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Cardiovascular risk factors and arterial thrombotic events in congenital heart disease patients

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Abstract

Introduction: As congenital patients get older, it can be hypothesised that cardiovascular risk factors increase.

Methods: Retrospective study of congenital heart disease (CHD) patients attended between January 2008 and September 2018. Cardiovascular risk factors, myocardial infarction, stroke, peripheral vascular disease, and analytical data such as serum glucose and lipid profile were determined.

Results: Eight hundred and eighteen CHD patients and 1955 control patients matched for age and sex were studied. CHD patients were distributed in simple (462 patients), moderate (228 patients) and great (128 patients) complexity. Median age in CHD patients was 33 (25-41) years old and 56% were male. CHD patients were significantly more hypertensive and diabetic but less dyslipidemic and smokers than patients in the control group. Twenty-seven (3.3%) CHD patients had an arterial thrombotic event: 3 coronary, 22 neurological and 2 peripheral vascular disease. No significant differences were seen in the incidence of myocardial infarction between the control and the CHD groups. However CHD patients had a significant higher incidence of arterial thrombotic events (coronary, neurological and peripheral vascular events) at the expense of strokes and transient ischaemic attacks (22 vs 2 events in CHD and control patients, respectively). Also, no significant differences were seen in age, sex, BMI, arterial hypertension, diabetes mellitus, dyslipidemia, smoking habit, serum glucose, total and LDL cholesterol, statin treatment, myocardial infarction and arterial thrombotic events according to CHD complexity. Being older and having arterial hypertension, diabetes mellitus, dyslipidemia and smoking habit were more frequent among CHD patients with arterial thrombosis.

Conclusions: Congenital heart diseases are more hypertensive and diabetic but less dyslipemic and smokers than patients in the control group. CHD patients have a higher incidence of neurological events but not of myocardial infarction in relation to the control population.

1 | INTRODUCTION

Atherosclerosis is a cumulative process, starting at a fairly young age. In fact, the risk of coronary artery disease increases markedly with age[1] and currently evidence suggests that physical inactivity, obesity, diabetes and arterial hypertension may be at least as prevalent in patients with congenital heart disease (CHD) as in the general population.[2,3] Identification and control of cardiovascular risk factors may contribute to reduce ischaemic heart disease, heart failure and sudden death in CHD patients.

The aim of this study is to determine the incidence of cardiovascular risk factors and arterial thrombotic events (coronary, neurological and peripheral vascular disease) in CHD patients and an age and sex matched control population of a similar geographical area and a similar socioeconomic status.

What's known

- The prevalence of coronary heart disease in adults with CHD has been variably reported in the literature with very heterogeneous results.

What's new

- We determine and compare the incidence of classic cardiovascular risk factors and arterial thrombotic events in CHD patients with an age- and sex-matched control population of a similar geographical area and a similar socioeconomic status.
- This allows us to make a more accurate comparison of congenital patients with a normal population.

2 | METHODS

Retrospective study of CHD patients attended at our CHD unit between January 2008 and September 2018. The inclusion criteria specified patients older than 14 years with a structural congenital heart disease. Clinical data were acquired from patient records and CHD was verified by echocardiography, cardiovascular magnetic resonance and/or cardiac catheterisation. Patients with more than one defect were classified according to the prevalent lesion from a clinical and/or haemodynamic point of view. Consistent with published classification schema, cardiac defects were categorised as simple, of moderate complexity, or of great complexity.[4] Also CHD patients were divided into different groups according to the time of surgery (non-operated on, operated on in childhood, operated on in adulthood or treated by percutaneous approach) and the existence or not of associated cyanosis.

Control patients were obtained consecutively among patients attending the outpatient clinic of the community health centres of the same geographical area, between July and December 2017 because of trivial processes such as anxiety, palpitations, skin rash, itching, pain in muscles and back or common cold and matched for age and sex.

