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## Gender and Outcome in Adult Congenital Heart Disease

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**Background**—Gender differences in prognosis have frequently been reported in cardiovascular disease but less so in congenital heart disease. We investigated whether gender is associated with outcome in adult patients with congenital heart disease.

**Methods and Results**—From the CONgenital CORvitia (CONCOR) national registry for adults with congenital heart disease, 7414 patients were identified. All outcomes before entry into the registry and during subsequent follow-up were recorded, and differences between men and women were analyzed with the underlying congenital heart defect taken into account. Median age at the end of follow-up was 35 years (range, 17 to 91 years); 49.8% were female. No gender difference in mortality was found. Women had a 33% higher risk of pulmonary hypertension (odds ratio [OR]=1.33; 95% CI, 1.07 to 1.65;  $P=0.01$ ), a 33% lower risk of aortic outcomes (OR=0.67; 95% CI, 0.50 to 0.90;  $P=0.007$ ), a 47% lower risk of endocarditis (OR=0.53; 95% CI, 0.40 to 0.70;  $P<0.001$ ), and a 55% lower risk of an implantable cardioverter-defibrillator (OR=0.45; 95% CI, 0.26 to 0.80;  $P=0.006$ ). Furthermore, the risk of arrhythmias appeared to be lower in women (OR=0.88; 95% CI, 0.77 to 1.02;  $P=0.08$ ).

**Conclusions**—The risk of several major cardiac outcomes in adult patients with congenital heart disease appears to vary by gender. (*Circulation*. 2008;118:26-32.)

**Key Words:** complications ■ epidemiology ■ heart defects, congenital ■ sex

More than 95% of children with congenital heart defects now reach adulthood,<sup>1</sup> and the number of adults with congenital heart disease is estimated to be at least 1.2 million in Europe alone.<sup>2</sup> Despite major developments in diagnostic methods and treatment of congenital heart disease, cure is rarely achieved. A vast proportion of patients experience mild to life-threatening complications, for which lifelong medical surveillance is required.<sup>3,4</sup> Abundant evidence exists regarding gender differences in the incidence of congenital heart defects at birth,<sup>5,6</sup> but the impact of gender on the prognosis in adult congenital heart disease is unclear.<sup>7</sup>

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We used the Dutch nationwide CONgenital CORvitia (CONCOR) registry for adults with congenital heart disease to investigate whether there is an association between gender and outcome in adult patients with congenital heart disease.

## Methods

### Study Subjects

The CONCOR national registry database has been described in detail.<sup>8</sup> Briefly, CONCOR aims to facilitate research on the etiology of congenital heart disease and its outcome. Between January 2002 and January 2008, >8600 patients with congenital heart disease aged  $\geq 16$  years have been included in the registry. Every year, nearly 1500 patients are added. Clinical data such as main diagnosis, other diagnoses, clinical events and procedures, and patient and family history are obtained from each patient by research nurses. Patients are contacted through their treating cardiologist or advertisements in local media. Diagnoses, procedures, and clinical events are classified with the use of the European Pediatric Cardiac Code Short List coding scheme.<sup>9</sup> In case of multiple diagnoses in 1 patient, a prespecified hierarchical scheme founded on consensus-based classification of severity of diagnoses<sup>10</sup> is used, by means of which the most complex diagnosis or the diagnosis that is expected to have the most serious sequel in the future is established as the main diagnosis. For example, in a patient with an aortic coarctation and a bicuspid aortic valve or with an aortic coarctation and atrial septal defect, aortic coarctation is considered the main diagnosis. After entry into the database, data on major cardiac events are systematically

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recorded from medical letters on patients' condition written by their treating cardiologist to the family practitioner and entered into the database by 3 independent, permanently employed research nurses. This recording is done in a systematic fashion. A regular quality control is performed on the registry by the research nurses. Currently, 94 hospitals are participating, including all 8 tertiary referral centers from which  $\approx 6000$  patients (70%) originate.

