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Survival in Patients With Idiopathic, Familial, and Anorexigen-Associated Pulmonary Arterial Hypertension in the Modern Management Era

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Background—Novel therapies have recently become available for pulmonary arterial hypertension. We conducted a study to characterize mortality in a multicenter prospective cohort of patients diagnosed with idiopathic, familial, or anorexigen-associated pulmonary arterial hypertension in the modern management era.

Methods and Results—Between October 2002 and October 2003, 354 consecutive adult patients with idiopathic, familial, or anorexigen-associated pulmonary arterial hypertension (56 incident and 298 prevalent cases) were prospectively enrolled. Patients were followed up for 3 years, and survival rates were analyzed. For incident cases, estimated survival (95% confidence intervals [CIs]) at 1, 2, and 3 years was 85.7% (95% CI, 76.5 to 94.9), 69.6% (95% CI, 57.6 to 81.6), and 54.9% (95% CI, 41.8 to 68.0), respectively. In a combined analysis population (incident patients and prevalent patients diagnosed within 3 years before study entry; n=190), 1-, 2-, and 3-year survival estimates were 82.9% (95% CI, 72.4 to 95.0), 67.1% (95% CI, 57.1 to 78.8), and 58.2% (95% CI, 49.0 to 69.3), respectively. Individual survival analysis identified the following as significantly and positively associated with survival: female gender, New York Heart Association functional class I/II, greater 6-minute walk distance, lower right atrial pressure, and higher cardiac output. Multivariable analysis showed that being female, having a greater 6-minute walk distance, and exhibiting higher cardiac output were jointly significantly associated with improved survival.

Conclusions—In the modern management era, idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension remains a progressive, fatal disease. Mortality is most closely associated with male gender, right ventricular hemodynamic function, and exercise limitation. (*Circulation*. 2010;122:156-163.)

Key Words: exercise ■ hypertension, pulmonary ■ mortality ■ risk factors ■ sex

Pulmonary arterial hypertension (PAH) is a rare and severe condition characterized by vascular proliferation and remodeling of the small pulmonary arteries, resulting in a progressive increase in pulmonary vascular resistance and ultimately right ventricular failure and death.¹⁻⁵ PAH can be idiopathic, familial, associated with conditions such as connective tissue disease, or resultant

from drug or toxin exposure (eg, anorexigens).^{2,5} Mutations in the bone morphogenetic protein receptor 2 gene associated with PAH are found in >70% of cases of familial PAH and 10% to 40% of apparently sporadic or anorexigen-associated cases.⁶⁻¹⁰ Patients with idiopathic, familial, or anorexigen-associated PAH exhibit similar clinical, functional, and hemodynamic characteristics and

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overall survival. Different clinical outcomes have been observed, however, among patients with PAH associated with another disease.^{5,9–17}

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Data describing the natural history of idiopathic and familial PAH were derived from a 1980s National Institutes of Health (NIH)–supported US registry. This registry comprised 187 patients with incident or prevalent PAH (36% prevalent) who were described and followed up for up to 5 years. A very poor prognosis of PAH and a median survival of 2.8 years after diagnosis were observed.^{18,19} Based on estimates obtained from the proportional-hazards (PH) models, an NIH equation was devised to predict a patient's likelihood of survival according to baseline hemodynamic measurements,¹⁹ and it has been widely used since as a comparator in survival analyses.^{20–24}

Advances in the management of PAH, including the assessment of patients with objective parameters and novel medical therapies,^{20–27} have led to improved survival in PAH, as observed in a meta-analysis of randomized controlled trials.²⁷ Moreover, improved 1-, 2-, and 3-year survival has been described in long-term follow-up of patients with idiopathic PAH enrolled in clinical trials by comparison with the NIH equation.^{23,24} It should be emphasized, however, that most patients enrolled in clinical trials have to fulfill strict inclusion criteria to avoid enrollment of patients with unstable, severe disease.²⁸

Prompted by the evolution of knowledge in the field and the absence of a current large multicenter registry, the French Network on Pulmonary Hypertension initiated a national prospective registry to investigate real-world survival of PAH during a 3-year follow-up.²⁹ Here, we describe survival in a cohort of patients with idiopathic, familial, and anorexigen-associated PAH in the modern treatment era.