Clinical follow-up data in CHD patients were obtained from medial history or telephone interviews. Stroke was defined as an acute episode of focal cerebral, spinal or retinal dysfunction caused by infarction of central nervous system tissue, transitory ischaemic attack (TIA) as a transient episode of neurological dysfunction caused by brain, spinal and/or retinal ischaemia without acute infarction, myocardial infarction when there was evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia and peripheral vascular disease referred to any disease or disorder of the peripheral circulatory system that required acute revascularisation or hospitalisation.[5] The protocol of the study was approved by the Hospital's Ethics Committee.

2.1 | Clinical and analytical data

Arterial hypertension was defined as office systolic blood pressure values ≥140 mm Hg and/or diastolic blood pressure values ≥90 mm Hg according to the 2018 ESC/ESH Guidelines[6] or if the patient was receiving medication for arterial hypertension. Diabetes mellitus when fasting blood glucose levels was >126 mg/dL or the patient was treated with oral anti-diabetic agents or insulin.[7] Patients were defined as having dyslipidemia if their LDL cholesterol level was above 130 mg/dL or the patients were under statin treatment.[8] The patient was classified as smoker if at the time of inclusion he/she was an active smoker. Body weight and height were measured with the patients wearing light clothes and barefoot and body mass index (BMI) was determined as weight (kg)/[height (m) height (m)].

Blood samples were collected for subsequent laboratory analysis after an overnight fast of at least 10 hours. All blood samples were processed immediately after sampling. Serum glucose (normal values: 70-110 mg/dL), total cholesterol (20-220 mg/dL), LDL cholesterol (0-155 mg/dL), HDL cholesterol (35-65 mg/dL) and triglycerides (30-200 mg/dL) were measured by spectrophotometry with an Olympus AU 2700 equipment (Olympus Diagnostic, Hamburg, Germany).

2.2 | Statistical analysis

Quantitative variables were expressed as mean ± standard deviation or median and quartiles (25;75). Qualitative variables were expressed in percentages. A normal distribution was tested using the Kolmogorov-Sirmov test. Possible associations between categorical variables were evaluated by using the Pearson chi-square test. Continuous data were compared by Student´s t-test or Mann-Whitney test for variables with or without normal distribution, respectively. Kruskal-Wallis non-parametric test was used to determine whether the medians of two or more groups were different. Binary logistic regression analysis was performed to compare

CHD patients with and without arterial thrombosis with those independent variables that had a $p < 0.05$ in the univariate analysis. The results were expressed as odds ratios (ORs) with their 95% confidence intervals (CIs). A $p < 0.05$ was considered statically significant. Data analysis was carried out using SPSS 19.0 (SPSS, Chicago, IL).

3 | RESULTS

Eight hundred and eighteen CHD patients and 1955 control patients were included in the study. Table 1 shows CHD classification. According to complexity, CHD patients were distributed in simple (462 patients), moderate (228 patients) and great (128 patients) complexity.

Table 2 compares demographic, clinical and analytical data between CHD patients and the control population. CHD patients were significantly more hypertensive and diabetic but less dyslipidemic and smokers than patients in the control group. Meanwhile, control patients had significant higher serum glucose concentration and lipid profile levels than CHD patients although both parameters were within normal limits in both groups. In relation to medical treatment patients in the CHD group used more oral anticoagulation, aspirin, betablockers, angiotensin converting enzyme (ACE) inhibitor and

TABLE 1 Congenital cardiac classification system guided by the report of the 32nd Bethesda Conference[4]

Types of congenital heart disease according to complexity	Number of patients
Simple complexity	462
Aortic valve disease	69
Pulmonary valve disease	81
Atrial septal defect	90
Ventricular septal defect	139
Ductus	22
Other simple defects	61
Moderate complexity	228
Subvalvular or supravalvular aortic stenosis	27
Coarctation of the aorta	63
Subvalvular or supravalvular pulmonary stenosis	12
Tetralogy of Fallot	66
Ebstein	8
Atrioventricular septal defects	48
Sinus venosus septal defect	4
Great complexity	128
Dextro transposition of the great arteries	32
Levo transposition of the great arteries	13
Pulmonary atresia	9
Single ventricle	12
Double outlet right ventricle	14
Eisenmenger syndrome	40
Tricuspid atresia	6
Trucus arteriosus	2
Total of CHD	818

