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Mortality in adult congenital heart disease

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Aims Mortality in adults with congenital heart disease is known to be increased, yet its extent and the major mortality risks are unclear.

Methods and results The Dutch CONCOR national registry for adult congenital heart disease was linked to the national mortality registry. Cox's regression was used to assess mortality predictors. Of 6933 patients, 197 (2.8%) died during a follow-up of 24 865 patient-years. Compared with the general national population, there was excess mortality, particularly in the young. Median age at death was 48.8 years. Of all deaths, 77% had a cardiovascular origin; 45% were due to chronic heart failure (26%, age 51.0 years) or sudden death (19%, age 39.1 years). Age predicted mortality, as did gender, severity of defect, number of interventions, and number of complications [hazard ratio (HR) range 1.1–5.9, $P < 0.05$]. Several complications predicted all-cause mortality beyond the effects of age, gender, and congenital heart disease severity, i.e. endocarditis, supraventricular arrhythmias, ventricular arrhythmias, conduction disturbances, myocardial infarction, and pulmonary hypertension (HR range 1.4–3.1, $P < 0.05$). These risks were similar in patients above and below 40 years of age. Almost all complications predicted death due to heart failure (HR range 2.0–5.1, $P < 0.05$); conduction disturbances and pulmonary hypertension predicted sudden death (HR range 2.0–4.7, $P < 0.05$).

Conclusion Mortality is increased in adults with congenital heart disease, particularly in the young. The vast majority die from cardiovascular causes. Mortality risk, particularly by heart failure, is increased by virtually all complications. Complications are equally hazardous in younger as in older patients.

Keywords Epidemiology • Heart defects • Congenital • Mortality • Prognosis

Introduction

Current estimates of the ever expanding population of adults with congenital heart disease are 1.2 million in Europe[1] and over 1 million in the USA alone.[2] These large numbers result from major advances in both cardiothoracic surgery and cardiac care over the past five decades, which are reflected in abundant research on short-term survival of young patients with congenital heart disease. In contrast, little is known on the prognosis of adults with congenital heart disease. The notion that congenital heart disease in adulthood is still rather novel to many cardiologists makes the need for accurate information on long-term prognosis even more compelling.

Contemporary literature on survival in adults with congenital heart disease is sparse, yet suggests that they have a lower life expectancy than their healthy counterparts.[3,4] However, little is known about the causes of death in these patients; these are either available for only part of the patient population,[5] or merely described from cross-sectional data,[6] emphasizing the need for more detailed research.

Although the occurrence of complications requiring life-long medical surveillance has been recognized nearly two decades

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ago,[7] the number of studies has been too limited to substantiate the risk of mortality and complex morbidity.[8,9] This shortcoming is reflected in current guidelines.[10,11] Evidence on the prognostic value of complications regarding mortality is even more scarce, being mainly restricted to single complications,[12,13] or to adult patients with congenital heart disease confined to specific subgroups,[14–16] or settings.[17–20] Nonetheless, recent studies have indicated that adult patients with congenital heart disease would benefit from better attention to treatment of residua and serious cardiovascular complications.[21–23]

We used the Dutch CONgenital CORvitia (CONCOR) national registry for adults with congenital heart disease to assess mortality and causes of death, and to determine which cardiovascular complications predict mortality in adults with congenital heart disease.

Methods

CONCOR registry

The CONCOR Dutch national registry database has been described in detail.[24] Briefly, CONCOR aims to facilitate research into the aetiology of congenital heart disease and on its outcome. Between November 2001 and December 2009, over 11 400 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[25]—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 severity of diagnoses[26] 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 medical letters on patients' condition written by their cardiologist. Quality control of data has been performed by randomly verifying around 10% of data yearly. Currently, 102 Dutch hospitals are participating, including all eight tertiary referral centres from which 70% of patients originate.

From CONCOR, date of birth, inclusion date, gender, main congenital heart diagnosis, and complications were derived. The severity of main diagnosis was categorized as mild, moderate, or severe, using a consensus-based classification scheme.[26] Complications served as the primary determinant. The following complications were considered clinically important in adult congenital heart disease, either as a consequence of specific congenital heart defects or due to the risk of acquired heart disease with increasing age:[9] cerebrovascular accident (CVA) or transient ischaemic attack (TIA), endocarditis, supraventricular arrhythmias, ventricular arrhythmias, conduction disturbances, aortic complications (comprising aneurysm and dissection), myocardial

Table 1 Baseline characteristics of CONCOR patients

	All patients (n = 6933)		Alive patients (n = 6736)		Deceased patients (n = 197)	
	n	%	n	%	n	%
Age (years)[a]	32.4	15.1–90.6	32.3	15.1–90.6	46.2	18.2–89.7
Male gender	3500	51	3385	50	115	58
National ancestry						
Native Dutch	6088	88	5915	88	173	88
Non-native Western	480	7	465	7	15	8
Non-native non-Western	365	5	356	5	9	5
Severity of defect						
Mild	2716	39	2652	39	64	33
Moderate	3384	49	3307	49	77	39
Severe	833	12	777	12	56	28
Number of interventions						
0	2140	31	2086	31	54	27
1	2719	39	2669	40	50	25
2	1175	17	1142	17	33	17
3	501	7	471	7	30	15
≥4	398	6	368	5	30	15
Number of complications						
0	4828	70	4771	71	57	29
1	1493	22	1427	21	66	34
2	468	7	420	6	48	24
≥3	144	2	118	2	26	13

