study no additional data was available about the use of antibiotic prophylaxis. Although we found that IE with *S. aureus* had the highest prevalence in CHD patients (18%), Streptococci from the viridans group were, relative to non-CHD patients often found (16% versus 9%, respectively). Similarly, a systematic review [19] reported that the most common causative agents in CHD patients were Staphyloccus aureus and viridans group Streptococci (equally commonly). The portal of entry for the viridans bacteriae is often the dental route, consisting primarily of dental and periodontal disease or a dental procedure. In our opinion, this could suggest a compliance problem (low adherence to current IE-prophylaxis recommendations) or an efficacy problem (sub-optimal efficacy of the used antibiotic prophylaxis). Finally, it might be possible that we mistakenly suppose that all CHD patients without a prosthesis belong to a low-risk group for developing IE. Our study could be of interest for the recent discussion [20–23] about the legitimation and implementation of the substantial adaptation of the recommendations after 2007 [7]. In any case, the importance of educating congenital patients on endocarditis, in terms of clinical presentation and the need to call for help when there is any suspicion of it, is crucial. This education should start early in life and intensify during the transition process from pediatric to adult care.

Our study revealed that about 80% of the CHD patients underwent surgical treatment for IE. A previous study based on the Euro Heart Survey, published in 2005, showed that surgical treatment was required in approximately half of the patients (including non-CHD patients) [24]. This was considerably lower than the 75% use of surgery reported in 2015 by an international collaboration on endocarditis [25], suggesting that views about optimal timing for surgery have changed over the years [26]. In our study, the higher need for surgical treatment in CHD patients may also be explained by the high percentage of severe complications, such as abscess, pseudo-aneurysm, fistula, valve perforation and severe regurgitation, which are all signs of uncontrolled infection and indications for surgical treatment [10]. The higher rate of surgery in CHD patients could also be attributed, at least in part, to the younger age of these patients with less comorbidities.

Although surgical management of IE in CHD can be challenging, especially because it often concerns a reoperation for uncontrolled infection, any reluctance to perform a surgical intervention is not supported by our data, because not performing surgery, when indicated, was clearly an independent factor associated with mortality (HR 5.93). Having said that, we have to keep in mind that the IE patients, in whom was decided not to operate upon, often had a clear contra-indication (or combination of relative contra-indications) to renounce surgery, as these patients were older, had more co-morbidities like embolic events or pulmonary hypertension and previous IE episodes (data not shown).

Within the CHD patients with IE, the presence of fistula must be considered as the highest risk factor, because it was associated with a seven-times higher mortality rate. Other multivariable factors associated with mortality were cerebral emboli (HR 4.6), renal insufficiency (HR 3.4), *Staphylococcus aureus* as causative agent (HR 2.1). This is in line with a previous study by Moore [16] et al. ($n = 62$) in whom mortality was associated with cerebral emboli and acute renal failure. Niwa et al [27] described a retrospective cohort study in 137 CHD patients and found *Staphylococcus aureus* to be significantly associated with in-hospital mortality.

5. Limitations

Our study being a registry has the inherent limitation of selection and reporting bias, which was minimized by a prospective design in which we instructed the investigators to include consecutive patients. The current study included patients from a broad range of hospitals and did not include only patients with CHD. Therefore, the results in specialized,

tertiary referral hospitals for CHD patients may be different. However, a transfer to another hospital, either tertiary CHD center or not, did not affect the outcome of CHD patients (data not shown).

Secondly, 29 CHD patients were lost to follow-up, which could lead to attrition bias. However, this reflects the clinical reality that a significant number of patients are not followed in the aftermath of an IE episode. Thirdly, only common comorbidities such as diabetes were recorded, while CHD patients might suffer from a range of other comorbidities among which are syndromic disorders, mental retardation, thyroid dysfunction and scoliosis [28]. Fourth, our database precludes a sub-analysis between surgically and percutaneously implanted pulmonary bioprostheses in the CHD group. Finally, our cohort comprises an adult population and therefore our results cannot be extrapolated to children.

6. Conclusion

CHD patients are younger and less often have comorbidities. Prehospital delay is important and needs attention. As compared to non-CHD patients, CHD patients with IE have a better outcome in terms of all-cause mortality, despite the presence of more advanced disease at admission. The observed difference in microbiological profile of IE episodes between the CHD- and non-CHD-group IE (and its relation to prior antibiotic prophylaxis) warrants further study in CHD patients.

Author statement

Joost P van Melle: supervision of study site, drafting manuscript, analysis, verification of data.

Jolien Roos-Hesselink: supervision of study site, drafting manuscript, analysis, verification of data.

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Cécile Laroche & Eric Boersma were responsible for statistical analysis.

Patrizio Lancellotti: writing, analysis, verification of data.

Gilbert Habib: conceptualization, funding acquisition, methodology, supervision, verification of data, writing – original draft, and writing – review & editing.

All authors revised the manuscript critically and confirmed final approval of the version to be published.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.10.136.

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