Methods

The French Network on Pulmonary Hypertension comprised 17 university pulmonary vascular centers.²⁹ The registry was opened in 2002, enrolled all consecutive patients aged ≥ 18 years with PAH seen by these centers between October 2002 and October 2003, and followed them up prospectively for 3 years.²⁹ This study was compliant with requirements of the Commission Nationale de l'Informatique et des Libertés, and all patients provided informed consent to participate.

PAH was defined as mean pulmonary arterial pressure ≥ 25 mm Hg at rest and pulmonary artery wedge pressure ≤ 15 mm Hg measured during right heart catheterization.³⁰ To assess a homogeneous population, patients with known severe pulmonary function abnormalities (defined as forced vital capacity, total lung capacity, or forced expiratory volume in 1 second $< 60\%$), who are prone to develop pulmonary hypertension secondary to chronic respiratory diseases and/or hypoxemia,⁵ were excluded.

PAH was classified as idiopathic, familial, or associated with anorexigen exposure. Patients with associated conditions (eg, connective tissue disease, portal hypertension, HIV infection, and congenital heart disease) that may influence patient survival were not analyzed.^{5,12–17} Incident cases were defined as patients who received a diagnosis of PAH confirmed by right heart catheterization during the recruitment phase of the study (October 2002 to October 2003).²⁹ Prevalent cases were defined as patients diagnosed before the start of

the study.²⁹ Date of diagnosis corresponded to date of confirmatory right heart catheterization.

No specific treatment algorithm was used. Targeted therapies such as prostacyclin derivatives (intravenous epoprostenol or nebulized iloprost), an endothelin receptor antagonist (bosentan), and a phosphodiesterase type-5 inhibitor (sildenafil) were begun as considered appropriate at each center, according to recommendations^{25,26,31} and availability (In France, epoprostenol, bosentan, iloprost, and sildenafil were approved for PAH in March 1998, May 2002, September 2003, and October 2005, respectively).

Survival Analysis

Patients who underwent lung transplantation were censored at the time of operation. Patients lost to follow-up were censored at the time of their last visit. All-cause mortality was used for analyses because cause of death could not always be confidently ascribed.

Patients were followed up prospectively for 3 years after inclusion in the study. One-, 2-, and 3-year survival was assessed in the incident population; date of diagnostic catheterization was considered the baseline from which survival was measured. In a subsequent analysis, data from the incident population were combined with those from prevalent patients who were diagnosed within 3 years before study entry (combined analysis population). To remove survivor bias that results from the inclusion of prevalent patients, survival estimates and Cox PH model from time to diagnosis were adjusted for the left truncation arising from the delay between diagnosis and study entry. Patients were in the risk set only from their time of study entry; eg, a patient recruited 1 year after diagnosis and followed up for another 3 years was considered to enter the risk set at 12 months and was right censored at 36 months (ie, 24 months from study entry). Kaplan-Meier analysis was used to estimate survival from point of diagnosis to 3 years after diagnosis.