[a]Age is at inclusion and is stated in median and range.

infarction, systemic hypertension, and pulmonary hypertension. Supraventricular arrhythmias comprised atrial flutter, atrial fibrillation, and all other forms of tachycardia, except premature atrial complexes. Rhythm disturbances at the level of atrioventricular junction include nodal tachycardias and re-entry tachycardias, except for Wolff–Parkinson White and accessory pathways, which were coded as separate diagnoses. Ventricular arrhythmias—as recorded from medical letters on patient's condition written by the treating cardiologist to the general practitioner—consisted of ventricular flutter, ventricular fibrillation, sustained and non-sustained tachycardias, and cardiac arrest, yet did not include premature ventricular complexes. Conduction disturbances constituted of sick sinus syndrome, sinoatrial block, all types of atrioventricular block, congenital complete heart block, complete left bundle branch block, and right bundle branch block. Analyses were also performed for conduction disturbances without right bundle branch block, as the latter typically ensues intracardiac surgery. Aortic aneurysm was defined as ≥1.5 times the largest diameter of the aorta measured at the level of the diaphragm.[27] Systolic pulmonary pressure was estimated on the basis of echocardiographic evaluation (tricuspid regurgitation jet velocity measurements in the absence of right ventricular outflow tract obstruction), as invasive data were generally not available. The most recently recorded pulmonary arterial pressure value was used. Pulmonary arterial hypertension was defined as a systolic pulmonary pressure above 40 mmHg.[28] Pulmonary hypertension was considered to be Eisenmenger syndrome after shunt reversal of the original systemic-to-pulmonary shunt, accompanied by cyanosis. Finally, all interventions (surgical and percutaneous) were recorded, including implantation of a pacemaker or an implantable cardioverter defibrillator, catheter ablation, and all (re-)operations including Fontan.

Mortality data

Mortality data were obtained by linkage of the CONCOR database (n = 7277 on the date of linkage, 15 March 2007) to the national Dutch mortality registry of the Central Bureau of Statistics (http://www.cbs.nl/), from 1 January 2002 to 1 January 2008. Using a combination of zip code, gender, and date of birth, the vital status of 95% of patients was assessed; 344 patients (5%) could not be linked due to missing or erroneously registered zip codes. No patients were lost during subsequent follow-up. Linkage also provided national ancestry as an approximation of ethnic origin to the CONCOR registry, and distinguished between native Dutch, non-native Western [originating from a European country (excluding Turkey), North America, Oceania, Indonesia or Japan], and non-native non-Western [Africa, South America, Asia (excluding Indonesia and Japan), or Turkey].

The date and causes of death were obtained as coded by a physician according to the 10th revision of the International Classification of Diseases.[29] The cause of death was defined as the illness, situation, or occurrence which triggered a series of events, ultimately leading to death. If the cause of death was merely stated as congenital heart defect, medical

Table 2 Hazard ratios of all-cause mortality by baseline characteristic in CONCOR patients

	HR, adjusted for age	95% CI	*P*-value	HR, additionally adjusted[b]	95% CI	*P*-value
Age (years)[a]	1.1	1.0–1.1	*<0.001*	1.1	1.0–1.1	*<0.001*
Male gender	1.5	1.1–1.9	0.009	1.4	1.0–1.8	*0.03*
National ancestry						
Native Dutch	1.0	—	—	1.0	—	—
Non-native Western	1.0	0.6–1.7	0.93	1.0	0.6–1.8	0.89
Non-native non-Western	1.3	0.6–2.5	0.51	1.5	0.8–2.9	0.25
Severity of defect						
Mild	1.0	—	—	1.0	—	—
Moderate	1.3	0.9–1.8	0.15	1.2	0.9–1.7	0.27
Severe	5.9	3.9–8.8	*<0.001*	4.1	2.7–6.2	*<0.001*
Number of interventions						
0	1.4	0.9–2.0	0.12	1.3	0.9–2.0	0.15
1	1.0	—	—	1.0	—	—
2	1.5	1.0–2.3	0.07	1.2	0.8–1.9	0.37
3	3.1	2.0–4.9	*<0.001*	2.3	1.5–3.7	*<0.001*
≥4	4.1	2.6–6.5	*<0.001*	2.9	1.8–4.7	*<0.001*
Number of complications						
0	1.0	—	—	1.0	—	—
1	2.5	1.7–3.6	*<0.001*	2.0	1.4–2.9	*<0.001*
2	5.1	3.4–7.7	*<0.001*	4.0	2.6–5.9	*<0.001*
≥3	8.2	5.1–13.4	*<0.001*	5.9	3.6–9.6	*<0.001*

HR, hazard ratio; 95% CI, 95% confidence interval.
P-values below 0.05 are in italic font.
[a]Age is at inclusion and is stated in median and range; hazard ratios of age apply to each increasing year from age 16.
[b]Additionally adjusted for gender, national ancestry, severity of defect, and number of complications (number of interventions is not adjusted for number of complications and vice versa).

records were reviewed (39% of deaths). If death occurred during or within 30 days after a cardiac (re)operation, death was considered perioperative, regardless of its underlying cause such as heart failure or sudden death. Sudden death was defined as death within 1 h of the patient's usual state of health or unwitnessed death during sleep,[30] having no clear vascular origin. Heart failure death was defined as death due to progressive dysfunction of either the systemic or pulmonary ventricle. Other cardiac causes of death were myocardial infarction, endocarditis, and baffle rupture. Vascular death comprised stroke, haemorrhage, pulmonary embolism, rupture of aneurysm, and dissection. Non-cardiovascular death included malignancy, pneumonia, peritonitis, other infections, renal failure, hip fracture, car accident, suicide, and unknown.