TABLE 2 Demographic, clinical and analytical data in CHD patients and the control population

	CHD	Control population	*p* value
n	818	1955	
Age (years)	33 (25-41)	30 (22-42)	0.101
Sex (male), n	460 (56)	1052 (53)	0.229
Arterial hypertension, n	101 (12)	186 (10)	0.022
Diabetes mellitus, n	36 (4)	48 (2.5)	0.005
Type 1	4 (0.5)	10 (0.4)	
Type 2 under oral antidiabetics	25 (3)	35 (2)	
Type 2 with insulin	7 (1)	3 (0.2)	
Dyslipidemia, n	117 (14)	481 (25)	<0.001
Smoking, n	35 (4)	317 (16)	<0.001
Serum glucose (mg/dL)	93 (87-100)	94 (89-101)	0.006
Total cholesterol (mg/dL)	161 (137-188)	177 (153-204)	<0.001
LDL cholesterol (mg/dL)	92 (72-114)	104 (85-127)	<0.001
HDL cholesterol (mg/dL)	49 (41-57)	52 (45-60)	<0.001
Tryglicerides (mg/dL)	84 (61-114)	88 (63-125)	0.014
Oral anticoagulation, n	109 (13)	6 (0.3)	<0.001
Aspirin, n	74 (9)	25 (1.2)	<0.001
β-blockers, n	107 (13)	47 (0.8)	<0.001
ACE inhibitor, n	69 (8)	63 (3)	<0.001
ARBs, n	40 (5)	71 (4)	0.186
CCB, n	27 (3)	28 (1.5)	0.001
Diuretics, n	102 (12)	61 (3)	<0.001
Anti-aldosterone, n	57 (7)	4 (0.2)	<0.001
Statins, n	59 (7)	138 (7)	0.721
Coronary artery disease, n	3 (0.4)	7 (0.4)	0.982
Arterial thrombosis, n	27 (3)	9 (0.5)	<0.001

Note: The data are expressed as median and quartiles (25;75) and as number and percentage. Categorical variables are evaluated by the Pearson chi-square test and continuous data without normal distribution by Mann-Whitney test.
Abbreviations: ACE inhibitor, angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blockers; CCB, calcium channel blockers; CHD, congenital heart disease; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; n, number of patients; β-blockers, beta-adrenoceptor blocking agents.

diuretics than patients in the control group ($p < 0.001$). On the contrary, no significant differences were seen in relation to angiotensin receptor blockers (ARBs) or statins. Similarly, no significant differences were seen in the incidence of myocardial infarction between the control and the CHD groups although CHD patients showed a significant higher incidence of arterial thrombotic events (coronary, neurological and peripheral vascular events) at the cost of a greater number of neurological events (22 vs 2 events in CHD and control patients, respectively). Likewise, at the time of the thrombotic event no significant differences were seen in sex but in age among CHD patients and the control population [51 (38-62) vs 53 (46-55) years old, $p < 0.001$).

Table 3 shows the distribution of arterial thrombotic events (coronary, neurological and peripheral vascular disease) in CHD patients and the control population and in CHD according to their complexity. Of the 22 CHD patients who had a neurological event, 16 patients had a stroke and 6 patients had a TIA. On the contrary, in the control group there were only two neurological events (one stroke and one TIA). However in both groups most of patients who had suffered an arterial thrombotic event were under oral anticoagulation or antiaggregation treatment. On the contrary, statin treatment in CHD patients with cardiac and neurological events was low (33% and 36%, respectively) as opposed to what happened in the control population (100% and 50%, respectively). However, one of the three CHD patients who had an acute coronary event debuted as a myocardial infarction with sudden death, reason why he was not antiaggregated or under statin treatment at the time of the event. In relation to cyanosis, 7 cyanotic CHD patients out of 53 (13%) had an arterial thrombotic events in comparison to 21 out of 765 (3%) in the non-cyanotic group ($p < 0.001$).