From the CONCOR database, the following patient characteristics were obtained: gender, date of birth, age at the time of data extraction (January 3, 2007), and the main congenital heart diagnosis. Moreover, for each patient the occurrence of outcomes before entry into the registry and during subsequent follow-up (median, 2.7 years from registration [2.8 years in men, 2.5 years in women]) was recorded. The following outcomes were considered clinically important in adult congenital heart disease<sup>1</sup>: all-cause death and age at death, pulmonary hypertension (both pulmonary arterial and venous hypertension), systemic hypertension, aortic outcomes (aneurysm, dissection, and aortic surgery), cerebrovascular accident or transient ischemic attack, endocarditis, pacemaker implant, implantable cardioverter-defibrillator (ICD) implant, and supraventricular and ventricular arrhythmias. Supraventricular arrhythmias comprised the following rhythm disturbances: sick sinus, flutter, fibrillation, and all other forms of tachycardia, except premature atrial complexes. Rhythm disturbances at the level of atrioventricular junction include nodal tachycardias and reentry tachycardias, except for Wolff-Parkinson-White and accessory pathways. Ventricular arrhythmias consisted of flutter, fibrillation, sustained and nonsustained tachycardias, and cardiac arrest but did not include premature ventricular complexes. Aneurysm was defined as dilatation of the aortic root and ascending aorta  $>3.7$  cm and dilatation of the descending aorta  $>3.0$  cm. Indications for aortic surgery were either elective (diameter of the aorta of 5.5 cm; diameter of 5.0 cm if there was a family history of aortic dissection, when valve-sparing surgery was planned, or in case of rapid aneurysm growth) or acute surgery because of an aortic rupture or dissection. Systolic pulmonary pressure was estimated on the basis of echocardiographic evaluation (tricuspid regurgitation jet velocity measurements) because 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  $>40$  mm Hg.<sup>11</sup> Pulmonary hypertension was considered to be Eisenmenger syndrome after shunt reversal of the original systemic-to-pulmonary shunt, accompanied by cyanosis.

## Data Analysis

Outcome frequencies were calculated by congenital heart defect and by gender.

To examine the association between gender and outcome with adjustment for underlying heart defect, each defect occurring  $>5$  times within an outcome (or, if the total frequency of an outcome surpassed 200, each defect occurring  $>10$  times) was considered in both main and subgroup analyses. The rationale for this selection was the need to find a balance between the inclusion of many types of congenital heart disease to adjust for within each outcome and optimal statistical power. Choosing an occurrence of  $<5$  dramatically decreased statistical power and led to wide confidence intervals (CIs) for the individual diagnosis dummy variables, whereas a threshold well  $>5$  rendered fewer defects to adjust for and thus less accuracy. For outcomes  $>200$ , however, a threshold of 5 yielded a surplus of types of congenital heart disease, and therefore the number of 10 was chosen. Each congenital heart defect selected for a particular outcome was included in the analyses of that outcome as an individual dummy category. All types of congenital heart disease underlying the outcome  $\leq 5$  times were taken together as 1 reference category in logistic regression analyses. Thus, for every outcome, a specific model was created with different dummy variables. For example, the model for aortic outcomes comprised dummy variables of the following types of congenital heart disease: aortic coarctation, aortic stenosis, bicuspid aortic valve, Marfan syndrome, ventricular septal defect, and a reference category.

