Heart Valve Regurgitation, Pergolide Use, and Parkinson Disease

An Observational Study and Meta-analysis

Jean-Christophe Corvol, MD, PhD; Jean-Baptiste Anzouan-Kacou, MD; Elodie Fauveau, MD; Anne-Marie Bonnet, MD; Bénédicte Lebrun-Vignes, MD; Camille Girault, PharmD; Yves Agid, MD, PhD; Philippe Lechat, MD, PhD; Richard Isnard, MD; Lucette Lacomblez, MD

Objective: To investigate the prevalence and risk factors of heart valve disease in patients having PD treated with pergolide.

Design: Prospective observational study.

Setting: Patients were recruited at the Hôpital de la Pitié-Salpêtrière, Paris, France.

Patients: Ninety-six patients having PD treated with pergolide for longer than 3 months vs 50 control subjects.

Intervention: Standardized echocardiography performed by an investigator blinded to treatment status.

Main Outcome Measure: Moderate to severe regurgitation in at least 1 heart valve.

Results: One hundred thirty-three echocardiograms (86 in the pergolide-treated group and 47 in the control group) were analyzed in the study. Moderate to severe regurgitation was found in 15 patients treated with pergolide (17.4%) and in 2 control subjects (4.3%) (odds ratio [OR], 4.75; 95% confidence interval [CI], 1.02-22.1; P = .03). Including the present study, the meta-analysis comprised 7 trials (394 patients treated with pergolide and 280 controls). The overall OR for moderate to severe regurgitation was 3.1 (95% CI, 1.7-5.6; P < .001) in the pergolide-treated group. Risk differences were correlated with the mean cumulative dose of pergolide (r = 0.90, P < .001).

Data Sources: Using an end point of moderate to severe heart valve regurgitation, we performed a meta-analysis of patients having Parkinson disease (PD) treated with pergolide mesylate vs control subjects by searching PubMed (January 1, 1966, to April 1, 2007) and the Cochrane databases to identify English-language prospective observational studies that reported echocardiographic data.

Conclusion: Heart valve disease is independently associated with the use of pergolide treatment in patients having PD and correlates with its cumulative dose.

Trial Registration: clinicaltrials.gov Identifier: NCT00202657

Arch Neurol. 2007;64(12):1721-1726

Pergolide mesylate is an ergot-derived dopamine receptor agonist used to treat Parkinson disease (PD) and restless leg syndrome. Pergolide is known to induce pulmonary, pleural, and retroperitoneal fibrosis similar to that induced by other ergot derivatives.1,2 Following occasional anecdotal case reports, comparative studies3-8 reported heart valve disease (HVD) associated with pergolide intake. A recent large case-control study9,10 found an association between HVD and pergolide or cabergoline intake, but other studies11 did not demonstrate this association. A causal relationship between pergolide use and a potential adverse effect remains to be established.

Although the first reported cases were symptomatic, most of the following studies found asymptomatic HVD in patients using pergolide.12 The prevalence was rare based on cases registered in drug vigilance databases, whereas studies3,5,13 that included systematic echocardiographic findings reported abnormal heart valves in up to 40% of patients having PD treated with pergolide. A dose association was found,5,7,8 although there were some controversies about the relative importance of the daily and cumulative doses. On discovery of asymptomatic heart valve regurgitation in a pergolide-treated patient with PD, an accurate diagnosis may be difficult in clinical practice because of the association between age and heart valve
regurgitation. The prevalence and risk factors of this drug-induced adverse effect are of particular interest because moderate to severe valve regurgitation was recently associated with higher mortality in the general population. We conducted a prevalence study and performed a meta-analysis of similar published studies to investigate the prevalence and potential risk factors of moderate to severe heart valve regurgitation associated with pergolide treatment in PD.

### STUDY DESIGN

Patients were recruited from April 1, 2005, to August 31, 2006, in the Department of Neurology, Hôpital de la Pitié-Salpêtrière, Paris, France. Inclusion criteria were diagnosis of PD, age older than 18 years, Hoehn and Yahr score of 1 to 4, treatment with pergolide for more than 3 months (pergolide-treated group), or no treatment with pergolide (control group). Patients with a history of HVD were excluded. Previous or current treatment with other dopaminergic agonists was allowed in both groups. Treatment history was retrospectively reviewed from patients' medical records and historical data. The cumulative dose of pergolide was calculated as the mean daily dose (cumulative dose per exposure duration). Data were available for all but 1 patient, who was subsequently excluded from the multiple regression analysis. Echocardiography was performed by a cardiologist (J.-B.A.-K. or E.F.) blinded to treatment status. The primary end point was moderate to severe regurgitation in at least 1 heart valve. All patients provided written informed consent; the study was approved by the local ethics committee and was registered on the Web site for clinical trials.