Data on mortality rates in the general Dutch population were obtained online from the Central Bureau of Statistics (http://statline.cbs.nl/). The number of deaths in the year 2007 and the number of inhabitants on 1 January 2007, were recorded.

Data analysis

Age at inclusion, follow-up, and death were summarized using medians (range). Survival time of patients was defined as the period from inclusion date to the date of death or censored at 1 January 2008. The causes of death were classified as cardiac (comprising heart failure, sudden death, and other), vascular, or non-cardiovascular. Differences in group means or medians were tested using Student's *t*-test for independent samples or Mann–Whitney *U* test.

To study the effect of complications on mortality, we fitted Cox proportional hazard models to the data with time to (all-cause) mortality as outcome; both patient characteristics and complications served as predictors. Proportionality of hazards over time was evaluated with log minus log graphs for each complication. All analyses were adjusted for age, gender, and severity of underlying defect using dummy variables; analyses on patients' characteristics were additionally adjusted for national ancestry and number of complications. For complications, analyses were performed for all-cause, cardiovascular, and non-cardiovascular mortality. Analyses were also performed for specific cardiovascular causes. Moreover, we speculated that the effect of complications on mortality might differ with advancing age of patients and gender. Therefore, the modifying effect of age on all-cause mortality risk was assessed by performing analyses using two (arbitrary) age groups of patients below and above 40 years of age as well as median age (32.4 years), with age category—complication interaction terms added to the models. Similar analyses were performed with gender.

To describe mortality in CONCOR in comparison with the general Dutch population, the mortality rate in CONCOR was calculated by dividing the number of all-cause deaths in 2007 ($n = 54$) by the number of linked patients on 1 January 2007 minus patient deaths prior to this date ($n = 6790$) by age decades. Similarly, the mortality rate in the general population was assessed by dividing the number of all-cause deaths by the number of inhabitants in 2007 within the 10-year age groups.

Results are summarized by hazard ratios (HRs) with 95% confidence intervals (95% CI); 95% CI not including 1.0, corresponding to two-sided *P*-values of less than 0.05, were considered statistically significant. We used SPSS 14.0 (SPSS Inc., Chicago, IL, USA) for analysis.

Results

Of the 6933 patients linked to the national mortality registry, 197 (2.8%) died during a total follow-up of 24 860 patient years. Median age at death was 48.8 years (range: 20.3–91.2 years); 58% of the deceased patients were male.

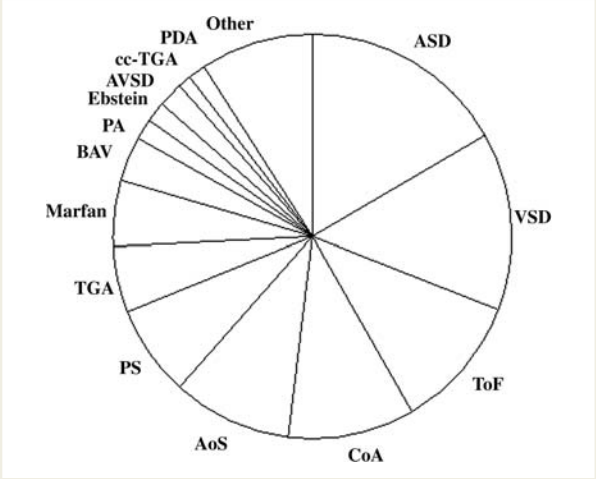

Figure 1 Proportional distribution of main diagnoses among study subjects ($n = 6933$). ASD, atrial septal defect (17%); VSD, ventricular septal defect (14%); ToF, tetralogy of Fallot (11%); CoA, aortic coarctation (10%); AoS, aortic stenosis (10%); PS, pulmonary stenosis (7%); TGA, transposition of the great arteries (5%); Marfan, Marfan syndrome (5%); BAV, bicuspid aortic valve (4%); PA, pulmonary atresia (2%); Ebstein, Ebstein's anomaly (2%); AVSD, atrioventricular septal defect (2%); cc-TGA, congenitally corrected transposition of the great arteries (1%); PDA, patent arterial duct (1%); other, other congenital heart defects with $n < 65$ (9%).