We examined the relationship between potential prognostic variables measured at diagnostic catheterization and mortality in the combined analysis population. Individual analyses based on the Cox PH model were used to examine relationships between survival and selected demographic, New York Heart Association functional class (NYHA FC), medical history, 6-minute walk distance (6MWD), and hemodynamic variables measured at diagnosis. Goodness of fit in each of the individual Cox PH models was established via examination of martingale residuals. Stepwise-forward multivariable Cox PH analysis was used to examine the independent effect on survival of selected variables (those with $P \leq 0.20$ from individual analysis), controlling for possible confounders. The stepwise addition of covariates was established via examinations of significant ($P < 0.05$) differences in log likelihoods between models. This multivariable analysis also investigated the prognostic effect of potential, clinically important 2-way interactions (NYHA FC with 6MWD and age with gender). For patients who did not have 6MWD evaluated at diagnosis because of ambulation problems or medical practice variations, an additional categorical variable (ie, test not done, test done) was included to enable evaluation of these patients in Cox PH regression analyses when the prognostic effect of distances walked was under investigation. The predictive discrimination concordance (C) index and associated 95% confidence interval (CI) for the multivariable model were evaluated. The 2-sided significance level was set at 5%. Statistical analyses were performed with SAS software (version 9.1, SAS Institute, Cary, NC).

Results

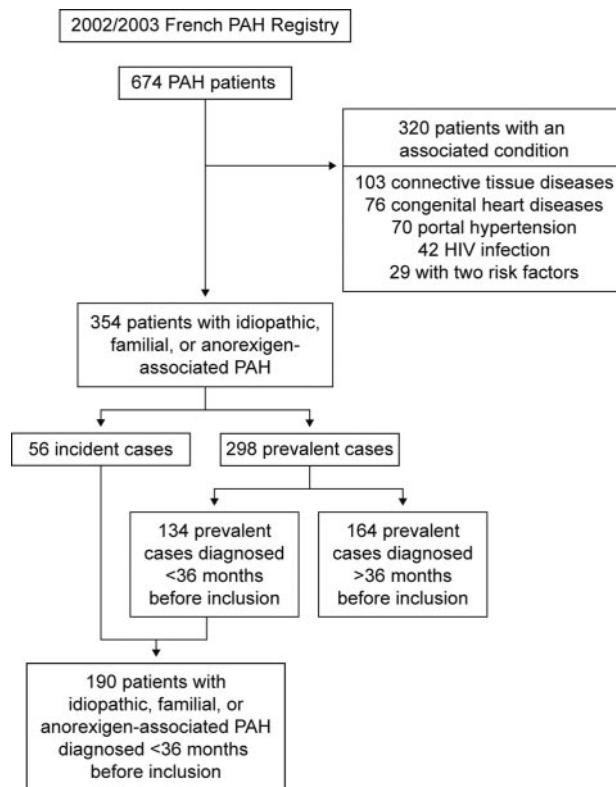
Study Population

In total, 354 consecutive adult patients with idiopathic ($n=264$), familial ($n=26$), or anorexigen-associated ($n=64$) PAH were prospectively enrolled.²⁹ Characteristics of patients in the incident ($n=56$) and combined analysis ($n=190$) populations are described in Table 1; 164

Table 1. Baseline Clinical, Functional and Hemodynamic Data and Deaths

	Incident Population (n=56)	Combined Analysis Population (n=190)
Age, y	54 (18)	52.5 (16.1)
Female:male	34:22	120:70
Female, %	61	63
Female:male ratio	1.5:1	1.7:1
Diagnosis, %		
Idiopathic PAH	87.5	80.5
Familial PAH	5.4	6.3
Anorexigen-associated PAH	7.1	13.2
NYHA FC, %		
I/II	21.4	17.4
III	66.1	68.4
IV	12.5	14.2
6WMD, m	306 (137)	311 (115)
Hemodynamics		
RAP, mm Hg	8 (5)	9 (6)
mPAP, mm Hg	52 (13)	54 (13)
PAOP, mm Hg	8 (3)	8 (3)
CO, L/min	3.8 (1.2)	3.9 (1.3)
Cardiac index, L/min/m ²	2.2 (0.6)	2.2 (0.7)
PVR, Wood units	12.9 (6.2)	13.1 (6.1)
PVRi, Wood units/m ²	21.9 (10.1)	22.4 (10.1)
Treatment at study inclusion, %		
Conventional therapy only	23.2	29.5
Epoprostenol	17.9	14.7
Bosentan	42.9	35.3
Sildenafil	7.1	2.1
Iloprost	5.3	2.1
Combination of targeted therapies	3.6	12.6
Beraprost	0	2.6
Treprostinil	0	0.5
Conventional therapy, %		
Warfarin	94.6	90.5
Diuretics	83.9	69.5
Oxygen	41.1	30.3
Calcium channel blockers	21.4	13.8
Time from diagnosis to study entry (prevalent patients only, n=134), mo		
<6, %		13.4
6-<12, %		25.4
12-<24, %		34.3
24-36, %		26.9
Patients who died, n (%)	25 (44.6)	55 (28.9)