On the basis of current medical literature, we hypothesized congenital heart disease to be a confounder in the association of gender and outcome, as opposed to an effect modifier. Because the data reflected the cumulative incidence of outcomes registered at adulthood, we used logistic regression analysis. Logistic regression was used with each outcome (yes/no) as outcome and gender as predictor. All analyses were adjusted for age and subsequently adjusted for type of congenital heart defect. For pulmonary hypertension, aortic outcomes, and arrhythmias, the data allowed for clinically meaningful subgroup analyses. In patients with pulmonary hypertension, diagnoses predisposing to pulmonary arterial hypertension<sup>11</sup> were distinguished from other diagnoses, which were hence considered to bear the risk of pulmonary venous hypertension. Aortic outcomes were classified as aortic aneurysm, dissection, and aortic surgery. Subjects with multiple outcomes appear in  $>1$  analysis. Age at death and age at closure were compared for men and women with an independent samples *t* test for comparison of means. Analyses on age at closure were performed for atrial septal defect and ventricular septal defect, separately. Analyses on atrial and ventricular septal defect closure were performed with a Pearson  $\chi^2$  test for comparison of proportions. Included in these analyses were subjects primarily diagnosed with an atrial septal defect or ventricular septal defect, thus excluding those with a concomitant ventricular septal defect or atrial septal defect, respectively, because a separate analysis on closure was performed within both defects. Results were expressed as odds ratios (ORs) and 95% CIs, and 2-sided probability values were calculated for effect estimates. Analyses were performed with SPSS version 14.0 (SPSS Inc, Chicago, Ill).

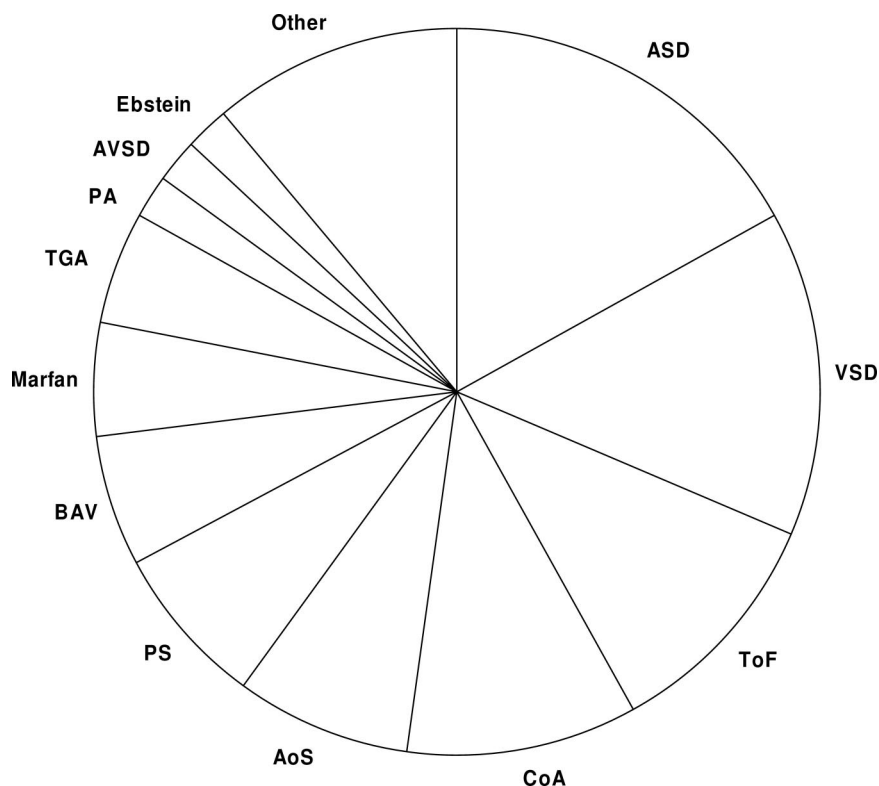
The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

## Results

Of 7414 subjects registered at the time of analysis, 3724 (50.2%) were male and 3690 (49.8%) were female. Median age of men was 34.2 years (range, 17.0 to 91.4) and of women was 36.0 years (range, 16.6 to 91.2). Patients with transposition of the great arteries, pulmonary atresia, atrioventricular septal defect, and tricuspid atresia had a median age  $>30$  years. Patients with atrial septal defect, Ebstein's anomaly, patent arterial duct, and mitral valvar prolapse had a median age  $>40$  years. Mean age at closure of atrial septal defect was higher in women (24.6 years) than in men (22.2 years), but this difference did not reach statistical significance ( $P=0.09$ ).

Figure 1 illustrates the distribution of diagnoses. Atrial septal defect, ventricular septal defect, tetralogy of Fallot, aortic coarctation, and aortic stenosis collectively accounted for 60% of all diagnoses.