Table 4 compares demographic, clinical and analytical data in CHD patients according to complexity. No significant differences were seen in age, sex, BMI, arterial hypertension, diabetes mellitus, dyslipidemia, smoking habit, serum glucose, total and LDL cholesterol, statin treatment, myocardial infarction and arterial thrombotic events according to CHD complexity. On the contrary, patients with great complexity used more anticoagulation, aspirin, beta-blockers and ACE inhibitors than patients with simple or moderate complexity.

Table 5 shows demographic, clinical and cardiovascular risk in CHD patients depending if they did not undergo surgery, were operated on in childhood, operated on in adulthood or treated by percutaneous approach. The results are also shown depending on whether CHD patients were cyanotic or not. Patients operated on in adulthood were significant older, had more arterial hypertension and higher serum glucose levels than the others. Meanwhile, cyanotic CHD patients were significant older and had lower serum glucose levels than non-cyanotic CHD patients.

Table 6 shows demographic and cardiovascular risk factors in CHD patients attending to the existence or not of arterial thrombosis. Being older and having more arterial hypertension, diabetes mellitus, dyslipidemia and smoking habit were significantly more frequent among CHD patients with arterial thrombosis. Finally, Table 7 shows the binary logistic regression analyses of congenital heart disease patients with and without arterial thrombosis. Crude OR, obtained when considering the effect of only one predictor variable, evidenced that age and all cardiovascular risk factors were risk

TABLE 3 Arterial thrombotic events and medical treatment in CHD and control patients

Type of arterial thrombosis	Coronary	Cerebral	Peripheral	*p*
CHD patients, n	3 (0.4)	22 (3)	2 (0.2)	<0.001
Control population, n	7 (0.4)	2 (0.1)	0 (0)	
CHD complexity				
Simple, n	2 (0.4)	12 (3)	2 (0.4)	0.569
Moderate, n	1 (0.4)	4 (2)	0 (0)	
Great, n	0 (0)	6 (5)	0 (0)	
CHD patients whit thrombotic events[a]				
Oral anticoagulation, n	1 (33)	10 (45)	1 (50)	<0.001
Aspirin, n	1 (33)	9 (41)	2 (100)	
Statins, n	1 (33)	8 (36)	1 (50)	
Control population with thrombotic events				
Oral anticoagulation, n	1 (15)	1 (50)	0 (0)	<0.001
Aspirin, n	7 (100)	0 (0)	0 (0)	
Statins, n	7 (100)	1 (50)	0 (0)	

Note: The data are expressed as number and percentage.
Abbreviations: CHD, congenital heart disease, n, number of patients.
[a]One of the patients with an acute coronary event suffered sudden death as the first cardiac symptom.

TABLE 4 Demographic, clinical and analytical data in CHD patients according to complexity

CHD complexity	Simple	Moderate	Great	*p* value
n	462 (56)	228 (28)	128 (17)	
Age (years)	29 (22-41)	31 (22-41)	34 (23-43)	0.245
Sex (male), n	257 (57)	130 (57)	73 (57)	0.936
BMI (kg/m^2)	23 (21-26)	24 (21-28)	23 (20-26)	0.233
Arterial hypertension, n	59 (13)	33 (14)	9 (7)	0.111
Diabetes mellitus, n	23 (5)	5 (2)	8 (6)	0.282
Type 1	2 (0.4)	0 (0)	2 (2)	
Type 2 under oral antidiabetics	17 (4)	4 (2)	4 (3)	
Type 2 with insulin	4 (0.9)	1 (0.5)	2 (1.5)	
Dyslipidemia, n	76 (16)	26 (11)	17 (13)	0.249
Smoking, n	21 (5)	12 (5)	2 (2)	0.344
Serum glucose (mg/dL)	94 (87-99)	94 (88-100)	91 (85-100)	0.116
Total cholesterol (mg/dL)	164 (139-194)	162 (136-185)	150 (131-186)	0.082
LDL cholesterol (mg/dL)	92 (72-118)	93 (76-112)	90 (67-115)	0.524
HDL cholesterol (mg/dL)	50 (43-58)	49 (40-57)	46 (39-54)	0.006
Tryglicerides (mg/dL)	84 (62-120)	83 (61-107)	84 (61-112)	0.588
Oral anticoagulation, n	54 (12)	17 (7)	38 (30)	<0.001
Aspirin, n	27 (6)	17 (7)	30 (23)	<0.001
β-blockers, n	46 (10)	29 (13)	32 (25)	<0.001
ACE inhibitor, n	26 (6)	19 (8)	24 (19)	<0.001
ARBs, n	21 (5)	11 (5)	8 (6)	0.786
CCB, n	20 (4)	30 (13)	4 (3)	0.108
Diuretics, n	41 (9)	20 (9)	41 (32)	<0.001
Anti-aldosterone, n	12 (3)	11 (5)	34 (27)	<0.001
Statins, n	39 (8)	13 (6)	7 (5)	0.284
Myocardial infarction, n	2 (0.4)	1 (0.4)	0 (0)	0.716
Arterial thrombosis, n	16 (3)	5 (2)	6 (5)	0.444