RAP indicates right atrial pressure; mPAP, mean pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; CO, cardiac output; PVR, pulmonary vascular resistance; and PVRi, indexed PVR. Data are presented as mean (SD) unless otherwise indicated.

**Figure 1.** Study sample selected for combined analysis.

prevalent patients whose diagnosis occurred >36 months before the study was initiated were excluded from the combined analysis (Figure 1).

Incident Population

Treatments at study inclusion in the incident population of patients with idiopathic, familial, or anorexigen-associated PAH are shown in Table 1. Medical management consisted solely of conventional therapy in 23.2% of patients, corresponding mostly to acute vasodilator responders who benefited from first-line calcium channel blocker therapy,³² patients in NYHA FC II,^{26,27,33} or patients who died prematurely before any specific therapy could be proposed. Targeted therapies were begun in 76.8% of cases. Although combinations of targeted therapies were offered to only 2 patients at study inclusion (Table 1), they were sequentially administered to 19 subjects over the 3-year period (32%). These combinations corresponded to epoprostenol plus bosentan (n=12), sildenafil plus bosentan (n=4), iloprost plus bosentan (n=2), and epoprostenol plus sildenafil (n=1).

One patient was lost to follow-up at 24.9 months after inclusion, and 1 patient was transplanted at 27.7 months. Three years after diagnostic right heart catheterization, 25 patients among the 56 incident cases had died. Cause of death was given as right ventricular failure (n=9, 36%), sudden death (n=7, 28%), sepsis (n=2, 8%), hemorrhagic shock (n=1, 4%), and uncertain (n=6, 24%). Kaplan-Meier survival estimates for the 56 patients with incident PAH at 1, 2, and 3 years were 85.7% (95% CI, 76.5 to 94.9), 69.6% (95%

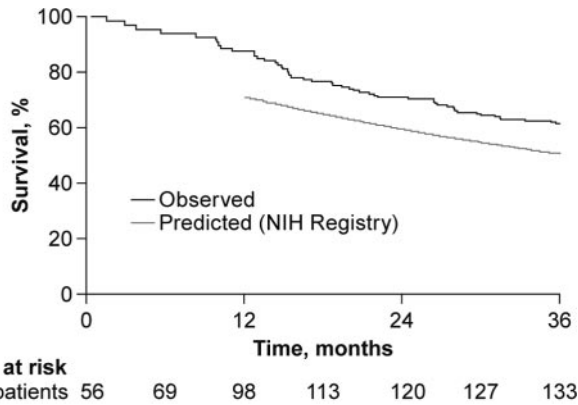


Figure 2. Kaplan-Meier survival estimates in the combined population of patients with PAH (black line). When the predictive modeling approach of the NIH registry was used, the estimated survival (gray line) was ≈10% lower than what was actually observed.

CI, 57.6 to 81.6), and 54.9% (95% CI, 41.8 to 68.0), respectively.