The Table shows the absolute numbers of congenital heart defects and the relative frequencies among women. Patent arterial duct, atrial septal defect, and pulmonary atresia occurred predominantly in women, whereas aortic stenosis, bicuspid aortic valve, and transposition of the great arteries were more common in men. Closure of atrial septal defects occurred equally often in men and women ( $P=0.42$ ); the relative proportions of closure in male and female patients with an atrial septal defect were 73.4% and 71.2%, respectively. However, closure of ventricular septal defects was more common in men ( $P=0.04$ ); the relative proportions of closure in men and women with a ventricular septal defect were 39.6% and 33.4%, respectively. Additionally, the Table displays the frequency of outcomes by type of congenital heart defect. Among 161 deceased patients, 12 deceased patients had Eisenmenger syndrome, 7 of whom were women.



**Figure 1.** Proportional distribution of main diagnoses among study subjects ( $n=7414$ ). ASD indicates atrial septal defect (17%); VSD, ventricular septal defect (14%); ToF, tetralogy of Fallot (11%); CoA, aortic coarctation (10%); AoS, aortic stenosis (8%); PS, pulmonary stenosis (7%); BAV, bicuspid aortic valve (6%); Marfan, Marfan syndrome (5%); TGA, transposition of the great arteries (5%); PA, pulmonary atresia (2%); AVSD, atrioventricular septal defect (2%); Ebstein, Ebstein's anomaly (2%); and Other, other congenital heart defects (11%).

Figure 2 shows the percentages of men and women with each outcome. Pulmonary hypertension appears to be more frequent in women, with aortic outcomes, endocarditis, and ICD implant more common in men.

Figure 3 shows the ORs of outcomes for women after adjustment for age and after additional adjustment for underlying congenital heart defects. Although absolute mortality risks were not significantly different, median age at death in women was 48 years, whereas median age at death in men was 43 years ( $P=0.04$ ). Women had a 33% higher risk of pulmonary hypertension, a 33% lower risk of aortic outcomes, a 47% lower risk of endocarditis, and a 55% lower risk of ICD implant (all  $P<0.05$ ). In addition, women had a borderline significant 12% lower risk of arrhythmias. Adjustment for underlying congenital heart defects did not materially change the results.

Figure 4 shows analyses in subsets of other outcomes after adjustment for age and adjustment for underlying congenital heart defects. Among patients with pulmonary hypertension, there were 360 patients (91%) with defects predisposing to pulmonary arterial hypertension and 36 patients (9%) with defects predisposing to pulmonary venous hypertension. Among those predisposing to pulmonary arterial hypertension, women had a borderline significant 25% higher risk of pulmonary arterial hypertension compared with men. Among Eisenmenger patients ( $n=95$ ; not in the Table), gender distribution was approximately equal (54% female;  $P=0.20$ ). In aortic outcomes, aneurysms developed in 98 patients (42%), dissections occurred in 51 patients (22%), and aortic surgery was performed in 156 patients (68%). Women had a 30% lower probability of aortic surgery. Moreover, 1125 patients (93%) suffered from supraventricular arrhythmias and 163 patients (13%) from ventricular

arrhythmias. Women had a borderline significant 12% lower risk of supraventricular arrhythmias.

## Discussion

The present study demonstrates a strong association between gender and the risk of several outcomes in adult congenital heart disease. Women were at higher risk for pulmonary hypertension and at lower risk for aortic outcomes, endocarditis, and ICD implant.

Certain limitations of our study need to be addressed. Because most patients originate from tertiary referral centers, patients with complex and thus complicated congenital heart disease may be overrepresented. However, we have no reason to suspect that the association between gender and outcomes would differ between patients with mild and complex congenital heart disease. Moreover, the association of gender with outcomes may be a reflection of gender-linked patient characteristics not included in the CONCOR database, such as lifestyle factors or comorbid conditions. Although we cannot exclude the possibility that some of these factors play a role in our results, this would not explain the different directions of our findings. Finally, the CONCOR database is not composed of patients with very mild congenital heart disease or patients with critical congenital heart disease who died before enrollment. Particular strengths of our study are the large number of patients and the rigorous and uniform methods of recording data.

