Improved Survival Among Patients With Eisenmenger Syndrome Receiving Advanced Therapy for Pulmonary Arterial Hypertension

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**Background**—Advanced therapy (AT) for pulmonary arterial hypertension in the context of congenital heart disease (Eisenmenger syndrome) improves pulmonary hemodynamics, functional class, and the 6-minute walk test. We examined the potential effect of AT on survival in this population.

**Methods and Results**—Data on all Eisenmenger patients attending our center over the past decade were collected. Survival rates were compared between patients on and off AT with the use of a modified version of the Cox model, which treats AT as a time-varying covariate. Baseline differences were adjusted for the use of propensity scores. A total of 229 patients (aged 34.5±12.6 years; 35.4% male) were included. The majority had complex anatomy, and 53.7% were in New York Heart Association class III at baseline assessment. Mean resting saturations were 84.3%. Sixty-eight patients (29.7%) either were on AT or had AT initiated during follow-up. During a median follow-up of 4.0 years, 52 patients died, only 2 of them while on AT. Patients on AT were at a significantly lower risk of death, both unadjusted and after adjustment for baseline clinical differences by propensity score regression adjustment (C statistic = 0.80; hazard ratio, 0.16; 95% confidence interval, 0.04 to 0.71; \( P = 0.015 \)) and propensity score matching (hazard ratio, 0.10; 95% confidence interval, 0.01 to 0.78; \( P = 0.028 \)).

**Conclusions**—AT for pulmonary arterial hypertension in a contemporary cohort of adults with Eisenmenger syndrome was associated with a lower risk of death. Survival benefits should be considered together with improved hemodynamics and functional class when decisions are made about AT in this population. (Circulation. 2010;121:20-25.)

**Key Words:** heart defects, congenital ■ hypertension, pulmonary ■ Eisenmenger Complex ■ vasodilator agents ■ survival

Approximately 10% of patients with congenital heart disease (CHD) develop pulmonary arterial hypertension (PAH), despite advances in diagnosis and therapy.1,2 A large intracardiac or extracardiac shunt, when not repaired, leads to progressive PAH with ultimate reversal of flow and cyanosis, the so-called Eisenmenger syndrome.3 PAH significantly affects rates of morbidity and mortality in these patients.4 Moreover, longstanding right-to-left shunting and associated cyanosis lead to multiorgan involvement and systemic complications.

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Management options for patients with Eisenmenger syndrome have been limited until recently to palliative measures or lung/heart-lung transplantation, the latter for a small, highly selected subgroup.5 Although conventional pharmacological treatment, including digitalis, diuretics, antiarrhythmics, anticoagulants, iron supplementation, and oxygen therapy, may be used empirically, it does not seem to alter survival rate.6,7

More recently, 3 classes of pulmonary vasodilators targeting the abnormal proliferation and contraction of the smooth muscle have emerged as advanced therapy (AT) for PAH: (1) prostanoids, (2) endothelin receptor antagonists, and (3) phosphodiesterase-5 inhibitors.8,9 After success in reducing exercise intolerance and symptoms in idiopathic PAH, AT was introduced to patients with PAH secondary to CHD. Continuous epoprostenol infusion was reported to improve functional class, oxygen saturation, and exercise capacity in patients with Eisenmenger syndrome.10 Nevertheless, legitimate concerns remain about the applicability of this type of therapy for this specific patient population, particularly in the presence of the right-to-left shunting (risk of systemic thromboembolism) and the risk of line sepsis associated with the

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chronicity of therapy. The Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5), the only double-blind, placebo-controlled study in patients with Eisenmenger syndrome, demonstrated that bosentan significantly improved hemodynamics and exercise capacity without compromising oxygen saturations. Phosphodiesterase-5 inhibitors were also shown to improve functional class and hemodynamic parameters in this population in smaller nonrandomized studies.

No studies to date have examined the potential survival benefit from AT in the Eisenmenger cohort, which was the subject of our investigation.