Note: The data are expressed as median and quartiles (25;75) and as number and percentage. Categorical variables are evaluated by the Pearson chi-square and Kruskal-Wallis non-parametric test was used to determine whether the medians of two or more groups were different.
Abbreviations: ACE inhibitor, angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blockers; β-blockers, beta-adrenoceptor blocking agents; BMI, body mass index; CCB, calcium channel blockers; CHD, congenital heart disease; n, number of patients.

factors for arterial thrombosis. However, when all these variables were included in the analysis (confounder variables) the only one that reached statistical significance (adjusted OR) was age [OR 1.04 (1.01-1.09), $p < 0.01$].

4 | DISCUSSION

Advances in surgical and clinical management of CHD have allowed patients to survive into adulthood and therefore to the development of atherosclerotic disease. Manifestations of cardiovascular disease include myocardial infarction, stroke, transient ischaemic attacks and peripheral vascular disease. In adults, cardiovascular risk factors reinforce each other in their effect on cardiovascular events. However, information is scant on the relationship between cardiovascular risk factors and acute thrombotic events. In this context, Billett et al[9] found that adults with CHD were more likely to have arterial hypertension and diabetes mellitus than age-matched controls without CHD. Moons et al,[2] for their part, found that at least 80% of adults with CHD had at least one cardiovascular risk factor, with significantly higher rates of hypertension and obesity than in the general population. Similarly, we found more arterial hypertension and diabetes mellitus but less dyslipidemia and smoking habit among our CHD cohort when compared with our control population.

The higher incidence of hypertension among our CHD patients may be because of patients with aortic coarctation. In fact arterial hypertension is endemic in patients with coarctation of the aorta even if no residual coarctation exists. In our series we had 63

TABLE 5 Demographic, clinical and cardiovascular risk factors in CHD patients depending on the time of surgery and having or not cyanosis

Types of CHD (n)	n	Age (years)	Gender (male)	BMI	HTN	DM	DLP	Smoking	Glucose (mg/dL)	LDLc (mg/dL)
Time of surgery										
Non-operated	344	29 (23-42)	183 (53)	23 (20-26)	42 (12)	15 (4)	52 (15)	11 (3)	93 (87-99)	91 (70-114)
Operated on in childhood	381	30 (22-38)	221 (58)	23 (20-27)	40 (10)	15 (4)	49 (13)	17 (4)	93 (87-99)	92 (72-115)
Operated on in adulthood	29	48 (39-60)	19 (65)	24 (23-28)	11 (38)	2 (7)	6 (21)	2 (7)	101 (94-106)	91 (76-107)
Percutaneous treatment	64	29 (20-43)	37 (58)	20 (21-27)	8 (12)	4 (6)	10 (16)	5 (8)	93 (88-100)	96 (72-115)
p value		<0.001	0.436	0.558	<0.001	0.601	0.596	0.675	0.020	0.680
Cyanosis										
Non-cyanotic CHD	765	30 (22-41)	431 (56)	23 (20-26)	97 (13)	32 (5)	110 (16)	35 (5)	94 (88-100)	92 (72-115)
Cyanotic CHD	53	37 (30-50)	29 (55)	22 (19-26)	4 (8)	4 (8)	7 (13)	0 (0)	90 (83-97)	90 (67-113)
p value		0.001	0.810	0.117	0.266	0.382	0.814	0.144	0.011	0.487