Gender disparities have been documented extensively in various fields of cardiovascular disease such as ischemic heart disease, heart failure, and stroke. Women have a distinctive clinical manifestation and outcome and appear to be underinvestigated, underdiagnosed, and undertreated.<sup>12</sup>

**Table. Frequency of Several Major Outcomes in Underlying Congenital Heart Defects in All Patients (n=7414)**

Defect	Frequency		Outcome								
	Total, n	Female, %	Death	Pulmonary Hypertension	Systemic Hypertension	Aortic Outcomes	CVA/TIA	Endocarditis	Pacemaker	ICD	Arrhythmia
Atrial septal defect	1267	62	28	93	70	3	68	10	81	6	344
Ventricular septal defect	1061	55	10	87	45	15	16	54	38	6	89
Tetralogy of Fallot	791	44	21	21	13	5	16	29	49	27	173
Aortic coarctation	756	40	7	26	171	38	13	15	10	1	45
Aortic stenosis	571	35	10	6	32	30	10	21	18	1	47
Pulmonary stenosis	549	58	5	7	23	1	9	2	7	0	39
Bicuspid aortic valve	419	34	5	5	39	28	11	29	13	2	33
Marfan syndrome	380	50	6	0	18	96	8	7	2	0	24
TGA	378	34	8	25	1	0	9	10	66	8	127
Pulmonary atresia	136	60	9	13	1	2	3	14	3	0	17
AVSD	125	59	6	50	0	0	0	7	5	1	12
Ebstein's anomaly	125	56	6	3	9	0	5	2	8	1	52
UVH/DILV	99	45	10	15	2	0	7	6	16	0	44
cc-TGA	96	38	6	4	1	0	1	7	27	0	35
Patent arterial duct	94	84	2	4	9	1	2	0	2	0	14
Mitral valvar prolapse	71	51	2	0	2	1	3	4	2	2	15
Tricuspid atresia	65	49	9	2	0	0	4	4	9	0	32
Other defects	431	55	11	35	18	11	14	13	28	5	70
All defects	7414	50	161	396	454	231	199	234	384	60	1212

CVA indicates cerebrovascular accident; TIA, transient ischemic attack; TGA, transposition of the great arteries; AVSD, atrioventricular septal defect; UVH, univentricular heart; DILV, double-inlet left ventricle; and cc-TGA, congenitally corrected transposition of the great arteries. Other defects comprise those defects with a total frequency below n=65. Subjects with multiple outcomes appear in >1 column.

However, evidence on gender differences in adult congenital heart disease is scarce.

Several factors may account for the observed gender differences in cardiovascular disease. One aspect likely to play a role is the biological distinction between men and women. Women have smaller arteries and more frequently develop endothelial and smooth cell dysfunction.<sup>13</sup> Female response to pharmaceutical therapy may differ because of endogenous hormone levels, a lower body weight, a higher proportion of body fat, and a lower glomerular filtration rate.<sup>14,15</sup> Another potential influence is the gender difference in clinical manifestation of cardiovascular disease because common symptoms are often less pronounced in women. Additionally, women have been reported to be more willing to undergo certain procedures.<sup>16</sup> However, this was shown not to influence gender disparities in use of cardiac procedures.<sup>16,17</sup> A third modifying factor is the physician's perception that women are at lower risk for cardiovascular complications than men, leading to reduced attention to early signs and symptoms of complications in women. As a result, women with cardiovascular disease may be treated less optimally, a phenomenon known as gender bias or the Yentl syndrome.<sup>18</sup> Studies addressing the impact of the physician's perception have yielded conflicting results.<sup>19,20</sup> Finally, the lack of gender-specific thresholds of diagnostic procedures in cardiovascular disease may render distorted detection rates of cardiac complications in either gender.