Methods

Study Subjects
This was a retrospective study. Data on all patients with Eisenmenger physiology under active follow-up at our center between June 1999 and August 2008 were obtained and studied. Inclusion criteria were evidence of PAH with a nonrestrictive intracardiac or extracardiac communication. Patients previously operated on for CHD were also included regardless of the presence of a residual shunt, provided that they had evidence of near-systemic PAH (eg, patients with late closure of a ventricular septal defect). A firm diagnosis of CHD and PAH had been established by echocardiography, cardiovascular magnetic resonance, or cardiac catheterization. Demographic and clinical data were collected from a dedicated clinical database and the patients’ clinical records and refer to the time of the earliest clinical assessment within the study period. Systemic ventricular function was assessed with the use of a 4-point semiquantitative scale (normal, mildly, moderately, and severely impaired) because of inherent difficulties in applying quantitative measures such as ejection fraction across the spectrum of adults with CHD.

Cardiac lesions were classified into 4 categories according to the shunt type: pretricuspid (atrial septal defect), posttricuspid (ventricular septal defect or patent ductus arteriosus in the absence of a pretricuspid shunt), complex anatomy (other shunt lesions including atroventricular septal defects, univentricular physiology, transposition of the great arteries, aortopulmonary window, and common arterial trunk), and operated lesions. In the context of univentricular physiology, severe PAH had occurred when the pulmonary artery was directly connected to the ventricular mass in the absence of pulmonary stenosis and the absence of an effective surgical pulmonary artery band. Patients with univentricular physiology were classified as having Eisenmenger syndrome when the aforementioned hemodynamics were combined with cyanosis. In the study design, patients with univentricular physiology and a Glenn or Fontan-type operation were excluded.

Survival status and time of death were ascertained through the health service computer system, linked to the national database held by the Office of National Statistics. Approval by the local Ethics Committee was obtained. 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.

Statistical Analysis
Analyses were performed with the use of R version 2.8.1 (http://cran.r-project.org/) and the packages Survival, Amelia, and MatchIt. Continuous variables were assessed for normality and are presented as mean±SD, with the exception of follow-up time, which is presented as median (interquartile range). Categorical variables are presented as percentage of total. Univariable and multivariable Cox regression analysis was used to assess the relation between AT and death. Patients who initiated AT during follow-up were treated as separate cases (right censored and left truncated), and clinical characteristics were reassessed at the time of initiation of treatment (Figure 1). AT was modeled as a time-dependent covariate as patients who were not previously on AT went on to AT during follow-up. Because intervals for a particular subject do not overlap, nonindependence relating to patients appearing in both groups (AT and non-AT) at different times can be accounted for in the modified version of the Cox model with a “start, stop” mechanism (counting process). Time “0” was the first full clinical assessment during the study period.

To adjust for differences in clinical and demographic characteristics between patients on AT and those not on AT, propensity score regression adjustment and propensity score matching were used. Propensity scores were computed with the use of logistic regression with AT as the dependent variable and baseline demographic and clinical variables as independent variables: age; sex; type of shunt (pretricuspid, posttricuspid, complex anatomy, operated lesions); New York Heart Association (NYHA) functional class; Down syndrome; resting oxygen saturation; systemic ventricular systolic function; treatment with diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, amiodarone, digoxin, or warfarin; and history of syncopal episodes.

Variables used in the generation of the propensity score for patients who started AT during follow-up refer to the time of initiation of AT. Missing data were accounted for by multiple imputation.

Propensity score quartiles were used for Cox regression analysis adjustment. Propensity scores were also used to perform 3:1 nearest neighbor matching (3 patients not on AT to 1 patient on AT) within a caliper of 0.15 SD of the propensity score. Balance was verified by assessing standardized differences between groups for all variables in the matched cohort. A target of <10% standardized difference for all variables was set and achieved. Cox analysis was performed to compare mortality between the 2 groups with the use of each of the 10 databases and also by combining matched sets into larger strata with propensity scores within the same quantile. The variance of the estimated log(hazard ratio [HR]) was calculated as the average of the estimated variances from each data set plus the sample variance in point estimates across data sets. Sensitivity analysis was performed with the exclusion of patients with systemic levels of pulmonary hypertension who had undergone previous repair of the intracardiac defect and who therefore do not strictly fulfill the definition of Eisenmenger syndrome.