Note: The data are expressed as median and quartiles (25;75) and as number and percentage. Categorical variables are evaluated by the Pearson chi-square test, continuous data without normal distribution by Mann-Whitney test and Kruskal-Wallis non-parametric test was used to determine whether the medians of two or more groups were different.
Abbreviations: BMI, body mass index; CHD, congenital heart disease; DLP, dyslipidemia; DM, diabetes mellitus; HTN, systemic arterial hypertension; n, number of patients; Smoking, active smoker.

patients with aortic coarctation (8% of the patients in our CHD series) of whom 18 (29%) had arterial hypertension. The aetiology of such high rates of baseline hypertension remains unclear but may be because of dysfunction of the normal control mechanisms regulating blood pressure during growth and development.[10,11]

In relation to diabetes, we found a higher incidence of diabetes mellitus in our CHD patients when compared with the control group and with data obtained from a random sampling population of the same geographical area.[12] Similarly, Moons et al[2] found twice as many diabetic CHD patients in their series (0.8% CHD group vs 0.4% in the control population) although without reaching statistical significance. Also, Bauer et al[13] found a high incidence of diabetic CHD patients (10.6%) in their series although there was no comparison with a control population being their patients older than ours (37.2 ± 17.4% years old). Similarly, Häcker et al[14] found 4% of diabetic patients in their series of CHD patients (43.9 ± 9.9 years old) with a high percentage of arterial hypertension. Altered insulin sensitivity and disordered glucose metabolism may be behind the high incidence of diabetes in CHD patients.

In relation to dyslipidemia, our CHD patients had lower total, LDL and HDL cholesterol than patients in the control group what is consistent with previously published data.[15] Similarly, the number of smoking patients was lower than in other European countries[9,14,16]

TABLE 6 Demographic and cardiovascular risk factors in CHD patients with/without thrombosis

	Arterial thrombosis		
	No	Yes	*p* value
n	791 (97)	27 (3)	
Age (years)	32 (23-41)	51 (40-55)	<0.001
Sex (male), n	445 (56)	15 (58)	0.085
Arterial hypertension, n	94 (12)	7 (30)	0.031
Diabetes mellitus, n	39 (5)	4 (15)	0.024
Dyslipidemia, n	106 (13)	11 (41)	<0.001
Smoking, n	32 (4)	3 (11)	0.001

Note: The data are expressed as median and quartiles (25;75) and as number and percentage.
Abbreviations: CHD, congenital heart disease, n: number of patients

TABLE 7 Results of the binary logistic regression analyses of congenital heart disease patients with and without arterial thrombosis

Covariates	OR (crude) (95% CI)	OR (adjusted) (95% CI)
Age (years)	1.05 (1.03-1.07)	1.04 (1.01-1.09)
Arterial hypertension	2.58 (1.06-6.26)	0.68 (0.22-2.10)
Diabetes mellitus	3.35 (1.10-10.17)	1.69 (0.49-5.89)
Dyslipidemia	4.44 (2.00-9.83)	1.95 (0.80-4.76)
Smoking	2.83 (1.55-5.19)	1.78 (0.92-3.44)

Abbreviations: OR: odds ratio, CI: confidence interval.

and similar to what is found in the United States.[17] This low number of smoking patients may be in relation to the awareness of the need for healthy habits.