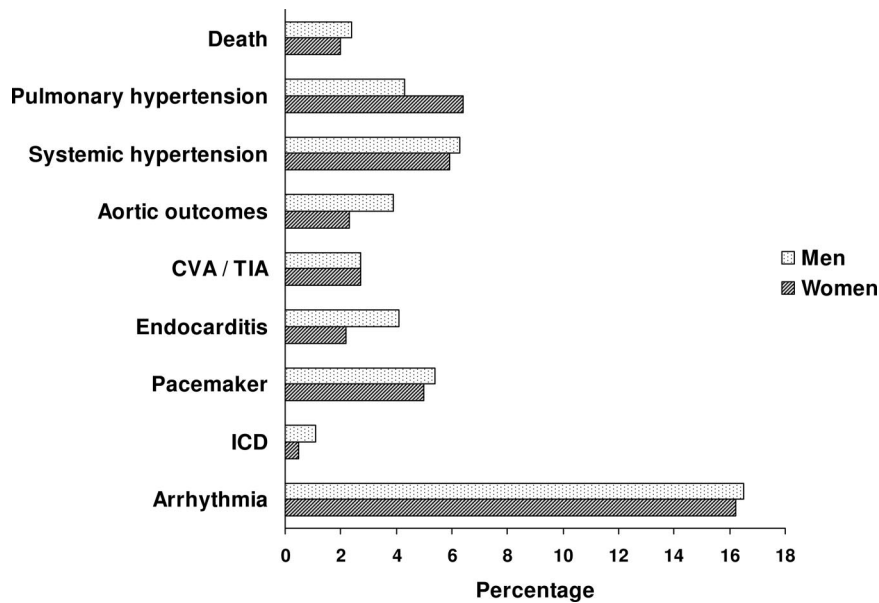
In congenital heart disease, numerous defects exhibit an association with gender at birth. Defects mainly involving the inflow tract of the heart such as atrial septal defect and

Ebstein's anomaly prevail in females, whereas outflow tract defects such as aortic stenosis and transposition of the great arteries predominate in males.<sup>5,6</sup> In the CONCOR database, the gender distribution of adults with congenital heart disease resembles the gender distribution at birth. This finding, which has been reported previously,<sup>7,21</sup> supports the hypothesis that overall mortality during childhood is not influenced by gender, a phase not covered by CONCOR.

In our study, no gender difference was found in mortality during the period of follow-up. However, a higher mortality in men with congenital heart disease has been reported.<sup>22</sup> In children, sudden cardiac death is more frequent in boys,<sup>23</sup> yet mortality ensuing surgery for congenital heart disease is more common in girls.<sup>24</sup> In coronary heart disease, evidence on gender disparities in mortality after revascularization is conflicting.<sup>25-27</sup> Additionally, female mortality has been reported to be higher after valvular surgery<sup>28</sup> but lower in heart failure.<sup>29</sup>

We found women to be at higher risk for pulmonary arterial hypertension. This agrees with previous findings<sup>7</sup> and may reflect hormonal differences in general and the burden of pregnancy in particular because this potentially has deleterious effects in congenital heart disease.<sup>7,30</sup> We found no difference in gender distribution of Eisenmenger syndrome, as in the Euro Heart Survey,<sup>31</sup> suggesting equal progression of pulmonary arterial hypertension.