Unadjusted and adjusted survival curves based on the Cox regression models were also constructed. Unpaired comparisons were performed with the use of the Fisher exact test for categorical data and the Wilcoxon rank sum test for continuous variables. Paired comparisons were performed with the Cochran-Mantel-Haenszel χ² test for count data and the Wilcoxon signed rank test for continuous variables. All P values were 2 sided, and a P value of <0.05 was prespecified as indicative of statistical significance.

Results
In total, 229 Eisenmenger patients (34.5±1.26 years of age; 35.4% male) fulfilled entry criteria. The majority of patients had...
complex anatomy (44.5%), followed by patients with a posttricuspid shunt (39.3%) and those with a pretricuspid shunt (10.5%). More than half of the patients (53.7%) were in NYHA class III at baseline assessment. Mean resting saturations were 84.3%. Down syndrome was present in 29.7%.

Demographic and clinical characteristics of patients at the time of assessment are described in the Table. Ten patients were on AT at their earliest baseline assessment. Fifty-eight patients were assessed twice as they started on AT during follow-up. Patients starting AT were more likely to be older (P=0.001) and to be more functionally impaired (P<0.0001) than those never on AT. Moreover, patients starting AT were more likely to be receiving anticoagulants (P<0.0001) and to have a history of syncopal episodes (P=0.007).

Most patients starting AT during follow-up had been significantly impaired (functional class ≥III) for many years, before the availability of AT for Eisenmenger syndrome. Moreover, 15 patients in functional class <III at their first baseline assessment progressed to functional class III during follow-up and were thus started on AT. The majority of patients (66.1%) were started on AT after 2005, when evidence of safety and efficacy of AT (bosentan) became available.11

Among a total of 68 patients who received AT, 73.5% were started on bosentan, 25% on sildenafil, and 1.5% (1 patient) on epoprostenol. Of patients who were started on bosentan, 2 (4.0%) were switched to sildenafil, and 3 (6.0%) were switched to combination therapy. Of patients who were started on sildenafil, 3 (17.6%) were switched to endothein

### Table. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1: Never on AT n=161</th>
<th>Group 2: AT at Baseline n=10</th>
<th>Group 3: AT During Follow-Up n=58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>65 (40.4)</td>
<td>2 (20)</td>
<td>14 (24.1)</td>
</tr>
<tr>
<td>Age, y</td>
<td>33.8±13.2</td>
<td>34.2±6.9</td>
<td>36.4±11.4</td>
</tr>
<tr>
<td>Down syndrome, n (%)</td>
<td>58 (36)</td>
<td>2 (20)</td>
<td>8 (13.8)</td>
</tr>
<tr>
<td>Cardiac defect, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretricuspid</td>
<td>13 (8.1)</td>
<td>3 (30)</td>
<td>8 (13.8)</td>
</tr>
<tr>
<td>Posttricuspid</td>
<td>61 (37.9)</td>
<td>1 (10)</td>
<td>28 (48.3)</td>
</tr>
<tr>
<td>Complex anatomy</td>
<td>82 (50.9)</td>
<td>3 (30)</td>
<td>17 (29.3)</td>
</tr>
<tr>
<td>Repaired lesion</td>
<td>5 (3.1)</td>
<td>3 (30)</td>
<td>5 (8.6)</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>83.8±8.3</td>
<td>91±7.2</td>
<td>84.3±7.6</td>
</tr>
<tr>
<td>History of syncope, n (%)</td>
<td>13 (8.1)</td>
<td>2 (20)</td>
<td>12 (20.7)</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>87 (54)</td>
<td>1 (10)</td>
<td>18 (31)</td>
</tr>
<tr>
<td>III/IV</td>
<td>74 (46)</td>
<td>9 (90)</td>
<td>40 (69)</td>
</tr>
<tr>
<td>Systemic ventricular function, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>133 (84.2)</td>
<td>10 (100)</td>
<td>55 (94.8)</td>
</tr>
<tr>
<td>Mildly impaired</td>
<td>17 (10.8)</td>
<td>0 (0)</td>
<td>3 (5.2)</td>
</tr>
<tr>
<td>Moderately impaired</td>
<td>7 (4.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Severely impaired</td>
<td>1 (0.6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitalis</td>
<td>20 (12.4)</td>
<td>1 (10)</td>
<td>6 (10.3)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>48 (29.8)</td>
<td>3 (30)</td>
<td>19 (32.8)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>12 (7.5)</td>
<td>0 (0)</td>
<td>8 (13.8)</td>
</tr>
<tr>
<td>ACE inhibitors or angiotensin receptor blockers</td>
<td>16 (9.9)</td>
<td>2 (20)</td>
<td>5 (8.6)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>12 (7.5)</td>
<td>0 (0)</td>
<td>6 (10.3)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>28 (17.4)</td>
<td>3 (30)</td>
<td>14 (24.1)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>36 (22.4)</td>
<td>6 (60)</td>
<td>20 (34.5)</td>
</tr>
<tr>
<td>Pacemaker, n (%)</td>
<td>3 (1.9)</td>
<td>0 (0)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>ICD, n (%)</td>
<td>4 (2.5)</td>
<td>0 (0)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Median follow-up, y (IQR)</td>
<td>4.7 (2.5–7.3)</td>
<td>4.2 (2.6–5.0)</td>
<td>2.4 (1.3–4.8)</td>
</tr>
</tbody>
</table>