### ECHOCARDIOGRAPHY

Echocardiographic examinations were performed (Siemens Acuson Sequoia; Siemens Acuson, Mountain View, California), and data were saved using commercially available software (Image Arena Tomtec, Unterschleissheim, Germany). Valve thickness was measured in 2 dimensions (diastolic measurements for mitral and tricuspid valves and systolic measurements for the aortic valve). A valve was considered restrictive when thicker than normal and associated with retraction. Tenting area and tenting distance of the mitral valve were measured. Severity of heart valve regurgitation was assessed using pulsed, continuous, and color Doppler imaging, according to the recommendations of the American Society of Echocardiography. Briefly, for mitral regurgitation, the assessment was based on a combination of the following variables: jet area color flow, vena contracta width, proximal isovelocity jet area, and calculation of flow and stroke volume at the mitral annulus and the left ventricular outflow levels. For aortic regurgitation, the assessment was based on jet width in the left ventricular outflow tract, vena contracta width, jet pressure half time on continuous Doppler imaging, and diastolic flow reversal in the descending aorta. Finally, for tricuspid regurgitation, the assessment was based on jet area color flow, vena contracta width, and hepatic vein flow. When present, regurgitation was graded as mild, moderate, or severe. Pulmonary regurgitation evaluation was not performed systematically, and the results were considered. Systolic pulmonary pressure was measured as described previously.

### META-ANALYSIS

We conducted an electronic search of PubMed (January 1, 1966, to April 1, 2007) and the Cochrane databases by means of the Quality of Reporting of Meta-analyses approach strategy to identify all English-language publications using the keywords pergolide, valvular heart disease, valvulopathy, and fibrosis. Studies included in the meta-analysis were prospective studies having a control group and reporting data on heart valve regurgitation. Of 60 articles reviewed, we excluded 33 (21 reviews, 21 studies without echocardiography data, 8 case reports, 1 retrospective study, 1 case-control study, and 1 study without a pergolide study group). The end point was defined as moderate to severe regurgitation (ie, greater than minimal, trace, or trivial) in 1 heart valve or more. In 1 study, because the valvular scoring system was different, the end point for meta-analysis was defined as "important valvular disease (regurgitant jet ≥ 2/4) suggestive for restrictive valvular disease or restrictive tricuspid disease even if less than 2/4," The mean values for age, pergolide cumulative dose, and exposure duration were collected. For 1 study, 2 patients (1 pergolide-treated patient and 1 control subject)
with restless leg syndrome rather than PD were excluded from the analysis.

**STATISTICAL ANALYSIS**

The $t$ test was used to compare continuous variables; the $\chi^2$ test or bilateral exact Fisher test for frequencies. Univariate and multivariate logistic regression analysis (logit) was performed using commercially available software (Statistica 7.1; Statsoft France, Maisons-Alfort, France) to analyze associations between the presence of moderate to severe regurgitation (dependent variable) and age, sex, duration of PD, body mass index, and bromocriptine mesylate and pergolide exposure (independent variables). For the meta-analysis, the pooled estimate of the overall odds ratio (OR) was calculated using the inverse variance weighted OR for each study (EasyMA 2001 software; Department of Clinical Pharmacology, Cardiological Hospital, Lyon, France). The inverse variance weighted linear regression model was used to test the relationship between risk difference and age, pergolide cumulative dose, and exposure duration.