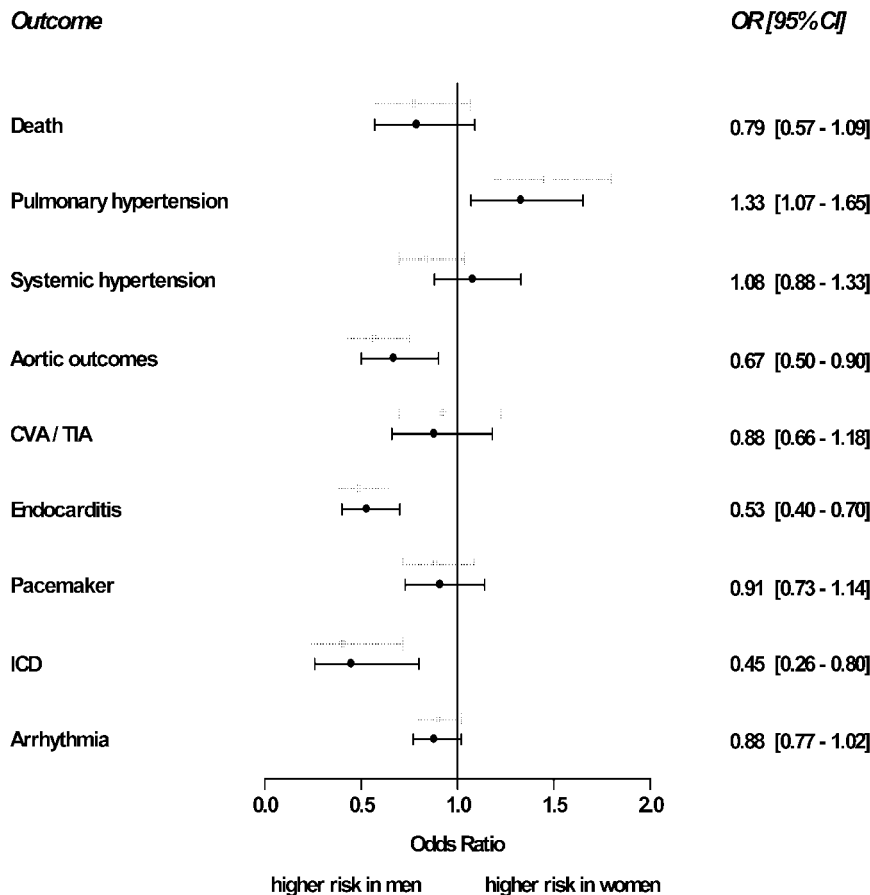
In our study, women were at lower risk for aortic outcomes, which was largely due to lower rates of aortic surgery. Because the female aorta is significantly smaller<sup>32</sup> and criteria for elective aortic surgery are not gender specific, men are



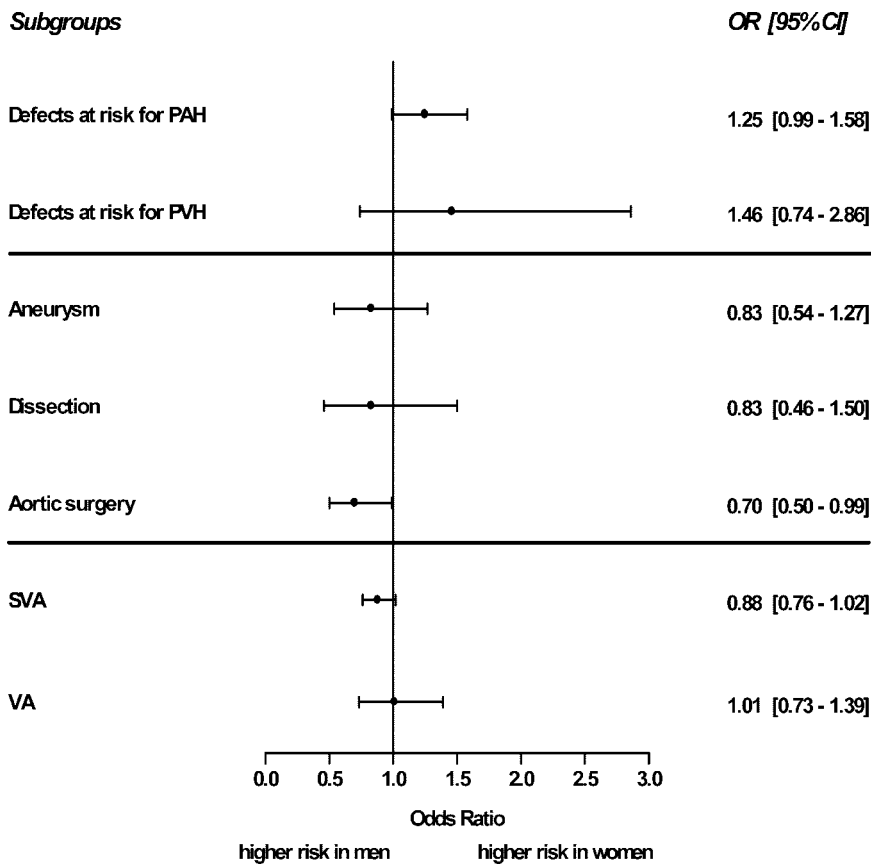
**Figure 2.** Percentages of outcomes in men (n=3724) and women (n=3690). Percentages are not adjusted for age and underlying congenital heart defects. CVA indicates cerebrovascular accident; TIA, transient ischemic attack.