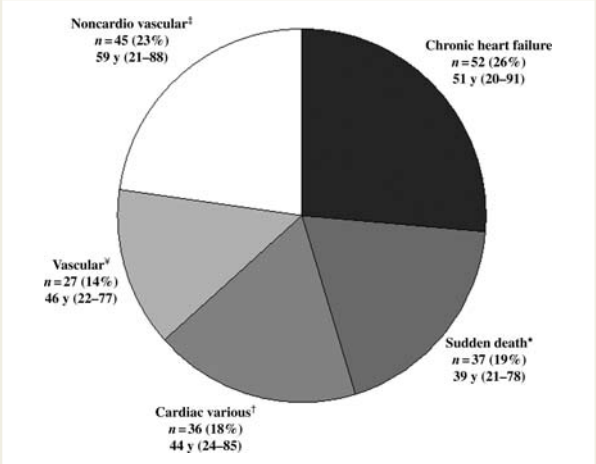

Figure 2 Causes of, and age at, death in CONCOR patients ($n = 197$). y is the year of age, stated in median (range). In six patients who died instantaneously, ventricular arrhythmia was confirmed as the cause of death (*). Perioperative ($n = 14$), endocarditis ($n = 11$), myocardial infarction ($n = 10$), and baffle rupture ($n = 1$) (†). Haemorrhage ($n = 10$; these include subarachnoidal, intracranial, respiratory, and gastrointestinal), stroke ($n = 9$), aortic dissection or rupture ($n = 6$), and pulmonary embolism ($n = 2$) (¥). Malignancy ($n = 18$), pneumonia ($n = 8$), peritonitis ($n = 5$), other infections ($n = 4$), renal failure ($n = 3$), other causes ($n = 6$), and unknown ($n = 1$) (‡).

Table 1 shows patient characteristics and medical history of all registrees and separately by vital status. *Table 2* shows the association of patient characteristics with all-cause mortality. Age, gender, severity of congenital heart defect, number of interventions, and number of complications predicted all-cause mortality.

Figure 1 illustrates the distribution of diagnoses. Atrial septal defect, ventricular septal defect, tetralogy of Fallot, aortic coarctation, and aortic stenosis collectively accounted for 62% of all diagnoses.

Figure 2 shows the causes of death in 197 patients. Chronic heart failure (26%) and sudden death (19%) were recorded most often. Median age at death from heart failure was 51.0 years (range: 20.3–91.2 years) and median age at sudden death was 39.1 years (range: 21.0–78.2 years). Two-thirds of patients died from a cardiac cause; 77% of deaths had cardiovascular origins. Among the 23% non-cardiovascular deaths, malignancy (9%) and pneumonia (4%) were the predominant causes. In total, 16 patients (8%) died during, or ensuing, a (re-)operation, 14 of which were cardiac.

Figure 3 shows the variation in proportional distribution of causes of death by defect in deceased patients. Defects with the highest mortality were univentricular complexes, tricuspid atresia, and double outlet right ventricle (all >10%).

Table 3 shows relative risks for all-cause, cardiovascular, and non-cardiovascular mortality by complication, adjusted for age and gender, and additionally adjusted for severity of congenital heart defect. Endocarditis, supraventricular arrhythmia, ventricular arrhythmia, conduction disturbances, myocardial infarction, and pulmonary hypertension were each associated with an increased risk of all-cause mortality. Analysis of conduction disturbances without right bundle branch block rendered similar results (HR 1.5, 95% CI 1.0–2.2, $P = 0.03$), but right bundle branch block alone did not reach statistical significance (HR 1.3, 95% CI 0.9–1.9, $P = 0.16$). Eisenmenger syndrome was also associated with all-cause mortality (HR 6.1, 95% CI 3.7–10.3, $P < 0.001$). Restriction of these analyses to cardiovascular mortality yielded equivalent results. CVA/TIA and aortic complications also appeared to be associated with an increased risk of cardiovascular mortality, yet did not reach statistical significance.

Table 4 shows HRs of cardiovascular causes of death by complication. Nearly all complications predicted death from heart failure; CVA/TIA and systemic hypertension did not reach statistical significance. Conduction disturbances and pulmonary hypertension predicted sudden death. Ventricular arrhythmia did not predict sudden death, when patients with an implantable cardioverter defibrillator