**RESULTS**

**PATIENT CHARACTERISTICS**

One hundred forty-six patients were enrolled in the study. Thirteen patients (10 in the pergolide-treated group) did not undergo echocardiography because of noncompliance (n=10), withdrawal of consent (n=2), or technical problems (n=1). Overall, 86 pergolide-treated patients and 47 control subjects underwent standardized echocardiography. The pergolide-treated patients had a mean±SD cumulative dose of 2555±1662 mg, daily dose of 1.8±0.9 mg, and exposure duration of 48±18 months (Table 1). Only 1 patient received a daily dose higher than 5 mg. Although there was no statistically significant difference for age, sex, body mass index, or cardiovascular risk factors, patients in the pergolide-treated group had a higher Hoehn and Yahr mean score and a longer mean duration of PD. These differences were expected because pergolide therapy is recommended only after the failure of other medications (ie, in patients with more severe disease). Bromocriptine use was similar in both groups. No patient received cabergoline; 5 patients treated with lisuride during 1 to 7 years had discontinued the drug more than 2 years before inclusion in the study. Nonergot dopamine agonists (pramipexole dihydrochloride or ropinirole hydrochloride) were prescribed to 28 control subjects (59.6%); these drugs had previously been taken by 22 patients (25.6%) in the pergolide-treated group.

### Table 2. Prevalence of Valve Regurgitation

<table>
<thead>
<tr>
<th>Valve</th>
<th>Group (n)</th>
<th>Moderate to Severe (%)</th>
<th>Control (n)</th>
<th>Moderate to Severe (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any valve</td>
<td>Pergolide</td>
<td>15 (17.4)</td>
<td>2 (4.3)</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>61 (70.9)</td>
<td>31 (66.0)</td>
<td>20 (23.3)</td>
<td>.39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 (5.8)</td>
<td>1 (2.1)</td>
<td>60 (69.8)</td>
<td>.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 (8.1)</td>
<td>1 (2.1)</td>
<td>12 (14.0)</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>66 (76.7)</td>
<td>43 (91.5)</td>
<td>8 (9.3)</td>
<td></td>
</tr>
</tbody>
</table>

*Data are given as number (percentage).*

### Table 3. Multiple Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Moderate to Severe Regurgitation in Any Valve</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per year increase</td>
<td></td>
<td>1.05 (0.99-1.12)</td>
<td>.08</td>
<td>1.06 (0.99-1.14)</td>
<td>.09</td>
</tr>
<tr>
<td>Sex (male to female)</td>
<td></td>
<td>1.28 (0.44-3.65)</td>
<td>.64</td>
<td>1.25 (0.40-3.87)</td>
<td>.70</td>
</tr>
<tr>
<td>Body mass index, per unit increase</td>
<td></td>
<td>0.95 (0.82-1.09)</td>
<td>.42</td>
<td>0.96 (0.84-1.13)</td>
<td>.74</td>
</tr>
<tr>
<td>Parkinson disease duration, per year</td>
<td></td>
<td>1.06 (0.98-1.14)</td>
<td>.18</td>
<td>1.00 (0.91-1.10)</td>
<td>.94</td>
</tr>
<tr>
<td>Pergolide mesylate use (yes to no)</td>
<td></td>
<td>4.75 (1.02-22.1)</td>
<td>.04</td>
<td>5.37 (1.05-27.5)</td>
<td>.04</td>
</tr>
<tr>
<td>Bromocriptine mesylate use (yes to no)</td>
<td></td>
<td>0.88 (0.26-2.95)</td>
<td>.64</td>
<td>0.94 (0.25-3.38)</td>
<td>.93</td>
</tr>
</tbody>
</table>

*Odds ratios (ORs), 95% confidence intervals (95% CIs), and P values were calculated by logistic regression for each factor (univariate analysis) or by multivariate logistic regression, including age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), Parkinson disease duration, pergolide use, and bromocriptine use as independent variables (multivariate analysis $[x^2=9.95, P=.13]$). Patients from both groups were included in the analyses. Odds ratios are given for 1-U increase of variables.*
Moderate to severe regurgitation in at least 1 heart valve was observed in 15 patients (17.4%) in the pergolide-treated group compared with 2 patients (4.3%) in the control group \( (P = .03) \) (Table 2). The OR was 5.5 (95% confidence interval [CI], 1.2-26) after adjustment for age. Valve analysis demonstrated a statistically significant higher proportion of tricuspid moderate to severe regurgitation in the pergolide group. No patient had severe valve regurgitation. Moderate to severe regurgitation in multiple valves was found in 4 pergolide-treated patients and in no control subjects. Tenting area, tenting distance, and systolic pulmonary arterial pressure were not different between the groups (data not shown). However, patients with primary criteria in the pergolide-treated group, that is, pergolide-treated patients with moderate to severe regurgitation, had a higher mean±SD systolic pulmonary arterial pressure (39±9 vs 32±6 mm Hg) and more frequent restrictive or thickened valves (67% vs 17%) \( (P < .001\) for both). No heart valve regurgitation due to valve prolapse, annular dilatation, or calcification was observed in patients with moderate to severe regurgitation.