Combined Analysis Population

The baseline characteristics of the combined analysis population, corresponding to the incident population together with those prevalent patients who were diagnosed within 3 years before study entry (n=190), are described in Table 1. Of 190 patients, 55 had died at 3 years. Survival estimates were 82.9% (95% CI, 72.4 to 95.0), 67.1% (95% CI, 57.1 to 78.8), and 58.2% (95% CI, 49.0 to 69.3) at 1, 2, and 3 years, respectively (Figure 2). Using the predictive modeling approach of the NIH registry,¹⁹ we found the estimated survival to be ≈10% lower than what was actually observed (Figure 2). In individual analysis, female gender, NYHA FC I/II, greater 6MWD, lower right atrial pressure, and higher cardiac output were significantly and positively associated with survival (Table 2 and Figure 3). Multivariable analysis indicated that being female, having a greater 6MWD, and exhibiting higher cardiac output were jointly significantly associated with improved survival (Table 3). The predictive discrimination concordance was estimated to be C=0.57 (95% CI, 0.29 to 0.82) in this model.

Discussion

In this study, we observed that survival in patients with idiopathic, familial, and anorexigen-associated PAH has improved compared with historical cohorts¹⁹ but remains unsatisfactory, highlighting that in the modern management era, PAH remains a progressive, fatal disease.

To analyze a homogeneous population, our study focused on patients with idiopathic, familial, and anorexigen-associated PAH, types of PAH that have similar outcomes and share clinical and genetic characteristics.^{9–11} In addition, to remove survivor bias in our study, survival estimates and Cox PH models from time to diagnosis accounted for the delay between diagnosis and study entry (patients were in the risk set only from their time of study entry, called the combined analysis popula-

Table 2. Individual Cox PH Analysis of Selected Baseline Variables

	Incident+Prevalent Cases (≤36-mo Diagnosis Delay With Adjustment for Diagnosis Delay) (n=190)		
	HR	95% CI	P
Age, y			
≤39	0.661	[0.332–1.316]	0.24
40–52	0.511	[0.230–1.133]	0.10
53–62	1.174	[0.625–2.204]	0.62
≥63	1.863	[1.077–3.223]	0.03
Gender			
Male	1		
Female	0.517	[0.302–0.887]	0.02
Diagnosis			
Idiopathic PAH	2.261	[0.814–6.281]	0.12
Familial PAH	0.399	[0.047–2.458]	0.29
Anorexigen-associated PAH	0.529	[0.165–1.701]	0.29
NYHA FC			
I/II	0.402	[0.158–1.019]	0.06
III	1.297	[0.687–2.450]	0.42
IV	1.753	[0.824–3.730]	0.15
6MWD*	0.996	[0.994–0.999]	0.01
Hemodynamics			
RAP	1.060	[1.016–1.107]	0.01
mPAP	0.994	[0.973–1.016]	0.60
PAOP	1.002	[0.920–1.091]	0.96
CO	0.746	[0.591–0.942]	0.01
Cardiac index	0.584	[0.379–0.899]	0.02
PVR	1.040	[0.993–1.089]	0.10
PVRI	1.023	[0.995–1.051]	0.11

Abbreviations as in Table 1, plus HR indicates hazard ratio. *Model includes the done/not done covariate.

tion).²⁹ Our study analyzed a population of PAH patients without associated conditions, broadly similar to those from the NIH Primary Pulmonary Hypertension Registry. Of note, 36% of these NIH registry patients were prevalent cases because they reported a previous diagnosis of primary pulmonary hypertension (the median time between first diagnosis and diagnosis at a registry center was 1.6 years in these prevalent cases).¹⁹ Compared with the NIH survival, our present data suggest “real-life” improvements in survival in the modern management era. Although improvements in survival compared with the predicted survival calculated with the NIH equation have been demonstrated in clinical trials of novel agents, such trials generally include patients with stable disease (mostly NYHA FC II and III) who are therefore less representative of real-life unselected patient populations.^{23,24,28,29,33,34}

In the combined analysis, independent predictors of survival included female gender, greater 6MWD, and higher cardiac output. This finding suggests that diagnosis and active management of patients with less advanced disease and relatively preserved right ventricular function