expected to reach the threshold for elective surgery earlier than women. In addition, in atherosclerotic disease, men are more likely to undergo aortic surgery,<sup>33</sup> although fatal ruptures are more common in women.<sup>34</sup> Worse surgical outcome and higher mortality in women have also been observed in acute dissection.<sup>35</sup> These findings may suggest inadequate diagnosis and treatment of aortic aneurysms in women.

Women were at lower risk for endocarditis, similar to reports on adults without congenital heart disease.<sup>36</sup> This may reflect differences in lifestyle factors such as poor oral hygiene<sup>37</sup> and intravenous drug abuse,<sup>38</sup> both of which are more common in men. However, gender differences in knowledge of endocarditis prevention such as antibiotic prophylaxis or need for optimal dental and skin care have not been reported.<sup>39</sup> Furthermore, the



**Figure 3.** ORs of outcomes in women compared with men. The gray lines represent ORs with 95% CIs adjusted for age only. The black lines represent ORs with 95% CIs additionally adjusted for underlying congenital heart defects. The numbers adjacent to the figure correspond to the black lines. CVA indicates cerebrovascular accident; TIA, transient ischemic attack.



**Figure 4.** ORs in subgroups of pulmonary hypertension, aortic outcomes, and arrhythmias in women compared with men. All ORs have been adjusted for age and underlying congenital heart defects. PAH indicates pulmonary arterial hypertension; PVH, pulmonary venous hypertension; SVA, supraventricular arrhythmia; and VA, ventricular arrhythmia.

gender difference in risk for endocarditis might have been influenced by gender differences in closure of ventricular septal defects, a diagnosis frequently underlying endocarditis. If so, however, we would have expected the risk for endocarditis to be lower in men because ventricular septal defects were closed more often in men compared with women.

We found a lower risk of ICD implant and a slightly lower risk of (mainly supraventricular) arrhythmias in women. No gender difference was found in ventricular arrhythmias, a major indication for ICD implant. The lower ICD implant rate in women may result from gender bias, which has been reported previously in coronary heart disease.<sup>40</sup> Of note, gender differences in events after ICD implant have not been described,<sup>40,41</sup> implying an equal benefit from ICD implant.

The current literature shows a considerable impact of gender on outcome within the scope of cardiovascular disease. Extending this evidence to congenital heart disease, we believe our results to be hypothesis generating on the role of gender. This should stimulate basic and clinical research to advance the knowledge on gender-specific issues.

In conclusion, the results of the present study support the view that the risk of several major cardiac outcomes in adult congenital heart disease appears to vary by gender.

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### Disclosures

None.

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### CLINICAL PERSPECTIVE

Gender differences in prognosis have frequently been reported in cardiovascular disease but less so in adult congenital heart disease. In the CONgenital CORvita (CONCOR) national registry of adults with congenital heart disease (n=7414), we found that women had a 33% higher risk of pulmonary hypertension, a 33% lower risk of aortic outcomes, a 47% lower risk of endocarditis, and a 55% lower risk of an implantable cardioverter-defibrillator implant. These findings should stimulate basic and clinical research to advance the knowledge on gender-specific issues in adult congenital heart disease.