To investigate possible confounding factors, we performed a logistic regression analysis (Table 3). In the univariate analysis, a positive and statistically significant association was only found for pergolide use. No association was found for any other drug, including bromocriptine, lisuride, or both (data not shown). There was a tendency for an association with age, as expected by previous findings in the general population.15 After adjustment for age, sex, and PD duration, moderate to severe regurgitation was still statistically significantly associated with pergolide use.

**Table 4. Risk Factors for Valvular Regurgitation in the Pergolide Mesylate Group**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Moderate to Severe Regurgitation in Any Valve</th>
<th>Moderate to Severe Regurgitation in Any Valve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate Analysis</td>
<td>Multivariate Analysis</td>
</tr>
<tr>
<td></td>
<td>OR (95% CI) P Value</td>
<td>OR (95% CI) P Value</td>
</tr>
<tr>
<td>Age, per year increase</td>
<td>1.04 (0.97-1.12) .21</td>
<td>1.04 (0.98-1.12) .20</td>
</tr>
<tr>
<td>Sex (male to female)</td>
<td>1.61 (0.51-5.04) .41</td>
<td>1.66 (0.52-5.27) .39</td>
</tr>
<tr>
<td>Parkinson disease duration, per year</td>
<td>1.03 (0.34-1.13) .56</td>
<td>1.01 (0.32-1.11) .87</td>
</tr>
<tr>
<td>increase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pergolide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative dose, per 10-mg/kg increase</td>
<td>1.34 (1.04-1.72) .02</td>
<td>1.37 (1.04-1.81) .03</td>
</tr>
<tr>
<td>Daily dose, per microgram per kilogram increase</td>
<td>1.05 (1.01-1.09) .02</td>
<td>1.04 (1.00-1.08) .03</td>
</tr>
<tr>
<td>Exposure duration, per month increase</td>
<td>0.99 (0.96-1.00) .07</td>
<td>0.99 (0.96-1.02) .61</td>
</tr>
<tr>
<td>Bromocriptine mesylate use (yes to no)</td>
<td>1.15 (0.32-4.18) .22</td>
<td>1.12 (0.30-4.18) .86</td>
</tr>
</tbody>
</table>

\( ^a \) Odds ratios (ORs), 95% confidence intervals (95% CIs), and \( P \) values were calculated by logistic regression for each factor (univariate analysis) or by multivariate logistic regression, including age, sex, Parkinson disease duration, pergolide cumulative dose, and bromocriptine use (multivariate analysis \( \chi^2 = 8.76, P = .19 \)). Similar multivariate analysis was performed using pergolide exposure duration \( \chi^2 = 2.99, P = .81 \) and pergolide daily dose \( \chi^2 = 7.73, P = .26 \). Patients from the pergolide-treated group were included in the analyses. Odds ratios are given for 1-U increase of variables.

**Figure 1.** Pergolide dose relationship with heart valve disease. A. Pergolide cumulative dose in patients with moderate to severe regurgitation in 0, 1, or 2 or more heart valves. B. Systolic pulmonary arterial pressure (PAP) as a function of pergolide cumulative dose. Each point represents 1 patient. Solid line indicates regression line; dotted lines, 95% confidence intervals.

**VALVE REGURGITATION PREVALENCE AND PERGOLIDE TREATMENT**

Moderate to severe regurgitation in at least 1 heart valve was observed in 15 patients (17.4%) in the pergolide-treated group compared with 2 patients (4.3%) in the control group \( (P = .03) \) (Table 2). The OR was 5.5 (95% confidence interval [CI], 1.2-26) after adjustment for age. Valve analysis demonstrated a statistically significant higher proportion of tricuspid moderate to severe regurgitation in the pergolide group. No patient had severe valve regurgitation. Moderate to severe regurgitation in multiple valves was found in 4 pergolide-treated patients and in no control subjects. Tenting area, tenting distance, and systolic pulmonary arterial pressure were not different between the groups (data not shown). However, patients with primary criteria in the pergolide-treated group, that is, pergolide-treated patients with moderate to severe regurgitation, had a higher mean±SD systolic pulmonary arterial pressure (39±9 vs 32±6 mm Hg) and more frequent restrictive or thickened valves (67% vs 17%) \( (P < .001\) for both). No heart valve regurgitation due to valve prolapse, annular dilatation, or calcification was observed in patients with moderate to severe regurgitation.