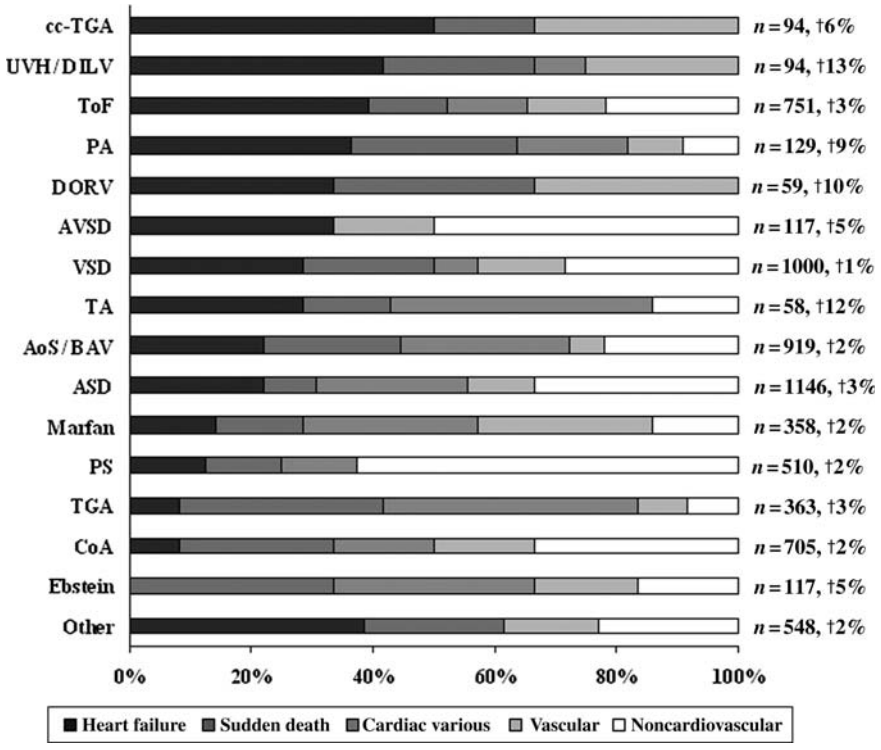

Figure 3 Proportional distribution of causes of death by defect in deceased patients ($n = 197$). cc-TGA, congenitally corrected transposition of the great arteries; PA, pulmonary atresia associated with ventricular septal defect; UVH/DILV, univentricular heart/double inlet left ventricle; AVSD, atrioventricular septal defect; ToF, tetralogy of Fallot; ASD, atrial septal defect; DORV, double outlet right ventricle; AoS/BAV, aortic stenosis/bicuspid aortic valve; PS, pulmonary stenosis; TA, tricuspid atresia; TGA, transposition of the great arteries; CoA, aortic coarctation; VSD, ventricular septal defect; Ebstein, Ebstein's anomaly; Marfan, Marfan syndrome. Other defects comprise defects without or less than three deaths [patent arterial duct (†$n = 3$), common arterial trunk (†$n = 2$), left ventricular outflow tract obstruction (†$n = 2$), mitral valvar prolapse (†$n = 2$), anomalous pulmonary venous connections (†$n = 1$), aortic regurgitation (†$n = 1$), aortopulmonary window (†$n = 1$), and atrial situs inversus (†$n = 1$)].

Table 3 Hazard ratios of all-cause, cardiovascular, and non-cardiovascular mortality by complication in all patients ($n = 6933$)

	n	All-cause mortality, adjusted for age and gender			All-cause mortality, also adjusted for CHD severity			Cardiovascular mortality			Non-cardiovascular mortality		
		HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR[a]	95% CI	*P*-value	HR[a]	95% CI	*P*-value
CVA/TIA	190	1.5	0.9–2.6	0.14	1.4	0.8–2.4	0.23	1.7	0.9–3.0	0.09	0.7	0.2–3.0	0.66
Endocarditis	223	2.1	1.3–3.5	*0.003*	2.0	1.2–3.2	*0.009*	2.2	1.3–3.8	*0.004*	1.1	0.3–4.4	0.93
Supraventricular arrhythmia	1013	2.3	1.7–3.1	*<0.001*	1.8	1.3–2.5	*<0.001*	2.0	1.4–2.9	*<0.001*	1.2	0.6–2.3	0.58
Ventricular arrhythmia	140	2.4	1.4–4.3	*0.002*	1.8	1.0–3.3	*0.04*	2.0	1.1–3.7	*0.03*	1.4	0.3–6.0	0.62
Conduction disturbances	1165	1.8	1.3–2.4	*<0.001*	1.4	1.1–2.0	*0.02*	1.5	1.0–2.1	*0.03*	1.3	0.6–2.5	0.49
Aortic complications	149	1.2	0.6–2.6	0.62	1.5	0.7–3.1	0.33	2.1	1.0–4.6	0.06	—	—	—
Myocardial infarction	45	2.0	0.9–4.5	0.11	2.3	1.0–5.2	*0.05*	2.9	1.2–7.2	*0.02*	1.0	0.1–7.5	0.99
Systemic hypertension	436	0.9	0.5–1.4	0.54	1.0	0.6–1.6	0.89	0.8	0.4–1.4	0.39	1.5	0.7–3.2	0.33
Pulmonary hypertension	361	3.8	2.7–5.4	*<0.001*	3.1	2.2–4.5	*<0.001*	3.6	2.5–5.4	*<0.001*	1.6	0.6–4.2	0.31

HR, hazard ratio; CI, confidence interval; CHD, congenital heart defect; CVA, cerebrovascular accident; TIA, transient ischaemic attack.
P-values <0.05 are in italic font.
[a]Adjusted for age, gender, and congenital heart defect severity.

were excluded from analyses. CVA/TIA, endocarditis, aortic complications, and pulmonary hypertension predicted vascular death.

Figure 4 displays the risk of all-cause mortality by complication within younger ($n = 4660$; 75 deceased) and older ($n = 2273$; 122 deceased) patients at inclusion. Complication rates in younger and older patients were 22 and 47%, respectively. Only myocardial infarction was a significantly stronger predictor for mortality in younger patients than in older patients (*P*-value for interaction = 0.002). Supraventricular arrhythmia and pulmonary hypertension were equally predictive of mortality. Using a cut-off point of the median, 32.4 years for age categories yielded similar results. Obviously, age was a predictor of mortality (*Table 2*). However, substantial excess mortality existed in all age groups in CONCOR compared with the general Dutch population (*Figure 5*), particularly among younger registrees.

HRs for all-cause mortality by complication did not significantly differ between men and women (data not shown). Analyses restricted to cardiovascular mortality rendered the same results.