Demographic and clinical characteristics of patients never on AT (group 1), patients starting AT at baseline (group 2), and those who started AT during follow-up (group 3) are shown. For the latter group, characteristics at the original baseline and at the time of initiation of treatment are presented. ACE indicates angiotensin-converting enzyme; ICD, implantable cardioverter-defibrillator; and IQR, interquartile range.

*P value for the comparison between patients never on AT (group 1) and those on AT (at baseline or during follow-up: groups 2 and 3b combined).

†P value for the comparison between the first baseline assessment and the assessment at the time of initiation of AT in the subgroup of patients who were started on AT during follow-up (group 3, paired comparison).
receptor antagonists, and 2 (11.8%) were switched to combination therapy. The patient who was started on epoprostenol was subsequently switched to combination therapy with bosentan and sildenafil. The median duration of AT was 2.4 years. One patient had heart-lung transplantation during follow-up and was censored at the time of transplantation.

During a median follow-up of 4.0 years, 52 of 229 patients died. The overall 5-year mortality rate was 23.3% and was higher in patients in NYHA class III (32.2% versus 14.1% in class II or less; log rank $P=0.006$; Figure 2). Of the 52 patients who died, only 2 were on AT at the time of death, and the remaining 66 patients who had been started on AT were still alive at the end of follow-up. Patients on AT were, in fact, at a significantly lower risk of death (unadjusted HR, 0.21; 95% confidence interval [CI], 0.05 to 0.86; $P=0.03$; Figure 3A).

Other univariable predictors of outcome were age at assessment, systemic ventricular dysfunction, NYHA functional class, resting oxygen saturations, and use of diuretics, digoxin, and amiodarone. The survival benefit from AT was even stronger after adjustment with the use of propensity scores and multiple imputation for missing data (n=10 imputations), with propensity score–adjusted Cox regression (average C statistic=0.80) as follows: HR, 0.16; 95% CI, 0.04 to 0.71; $P=0.015$ (Figure 3B).

Propensity score matching after multiple imputation for missing data generated 10 matched populations (median, 175 patients; range, 174 to 178). Adequate balance in clinical characteristics between the 2 treatment groups (with and without AT) was achieved, with a standardized difference for all variables within 10%, indicating a high degree of similarity between the matched groups. In the matched population, patients on AT were...
again at significantly lower risk of death than patients not on AT (HR, 0.10; 95% CI, 0.01 to 0.78; \( P = 0.028 \)). Similar results were obtained when matched sets with similar propensity scores were used as strata (HR 0.10; 95% CI, 0.01 to 0.76; \( P = 0.027 \)). Results were consistent even after exclusion of patients with previous repair of the intracardiac defect \(( n = 13 \) ) who did not strictly fulfill the criteria for Eisenmenger syndrome (HR, 0.20; 95% CI, 0.05 to 0.85; \( P = 0.03 \)).

**Discussion**

Patients with Eisenmenger syndrome are at high risk of death.\(^23\) The mortality rate is higher in more symptomatic patients (functional class \( \geq III \)) but is considerable even in mildly symptomatic patients (NYHA class \( < III \)). Advanced therapy for PAH in this retrospective study was associated with improved survival rate.