To investigate possible confounding factors, we performed a logistic regression analysis (Table 3). In the univariate analysis, a positive and statistically significant association was only found for pergolide use. No association was found for any other drug, including bromocriptine, lisuride, or both (data not shown). There was a tendency for an association with age, as expected by previous findings in the general population.15 After adjustment for age, sex, and PD duration, moderate to severe regurgitation was still statistically significantly associated with pergolide use.

**PERGOLIDE DOSE EFFECT**

Patients with moderate to severe regurgitation had higher mean±SD pergolide cumulative \( (34±14 vs 24±14 \text{ mg/kg}) \) and daily \( (49±30 vs 34±20 \text{ µg/kg}) \) doses \( (P = .01\) for both). Moderate to severe regurgitation was statistically sig-
significantly associated with cumulative and daily doses of pergolide ($P = .02$ for both) (Table 4). In contrast, the mean ± SD pergolide exposure duration was similar in patients with and without the primary end point (46 ± 18 vs 48 ± 18 months, $P = .68$) and was not associated with moderate to severe regurgitation. Higher cumulative doses were observed in patients with multiple valve regurgitation (Figure 1A). In addition, the presence of a thickened or restrictive valve was associated with the cumulative dose of pergolide (OR, 1.30; 95% CI, 1.04-1.63; $P = .02$). Systolic pulmonary arterial pressure was correlated with pergolide cumulative dose ($r = 0.29$, $P = .02$) (Figure 1B). Tenting area and tenting distance were not correlated with pergolide cumulative dose (data not shown).

META-ANALYSIS

Seven studies and the present study met the selection criteria (see the “Meta-analysis” subsection of the “Methods” section) and were included in the meta-analysis (394 patients treated with pergolide and 280 control subjects) (Table 5). All trials showed higher moderate to severe regurgitation prevalences in the pergolide-treated group, although only 2 were statistically significantly higher prevalences (Figure 2). Altogether, 86 patients in the pergolide-treated group (21.8%) and 20 patients in the control group (7.1%) had moderate to severe regurgitation in at least 1 heart valve, resulting in an overall OR of 3.1 (95% CI, 1.7-5.7) ($P < .001$). The risk difference of moderate to severe valve regurgitation was statistically significantly correlated with pergolide cumulative dose ($r = 0.90$, $P < .001$) (Figure 3). In contrast, no statistically significant correlation was found with age ($r = 0.11$, $P = .69$) or with pergolide exposure duration ($r = 0.05$, $P = .85$).

Our data support an association between pergolide treatment and HVD in patients with PD. However, the absence of echocardiographic data before treatment precluded demonstration of a direct cause-effect relationship. The overall estimated OR was 3.1 for moderate to severe regurgitation in the meta-analysis. Therefore, the lack of a statistically significant association in previous studies may be because of the small samples used.

In addition, we provide evidence for a cumulative dose relationship in this association. The lower prevalence and severity of HVD found in our population compared with those in other studies may be explained by the low doses.

<table>
<thead>
<tr>
<th>Group</th>
<th>Pergolide Mesylate-Treated, No.</th>
<th>Control, No.</th>
<th>Mean Age, y</th>
<th>Pergolide Cumulative Dose, mg</th>
<th>Pergolide Exposure Duration, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Camp et al.5, 2004</td>
<td>78</td>
<td>18</td>
<td>72</td>
<td>3003</td>
<td>18.2</td>
</tr>
<tr>
<td>Kim et al.9, 2006</td>
<td>36</td>
<td>20</td>
<td>64</td>
<td>1400</td>
<td>53.5</td>
</tr>
<tr>
<td>Yamamoto et al.11, 2006</td>
<td>66</td>
<td>85</td>
<td>67</td>
<td>2147</td>
<td>51.6</td>
</tr>
<tr>
<td>Peralta et al.21, 2006</td>
<td>29</td>
<td>33</td>
<td>64</td>
<td>5254</td>
<td>61.3</td>
</tr>
<tr>
<td>Zanettini et al.7, 2007</td>
<td>64</td>
<td>42</td>
<td>64</td>
<td>5019</td>
<td>62.7</td>
</tr>
<tr>
<td>Dewey et al.8, 2007</td>
<td>35</td>
<td>35</td>
<td>66</td>
<td>5307</td>
<td>Not reported</td>
</tr>
<tr>
<td>Present study</td>
<td>86</td>
<td>47</td>
<td>63</td>
<td>2555</td>
<td>48.0</td>
</tr>
</tbody>
</table>