Discussion

The present study is the first to assess the extent and predictors of mortality in a large nationwide population, showing that adult patients with congenital heart disease had excess mortality. The vast majority of patients died from cardiovascular causes, mainly chronic heart failure and sudden death. Mortality risk, particularly by heart failure, was increased by virtually all late cardiovascular complications. Complications were similarly hazardous in younger patients as in older patients.

Strengths and limitations of this study need to be addressed. Particular strengths of our study are the large number of patients, the rigorous and uniform methods of recording data, and the robust database linking process. Clinically, well-known phenomena such as the rising incidence of certain complications with age[9] are confirmed in CONCOR, supporting the quality of our data. Finally, CONCOR is one of the first large scale and nationwide registries of adults with congenital heart disease, thus adding substantially to evidence applicable to these patients. Limitations are that CONCOR neither comprises very mild congenital heart disease in patients lost to medical surveillance nor critical congenital heart disease that led to death prior to enrolment. Complex congenital heart disease may be overrepresented as most registrees originate from tertiary referral centres. However, we do believe that our findings generalize to the relevant domain of adults with congenital heart disease, who require regular medical monitoring. Our findings may partly reflect patient characteristics not registered, such as lifestyle factors or co-morbidity, although we consider these explanations unlikely for all associations found. Moreover, the number of patients that could not be linked to the national mortality registry was too small to explain our findings. Finally, we analysed specific causes of death, yet the number of events was low and thus there may have not been adequate power to detect statistically significant differences.

Our findings clearly showed excess mortality among adult patients with congenital heart disease, as compared with the general population. We found heart failure and sudden death to be the most frequent underlying causes of death, a finding

Table 4 Hazard ratios of cause of death by complication in all patients (n = 6933)

	Cause of death											
	Heart failure			Sudden death			Other cardiac			Vascular		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
CVA/TIA	2.0	0.9–4.9	0.11	0.7	0.1–5.1	0.71	0.6	0.1–4.6	0.64	3.2	1.1–9.6	*0.04*
Endocarditis	3.0	1.4–6.8	*0.007*	1.2	0.3–4.9	0.82	1.3	0.3–5.4	0.72	3.4	1.2–9.9	*0.02*
Supraventricular arrhythmia	5.1	2.8–9.5	*<0.001*	0.9	0.4–2.1	0.86	2.0	0.9–4.0	0.07	1.0	0.4–2.3	0.92
Ventricular arrhythmia	4.5	2.1–9.8	*<0.001*	1.5	0.3–6.2	0.60	—	—	—	0.9	0.1–6.7	0.91
Conduction disturbances	2.0	1.1–3.5	*0.02*	2.0	1.0–4.0	*0.05*	1.3	0.6–2.7	0.54	0.6	0.2–1.6	0.33
Aortic complications	—	—	—	3.0	0.7–12.7	0.14	2.7	0.6–11.4	0.19	5.6	1.6–19.7	*0.007*
Myocardial infarction	4.4	1.3–14.7	*0.02*	3.5	0.5–27.1	0.23	—	—	—	3.1	0.4–24.0	0.28
Systemic hypertension	0.4	0.1–1.5	0.15	0.4	0.1–2.9	0.36	1.0	0.3–3.5	0.96	1.9	0.6–5.6	0.28
Pulmonary hypertension	4.4	2.3–8.2	*<0.001*	4.7	2.3–9.9	*<0.001*	1.2	0.4–3.9	0.80	4.8	2.1–11.0	*<0.001*

HR, hazard ratio; CVA, cerebrovascular accident; TIA, transient ischaemic attack.
P-values <0.05 are in italic font. All hazard ratios are adjusted for age, gender, and severity of underlying congenital heart defect.