The prevalence of coronary heart disease in adults with CHD has been variably reported in the literature depending on the study cohort. Afilalo et al[18] in a geriatric adult CHD cohort documented a 7% prevalence of myocardial infarction which was higher than that of the general population (5%). Along the same lines Giannakoulas et al[19] reported 9.2% of significant coronary stenosis among CHD patients (51 ± 13 years old) that underwent cardiac catheterisation for reasons other than coronary artery disease. However, no patient with cyanosis or age <40 years had significant coronary artery disease in their series. Also, Yalonetsky et al[20] in a cohort of CHD patients identified coronary artery disease in 1% of them what is above 0.4% found in our series. However, the age of their patients at diagnosis was 56 ± 13 years old and 38% of them were asymptomatic which would be consistent with our results.

Adult CHD have also a higher risk of thromboembolism not only from their complex physiology and anatomy but also from substrates such as valvular heart disease, atrial arrhythmias, cyanosis, and ventricular dysfunction, resulting in significant morbidity and mortality.[21,22] This is the reason why we found many more neurological events among CHD patients compared with the normal population. However, we did not find differences according to CHD complexity probably because patients with great complexity used more prophylactic anticoagulation than patients with simple heart defects.

In relation to cyanosis it is argued that endothelial dysfunction, as a result of chronic hypoxia and hyperviscosity, may induce a hypercoagulable tendency with increased risks of thrombosis[23,24] and atherosclerosis. Although none of our cyanotic CHD patients had myocardial infarction as reported by other authors,[19] we did find a significant higher incidence of thrombotic events probably in relation to cardiac complexity.

With respect to medical treatment CHD patients had a higher incidence of oral anticoagulation, antiaggregation, beta-blockers, ACE inhibitors, diuretics and anti-aldosterone therapy than the general population because of the fact that many CHD patients have sequelae and complications of their cardiac defects which requires specific cardiological treatment.[25] On the other hand, there were no significant differences in relation to ARBs and CCAs since they are used routinely in the treatment of arterial hypertension in the general population.[26] In relation to the use of statins we found no significant differences between control population and the CHD patients.

In conclusion, CHD patients are significantly more hypertensive and diabetic but less dyslipidemic and smokers than the control population. The low incidence of cardiovascular risk factors and the young age of our patients would explain, at least in part, the low incidence of coronary events both in congenital patients and in the general population. However, special attention should be paid to older patients and patients with aortic coarctation. Also, we should monitor cardioembolic risk factors in CHD patients to start anticoagulant therapy as soon as necessary.

Efrén Martínez-Quintana, Juan Lizandro Rodríguez-Hernández and Fayna Rodríguez-González have contributed to concept/design, data analysis/interpretation, drafting article, critical revision of article and approval and Marta Riaño-Ruiz, Carla Fraguela-Medina, Angela Girolimetti, Sara Jiménez-Rodríguez have participated in data collection, critical revision and final approval.

DISCLOSURES

This manuscript has not been submitted for publication nor has it been published in whole or in part elsewhere. We attest to the fact that all authors listed on the title page have contributed significantly to the work, have read the manuscript, attest to the validity and legitimacy of the data and its interpretation. The authors of this manuscript have also certified that they comply with the Principles of Ethical Publishing. No author has conflict of interest.

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REFERENCES

1. Vartiainen E, Laatikainen T, Peltonen M, et al. Thirty-five-year trends in cardiovascular risk factors in Finland. *Int J Epidemiol*. 2010;39(2):504-518.
2. Moons P, Deyk KV, Dedroog D, Troost E, Budts W. Prevalence of cardiovascular risk factors in adults with congenital heart disease. *Eur J Cardiovasc Prev Rehabil*. 2006;13:612-616.
3. Lui GK, Fernandes S, McElhinney DB. Management of cardiovascular risk factors in adults with congenital heart disease. *J Am Heart Assoc*. 2014;3(6):e001076.
4. Care of the Adult with Congenital Heart Disease. Presented at the 32nd Bethesda Conference, Bethesda, Maryland, October 2–3, 2000. *J Am Coll Cardiol*. 2001;37:1161-1198.
5. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *J Am Coll Cardiol*. 2015;66(4):403-469.
6. Williams B, Mancia G, Spiering W, et al. ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39(33):3021.
7. Rydén L, Grant PJ, Anker SD, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J*. 2013;34(39):3035-3087.
8. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of clinical endocrinologists and american endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr Pract*. 2017;23(Suppl 2):1-87.
9. Billett J, Cowie MR, Gatzoulis MA, Vonder Muhll IF, Majeed A. Comorbidity, healthcare utilisation and process of care measures in patients with congenital heart disease in the UK: cross-sectional,

