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Gender and Outcome in Adult Congenital Heart Disease

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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,1 and the number of adults with congenital heart disease is estimated to be at least 1.2 million in Europe alone.2 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.3,4 Abundant evidence exists regarding gender differences in the incidence of congenital heart defects at birth,5,6 but the impact of gender on the prognosis in adult congenital heart disease is unclear.7

Methods

Study Subjects

The CONCOR national registry database has been described in detail.8 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 ≥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.9 In case of multiple diagnoses in 1 patient, a prespecified hierarchical scheme founded on consensus-based classification of severity of diagnoses10 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 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).

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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 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 χ² 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 prolase 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 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.12
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. 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. 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. However, this was shown not to influence gender disparities in use of cardiac procedures.

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. In children, sudden cardiac death is more frequent in boys, yet mortality ensuing surgery for congenital heart disease is more common in girls. In coronary heart disease, evidence on gender disparities in mortality after revascularization is conflicting. Additionally, female mortality has been reported to be higher after valvular surgery but lower in heart failure.

We found women to be at higher risk for pulmonary arterial hypertension. This agrees with previous findings and may reflect hormonal differences in general and the burden of pregnancy in particular because this potentially has deleterious effects in congenital heart disease. We found no difference in gender distribution of Eisenmenger syndrome, as in the Euro Heart Survey, 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 and criteria for elective aortic surgery are not gender specific, men are

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

<table>
<thead>
<tr>
<th>Defect</th>
<th>Frequency</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total, n</td>
<td>Pulmonary Hypertension</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>1267</td>
<td>28</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>1061</td>
<td>10</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>791</td>
<td>21</td>
</tr>
<tr>
<td>Aortic coarctation</td>
<td>756</td>
<td>7</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>571</td>
<td>10</td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>549</td>
<td>5</td>
</tr>
<tr>
<td>Bicuspid aortic valve</td>
<td>419</td>
<td>5</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>380</td>
<td>6</td>
</tr>
<tr>
<td>TGA</td>
<td>378</td>
<td>8</td>
</tr>
<tr>
<td>Pulmonary atresia</td>
<td>136</td>
<td>9</td>
</tr>
<tr>
<td>AVSD</td>
<td>125</td>
<td>6</td>
</tr>
<tr>
<td>Ebstein’s anomaly</td>
<td>125</td>
<td>6</td>
</tr>
<tr>
<td>UVH/DILV</td>
<td>99</td>
<td>10</td>
</tr>
<tr>
<td>cc-TGA</td>
<td>96</td>
<td>6</td>
</tr>
<tr>
<td>Patent arterial duct</td>
<td>94</td>
<td>2</td>
</tr>
<tr>
<td>Mitral valvar prolapse</td>
<td>71</td>
<td>2</td>
</tr>
<tr>
<td>Tricuspid atresia</td>
<td>65</td>
<td>9</td>
</tr>
<tr>
<td>Other defects</td>
<td>431</td>
<td>11</td>
</tr>
<tr>
<td>All defects</td>
<td>7414</td>
<td>161</td>
</tr>
</tbody>
</table>

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.
expected to reach the threshold for elective surgery earlier than women. In addition, in atherosclerotic disease, men are more likely to undergo aortic surgery, although fatal ruptures are more common in women. Worse surgical outcome and higher mortality in women have also been observed in acute dissection. 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. This may reflect differences in lifestyle factors such as poor oral hygiene and intravenous drug abuse, 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. Furthermore, the
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. Of note, gender differences in events after ICD implant have not been described, 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.

References

CLINICAL PERSPECTIVE

Gender differences in prognosis have frequently been reported in cardiovascular disease but less so in adult congenital heart disease. In the CONGentil 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.