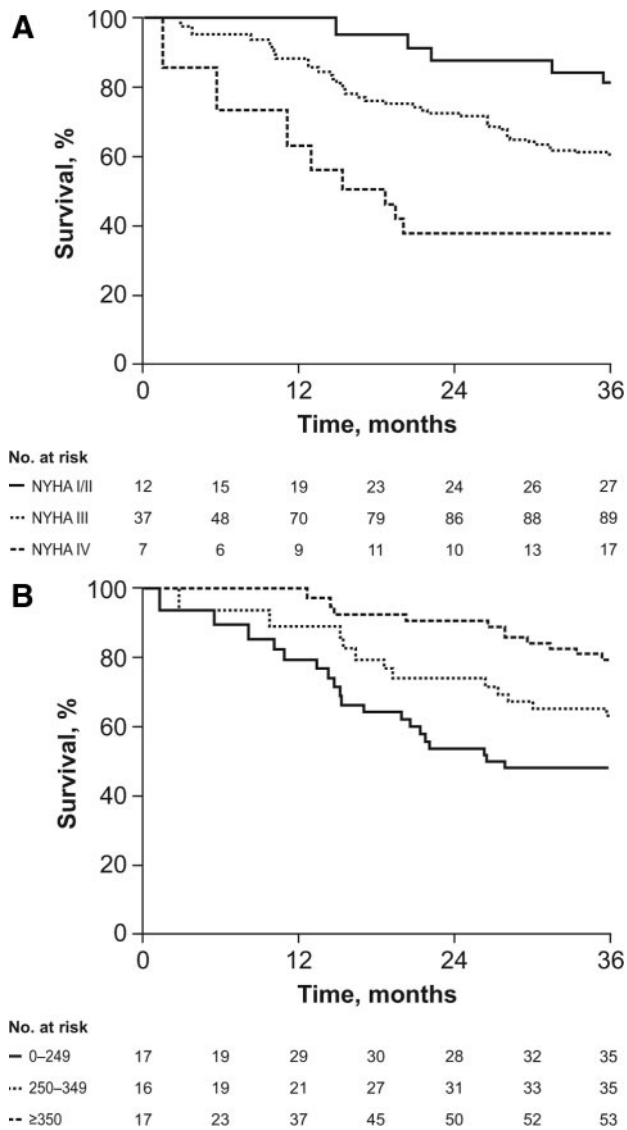


Figure 3. A, Kaplan-Meier estimates of survival among the combined population of patients with idiopathic, familial, and anorexigen-associated PAH stratified according to baseline NYHA FC. B, Kaplan-Meier estimates of survival among the combined population of patients with idiopathic, familial, and anorexigen-associated PAH stratified according to baseline 6MWD.

and exercise capacity may in turn lead to better outcomes. Conversely, later diagnosis and management of PAH in more disabled patients translate into worse survival.^{19–22} In our study, the majority of patients had severe functional impairment at diagnosis (>75% were in NYHA FC III or IV), indicating that action is required to improve early diagnosis. Two multicenter screening programs in large cohorts of patients with systemic sclerosis³⁵ or HIV infection³⁶ demonstrated that individuals with PAH diagnosed during screening have markedly better hemodynamic and clinical characteristics compared with patients with conventionally diagnosed disease. In these studies, the majority of screened patients were in NYHA FC II with mildly elevated mean pulmonary artery pressure and pulmonary vascular resistance and better exercise capacity

Table 3. Multivariable Cox PH Model

	Incident+Prevalent Cases (≤ 36 -mo Diagnosis Delay With Adjustment for Diagnosis Delay) (n=190)		
	HR	95% CI	P
6MWD	0.996	0.993–0.999	0.004
Gender			
Male	1		
Female	0.375	0.212–0.662	<0.001
Cardiac output	0.759	0.599–0.961	0.02