population-based study with case-control analysis. *Heart*. 2008;94:1194-1199.
10. Kenny D, Polson JW, Martin RP, Paton J, Wolf AR. Hypertension and coarctation of the aorta: an inevitable consequence ofdevelopmental pathophysiology. *Hypertens Res*. 2011;34(5):543-547.
11. Rinnström D, Dellborg M, Thilén U, et al. Hypertension in adults with repaired coarctation of the aorta. *Am Heart J*. 2016;181:10-15.
12. Cabrera de León A, Rodríguez Pérez Mdel C, Almeida González D, et al. Presentation of the "CDC de Canarias" cohort: objectives, design and preliminary results. *Rev Esp Salud Publica*. 2008;82(5):519-534.
13. Bauer U, Körten MA, Diller GP, et al. Cardiovascular risk factors in adults with congenital heart defects - Recognised but not treated? An analysis of the German National Register for Congenital Heart Defects. *Int J Cardiol*. 2019;277:79-84.
14. Häcker AL, Oberhoffer R, Hager A, Ewert P, Müller J. Age-related cardiovascular risk in adult patients with congenital heart disease. *Int J Cardiol*. 2019;277:90-96.
15. Martínez-Quintana E, Rodríguez-González F, Nieto-Lago V, et al. Serum glucose and lipid levels in adult congenital heart disease patients. *Metabolism*. 2010;59(11):1642-1648.
16. Engelfriet PM, Drenthen W, Pieper PG, et al. Smoking and its effects on mortality in adults with congenital heart disease. *Int J Cardiol*. 2008;127(1):93-97.
17. Lui GK, Rogers IS, Ding VY, et al. Risk estimates for atherosclerotic cardiovascular disease in adults with congenital heart disease. *Am J Cardiol*. 2017;119(1):112-118.
18. Afilalo J, Therrien J, Pilote L, Ionescu-Ittu R, Martucci G, Marelli AJ. Geriatric congenital heart disease: burden of disease and predictors of mortality. *J Am Coll Cardiol*. 2011;58:1509-1515.
19. Giannakoulas G, Dimopoulos K, Engel R, et al. Burden of coronary artery disease in adults with congenital heart disease and its relation to congenital and traditional heart risk factors. *Am J Cardiol*. 2009;103(10):1445-1450.
20. Yalonetsky S, Horlick EM, Osten MD, Benson LN, Oechslin EN, Silversides CK. Clinical characteristics of coronary artery disease in adults with congenital heart defects. *Int J Cardiol*. 2013;164(2):217-220.
21. Wan D, Tsui C, Kiess M, Grewal J, Krahn AD, Chakrabarti S. Anticoagulation for thromboembolic risk reduction in adults with congenital heart disease. *Can J Cardiol*. 2017;33(12):1597-1603.
22. Karsenty C, Zhao A, Marijon E, Ladouceur M. Risk of thromboembolic complications in adult congenital heart disease: a literature review. *Arch Cardiovasc Dis*. 2018;111(10):613-620.
23. Binotto MA, Maeda NY, Lopes AA. Evidence of endothelial dysfunction in patients with functionally univentricular physiology before completion of the Fontan operation. *Cardiol Young*. 2005;15(1):26-30.
24. Cordina RL, Celermajer DS. Chronic cyanosis and vascular function: implications for patients with cyanotic congenital heart disease. *Cardiol Young*. 2010;20(3):242-253.
25. Oliver Ruiz JM. Congenital heart disease in adults: residua, sequelae, and complications of cardiac defects repaired at an early age. *Rev Esp Cardiol*. 2003;56(1):73-88.
26. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens (Greenwich)*. 2014;16(1):14-26.

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