Despite the widespread use of AT in PAH, now including Eisenmenger patients, very little evidence on survival benefits is currently available.\(^23,24\) A meta-analysis of randomized controlled trials of AT in various types of PAH recently showed a 43% reduction in overall mortality rate.\(^25\) However, this effect did not address Eisenmenger patients, and BREATHE-5, the only randomized controlled trial of AT targeting Eisenmenger patients, could not be included in this analysis. Because the role of AT (particularly bosentan) in Eisenmenger syndrome is now established,\(^10-12,14\) initiation of placebo-controlled trials to assess the effects on mortality rate could be difficult and may raise ethical issues for patients allocated to the placebo group. Therefore, systematic cohort studies such as the one presented here have a role in examining the effect of AT on mortality rate.

Indeed, AT in our study was associated with significantly lower all-cause mortality rate in a large population of patients with Eisenmenger syndrome in a single center. It is striking that, even though 68 patients received AT for a median period of 2.4 years (the vast majority of them were in class III or IV at baseline), only 2 patients died, compared with 50 deaths in the remainder (not receiving AT). This marked difference was obvious even before adjustment for baseline differences between the 2 groups. Eisenmenger patients who receive AT were likely to be at the worst end of the spectrum and therefore at a higher risk of death. In accordance with this, patients on AT in our study were significantly older, were more impaired, and were more likely to receive anticoagulants and to have a history of syncopal episodes, indicating overall a more advanced disease stage. Therefore, direct unadjusted comparisons of outcome of these patients with those not on AT are likely to blunt any survival benefit deriving from therapy. However, in our study, a significant correlation between AT and survival was present on unadjusted comparison, which became more pronounced after adjustment for baseline characteristics, including disease complexity, Down syndrome, and anticoagulation.

A survival benefit of AT for PAH would provide a strong impetus toward treatment of all Eisenmenger patients. Even though lung or heart-lung transplantation had been, until recently, the only therapeutic option for these patients, a relatively slow progression of the disease and established multiorgan involvement in severely symptomatic patients, in combination with the relatively poor long-term results of lung transplantation, make this option unattractive to most.\(^26-30\) Eisenmenger patients appear to remain stable for many years, although quite symptomatic, with many of them making major lifestyle adjustment to poor functional capacity. Furthermore, physicians have been reluctant to introduce AT in such patients for both potential safety concerns and financial reasons. Our study, however, suggests that AT improves long-term survival rate, which makes a case for consideration of AT in these patients.

**Study Limitations**

This is a retrospective, nonrandomized, single-center study representative of a tertiary adult congenital heart disease and pulmonary hypertension practice. More explicitly, patients went on to AT as part of research protocols in the early 2000s when data on safety and efficacy were lacking. Only in the later part of the present study, when more evidence became available, were class III patients considered for AT, suggesting that if there was any bias toward AT, this involved patients with more advanced disease. This is clearly reflected in our data and, if anything, strengthens the validity of the survival benefit reported herein.

Even though all patients included in this study had congenital heart defects associated with near-systemic PAH, this remains a heterogeneous population with a spectrum of anatomic defects, which themselves could affect outcome. Furthermore, we opted to include patients with late repair of nonrestrictive shunt lesions, when near-systemic PAH was present, who do not fulfill strict criteria for Eisenmenger syndrome. Nevertheless, results were consistent even after exclusion of these patients from the analysis.

Although cardiac catheterization immediately before commencement of AT is essential for establishing the diagnosis in idiopathic and other types of PAH, this is not the case in Eisenmenger syndrome or in our routine practice. This is especially true in patients with posttricuspid shunts in whom the diagnosis is unambiguous, often established in early childhood. We have therefore not presented any catheterization data, which would have been incomplete in our population.

Finally, no distinction between specific types and dosages of AT was made in this study purely for practical reasons. Despite our study being one of the largest Eisenmenger populations observed, adjustment for the type and dose of AT was not possible. Further studies are clearly needed to validate our results and to explore the impact of specific drugs on survival in Eisenmenger patients.

**Conclusions**

AT for pulmonary arterial hypertension in this contemporary cohort of adult patients with Eisenmenger syndrome was associated with a lower risk of death. Survival benefits should be considered together with the potential improvement in hemodynamics and functional class when decisions are made on AT in this population.

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Disclosures
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