**Table 5. Trial Characteristics**

**Figure 2.** Meta-analysis of moderate to severe valve regurgitation (fixed model). CI indicates confidence interval; OR, overall odds ratio. $x^2$ Test for association was performed on the estimated odds ratio.

**Figure 3.** Relationship between risk differences and pergolide cumulative doses. Solid line indicates inverse variance regression line; dotted lines, 95% confidence intervals.
used. Studies\textsuperscript{9,11} with the lowest cumulative doses of pergolide failed to find a statistically significant increase in HVD prevalence. Furthermore, a positive correlation between pergolide dose and tenting area of the mitral valve was found in some studies,\textsuperscript{3,10} although this was not confirmed in our study. No association was found between HVD and treatment duration in our study.

Pergolide-associated valvulopathies have been reported as fibrotic and restrictive according to histologic findings and as similar to those associated with fenfluramine hydrochloride treatment or with serotonin-secreting carcinoid syndrome.\textsuperscript{3,22} Because fenfluramine metabolite is a potent serotonin receptor agonist, pergolide valvulopathies have been postulated to be related to a serotoninergic mechanism.\textsuperscript{23} Fenfluramine and pergolide, as well as cabergoline, share agonist properties with serotonin 2\textsubscript{B} receptors.\textsuperscript{3,22,24,25} Heart valve disease was associated with cabergoline use and not with the use of other dopaminergic drugs without serotonin 2\textsubscript{B} receptor agonist properties.\textsuperscript{9,23} Together, these data suggest that HVD may occur through a serotoninergic-mediated mechanism involving serotonin 2\textsubscript{B} receptors.

Observational studies always introduce some limitations inherent to the absence of a treatment control group. Therefore, no cause-effect relationship between pergolide use and HVD can be discerned. However, cases of regressive HVD after pergolide treatment withdrawal have been reported,\textsuperscript{9,12} arguing for its direct implication. In addition, in our study no drug interaction was found as a risk factor for HVD, although subgroup analysis might have been underpowered.

In conclusion, we found a dose-dependent association of HVD with pergolide treatment in patients with PD. Prospective pharmacoepidemiological studies are needed to determine whether this association is a cause-effect relationship.

Accepted for Publication: April 26, 2007.

Correspondence: Jean-Christophe Corvol, MD, PhD, Service de Pharmacologie, Hôpital de la Pitié-Salpêtrière, 43/83 Boulevard de l’Hôpital, 75651 Paris CEDEX 13, France (jean-christophe.corvol@psl.aphp.fr).

Author Contributions: Study concept and design: Corvol, Bonnet, Lebrun-Vignes, Agid, Lechat, Isnard, and Lacomblez. Acquisition of data: Anzouan-Kacou, Faveau, Bonnet, Girault, and Isnard. Analysis and Interpretation of data: Corvol, Girault, and Isnard. Drafting of the manuscript: Corvol. Critical revision of the manuscript for important intellectual content: Anzouan-Kacou, Faveau, Bonnet, Lebrun-Vignes, Agid, Lechat, Isnard, and Lacomblez. Statistical analysis: Girault and Lechat. Obtained funding: Corvol and Agid. Administrative, technical, and material support: Anzouan-Kacou, Faveau, Lebrun-Vignes, Agid, and Lacomblez. Study supervision: Corvol and Isnard.

Financial Disclosure: None reported.

Funding/Support: This study was supported by the Institut National de la Santé et de la Recherche Médicale and was promoted by the Société Française de Cardiologie.

Additional Contributions: Jean-François Savouret, PhD, corrected the English language.

REFERENCES