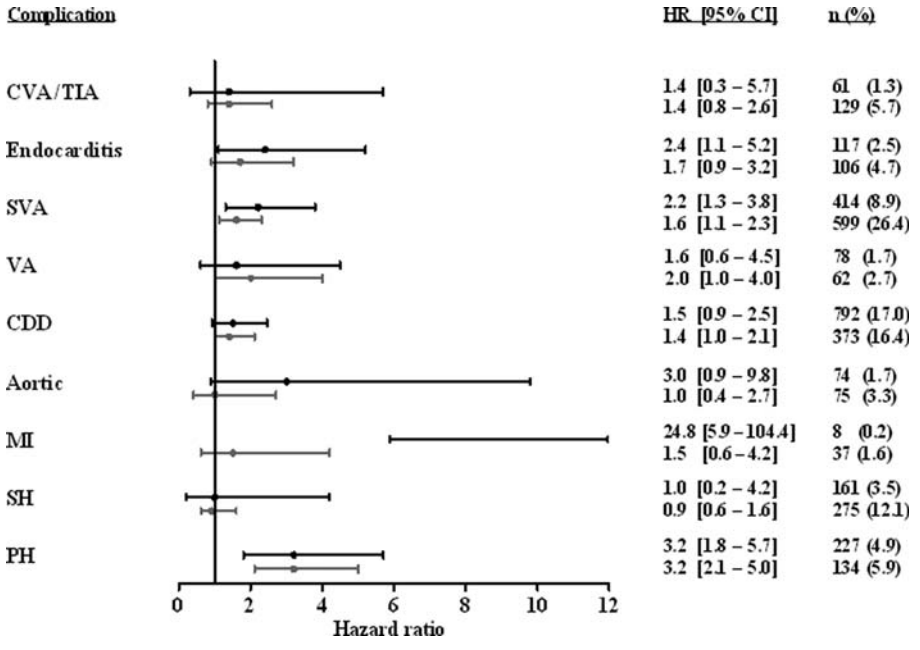

Figure 4 Hazard ratios of all-cause mortality by complication in patients below (dark line) and above (grey line) 40 years. CVA/TIA, cerebrovascular accident/transient ischaemic attack; SVA, supraventricular arrhythmia; VA, ventricular arrhythmia; CDD, conduction disturbances; Aortic, aortic complications (aneurysm or dissection); MI, myocardial infarction; SH, systemic hypertension; PH, pulmonary hypertension. The bars correspond to the numbers in the left column adjacent to the figure. These numbers are hazard ratios with 95% confidence intervals. All hazard ratios are adjusted for age, gender, and severity of defect. The right column comprises the absolute and relative frequency of complications.

previously described in both children and adults.[4,6] Registrees who died suddenly were more than 10 years younger than those who died from chronic heart failure. This age difference has been suggested previously from cross-sectional data,[6] and has also been found in patients with hypertrophic cardiomyopathy, a patient population not included in our database.[31] Moreover, the congenital heart defects that had the highest patient mortality were similar to those described earlier by Oechslin *et al.*[6] However, this study also reported a substantially higher proportion of perioperative deaths compared with

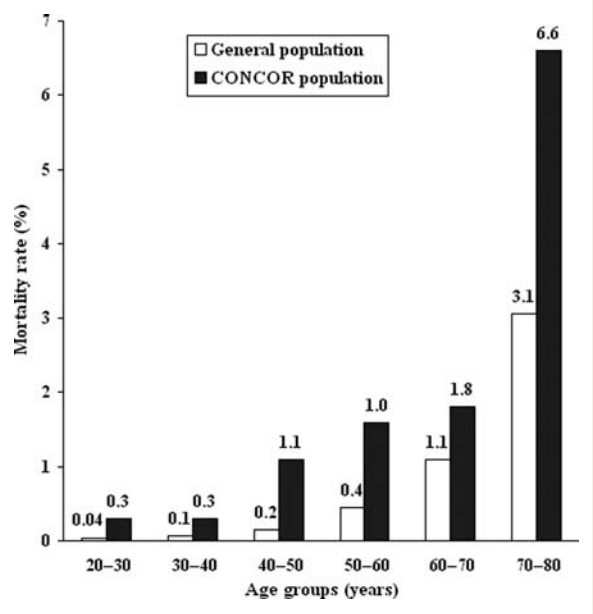

Figure 5 Mortality rate in CONCOR patients and in the general Dutch population by decade in 2007. Sample sizes in CONCOR by age group 20–30 ($n = 1967$), 30–40 ($n = 1378$), 40–50 ($n = 837$), 50–60 ($n = 514$), 60–70 ($n = 246$), and 70–80 ($n = 101$).

our results. This discrepancy may lie in the fact that our study population is a cohort, whereas the study by Oechslin *et al.* is cross-sectional.

Expectedly, age, gender, and severe congenital heart disease with associated numbers of interventions and complications were all predictors of mortality. These complications also predicted the predominant underlying causes, i.e. cardiovascular death and particularly deaths from heart failure, emphasizing their importance. A remarkable and somewhat counterintuitive finding is that complications were as lethal in younger as in older patients, whereas we expected complications to be more hazardous in older patients. This has substantial clinical impact because, consistent with current literature,[5,9] the cumulative number of sustained complications in CONCOR was considerable in both younger and older patients. Moreover, excess mortality was particularly present in younger patients. Our inference is that age of patients with congenital heart disease should not play a role in clinical decision making concerning cardiovascular complications.

We found endocarditis to be a predictor for mortality at any age, and in both genders, as has been indicated in previous reports.[32,33] Moreover, we found ventricular arrhythmias to predict cardiovascular death, which was suggested in Fallot patients to be particularly associated with sudden death.[34,35] However, in our study, ventricular arrhythmia predicted heart failure yet not sudden death. This finding is described by previous reports, in which few patients die suddenly despite a high frequency of ventricular arrhythmias on Holter monitoring.[36,37]

In summary, there is an increased mortality in adults with congenital heart disease, particularly in the young. The vast majority die from cardiovascular causes. Mortality risk, particularly by heart failure, is increased by virtually all complications, which are equally hazardous in younger as in older patients. However, there is no evidence on the effects of such general measures in these patients. Indeed, current international guidelines on adult congenital heart disease are lacking recommendations on these preventive measures.[10,11] Moreover, existing guidelines barely suffice in providing solid and evidence-based information on the treatment of adult congenital heart disease patients, in whom a large proportion of disorders is afflicting the right heart. We believe that our findings warrant further studies providing evidence for risk-reducing measures in young adults with congenital heart disease.

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Appendix

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Havenziekenhuis, Rotterdam: C.M. Leenders; Hofpoort Ziekenhuis, Woerden; IJsselland Ziekenhuis, Capelle aan den IJssel; IJsselmeer Ziekenhuizen, Lelystad/Emmeloord: J.M. Ansink; Ikazia Ziekenhuis, Rotterdam: J.P. Kerker; Isala Klinieken Weezenlanden/Sophia, Zwolle: J.C.A. Hoorntje; Jeroen Bosch ziekenhuis, locatie Carolus, 's-Hertogenbosch: E.C.M. Schavemaker; Jeroen Bosch Ziekenhuis, locatie Groot Ziekengasthuis, 's-Hertogenbosch: E. Krivka; Kennemer Gasthuis, locatie Zuid, Haarlem: R. Tukkie; 't Lange Land Ziekenhuis, Zoetermeer; Laurentius Ziekenhuis, Roermond: C.J.P.J. Werter; Leids Universitair Medisch Centrum, Leiden: H.W. Vliegen; Maasziekenhuis Pantein, Boxmeer; Maasland Ziekenhuis, Sittard: L.G.H. Brunnikhuis; Maasstadziekenhuis, locatie Clara/Zuider, Rotterdam; Martini Ziekenhuis, Groningen: L. Bartels; Máxima Medisch Centrum, Veldhoven/Eindhoven: R.F. Visser; Meander Medisch Centrum, Amersfoort: S.M. Roeffel; Medisch Centrum Alkmaar, Alkmaar: C.L.A. Reichert; Medisch Centrum Haaglanden, locatie Antoniushove, Leidschendam; Medisch Centrum Haaglanden, locatie Westeinde, 's-Gravenhage; Medisch Centrum Leeuwarden, Leeuwarden: C.J. de Vries; Medisch Spectrum Twente, Enschede: E.M.C.J. Wajon; Onze Lieve Vrouwe Gasthuis, Amsterdam: R. Riezebos; Oosterschelde Ziekenhuizen, Goes: H.W.O. Roeters van Lennep; Refaja Ziekenhuis, Stadskanaal: A.G. Vijn; Reinier de Graaf Ziekenhuis, Delft; Rijnland Ziekenhuis, Leiderdorp/Alphen aan den Rijn; Rivas Zorggroep, Gorinchem; Rode Kruis Ziekenhuis, Beverwijk: J.H.M. Spekhorst; Röpcke-Zweers Ziekenhuis, Hardenberg/Coevorden: A.J. Schaap; Ruwaard van Putten Ziekenhuis, Spijkenisse; Scheper Ziekenhuis, Emmen: L. van de Merkhof; Sint Anna Ziekenhuis, Geldrop: P.E. Polak; Sint Antonius Ziekenhuis, Nieuwegein: H.W.M. Plokker; Sint Elisabeth Ziekenhuis, Tilburg; Sint Franciscus Ziekenhuis, Rotterdam: M.J. Veerhoek; Sint Jans Gasthuis, Weert: H.C. Klomps; Sint Lucas Andreas Ziekenhuis, Amsterdam: R.G.E.J. Groutars; Sint Lucas Ziekenhuis, Winschoten: N.M. de Groot-van Popele; Slingeland Ziekenhuis, Doetinchem: J.M.C. van Hal; Slotervaart Ziekenhuis, Amsterdam: A.G. Veerbeek; Spaarne Ziekenhuis, Hoofddorp: A.F.M. Kuijper; Streekziekenhuis Koningin Beatrix, Winterswijk: C. van der Lee; Talma Sionsberg, Dokkum: A.W. Hagoort-Kok; Tergooiziekenhuizen, locatie Blaricum, Blaricum: G. Hoedemaker; Tergooiziekenhuizen, locatie Hilversum, Hilversum: J. Plomp; Tweesteden Ziekenhuis, Tilburg: M.S. Hulsbergen-Zwarts; Universitair Medisch Centrum Groningen, Groningen: P.G. Pieper; Universitair Medisch Centrum Sint Radboud, Nijmegen: A.P.J. van Dijk; Universitair Medisch Centrum Utrecht, Utrecht: B.J.M. Mulder, G.T.J. Sieswerda; Universitair Ziekenhuis Gent, Gent; VieCuri Medisch Centrum, Venlo/Venray: B.M. Rahel; Vlietland Ziekenhuis, Vlaardingen/Schiedam; VU Medisch Centrum, Amsterdam: G. Veen, T.C. Konings; Waterland Ziekenhuis, Purmerend: M. Mihciokur; Westfriesgasthuis, Hoorn: P.F.M.M. van Bergen; Wilhelmina Ziekenhuis, Assen: I.J. van Eede; Ziekenhuis Amstelland, Amstelveen; Ziekenhuis Bernhoven, Oss/Veghel; Ziekenhuis Bethesda, Dirksland; Ziekenhuis de Gelderse Vallei, Ede: T.T. van Loenhout; Ziekenhuis de Heel, Zaandam; Ziekenhuis Lievensberg, Bergen op Zoom; Ziekenhuis Nij Smellinge, Drachten: R.P.L.M. van der Aa; Ziekenhuis Rivierenland, Tiel; Ziekenhuis Sint Jansdal, Harderwijk: R. Dijkgraaf; Ziekenhuis de Tjongerschans, Heerenveen: S.K. Oei; Ziekenhuis Walcheren, Vlissingen: W.H. Pasteuning; Ziekenhuisgroep Twente, Streekziekenhuis Midden-Twente, Hengelo: L. Pos; Ziekenhuisgroep Twente, Twenteborg Ziekenhuis, Almelo: G.C.M. Linssen; ZorgSaam Zeeuws-Vlaanderen, Terneuzen: C.A.W. Janssens.

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