HR indicates hazard ratio. Variables that were considered in this model ($P \leq 0.2$ from Table 2) were age quartiles (4 levels), gender, 6MWD, NYHA FC (3 levels), right atrial pressure, cardiac output, cardiac index, pulmonary vascular resistance, pulmonary vascular resistance index, diagnosis, and interaction covariates (6MWD \times NYHA FC I, 6MWD \times NYHA FC II, gender \times age quartile 1, gender \times age quartile 2, gender \times age quartile 3).

and outcomes.^{35,36} Increased awareness of PAH should allow earlier diagnosis and management and thus improve outcomes in patients with idiopathic, familial, and anorexigen-associated PAH.^{35–37}

Our results confirm that exercise limitation, as demonstrated by reduced 6MWD, is an excellent predictor of death in PAH. Similarly, hemodynamic impairment with reduced cardiac output predicts poor outcome, further highlighting the importance of early diagnosis before the occurrence of advanced right ventricular failure. Our data also indicate that female patients with PAH exhibit better survival compared with male patients, although the reason underlying this observation remains unknown. Idiopathic, familial, and anorexigen-associated PAH are all characterized by a female predominance, suggesting hormonal influences on disease occurrence.³⁸ Our data confirm female predominance but also indicate that male patients are at greater risk of mortality, despite similar management. Further studies are needed to investigate the reasons underlying this difference.

Therapy was proposed in accordance with national recommendations for PAH treatment.³¹ The percentage of patients on first-line calcium channel blockers was slightly higher than that recently described.³² Indeed, we have previously shown that long-term calcium channel blocker responders represent <10% of idiopathic PAH patients referred to a specialized pulmonary vascular referral center.³² In our published retrospective study, 12.6% of patients with idiopathic PAH had evidence of acute pulmonary vasoreactivity and received calcium channel blocker therapy.³² Of them, only 6.8% had long-term response.³² Similarly, in our previous report of the French registry, we found that 10.3% of patients with idiopathic PAH had a positive vasoreactivity test.²⁹ Despite these relatively low numbers, we show in the present study that calcium channel blocker therapy was given to 21.4% of incident patients and to 13.8% of the combined population. Our interpretation of these higher numbers is that “borderline responders” were often offered vasodilator therapy in real-life settings at the time of recruitment in the study. This is well in keeping with other published populations such as patients enrolled in random-

ized placebo-controlled trials. For instance, calcium channel blocker therapy was given to half of the patients in the Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE-1) reported in 2002.²⁸

The relatively high rate of subjects treated with only supportive measures reflects the availability of therapies for the less severely ill in France between 2002 and 2006. With improved knowledge of PAH care since 2006, this observation may no longer reflect current management. Approved treatment strategies in PAH are currently based on 3 classes of drugs that mostly target endothelial cell dysfunction (prostacyclin, nitric oxide, and endothelin-1 pathways), which can improve functional capacity, exercise tolerance, and hemodynamics.^{26,27} Although this study was not designed to compare treatment strategies with the previous management era, we nevertheless observed that despite novel therapeutic strategies, PAH remains a progressive, fatal disease.

Several strategies are currently being investigated in PAH, including early treatment³⁷ and combinations of targeted therapies.^{39–44} Long-term, adequately powered, prospective, randomized, double-blind, placebo-controlled studies are still needed to conclusively determine the effect of such combination therapy in PAH.^{39–44} Of note, despite nearly one third of incident patients having received sequential combinations of approved targeted therapies, the incident patients included in the present study still exhibited progressive, fatal disease. Many patients enrolled in the study had a fatal progressive evolution that would have indicated lung transplant in eligible individuals.⁴⁵ However, few patients received lung transplantation during the 3-year study period, reflecting a shortage of organ donors.

Our analysis focused on a homogeneous patient population with idiopathic, familial, and anorexigen-associated PAH; therefore, our results cannot be readily generalized to patient groups with PAH associated with other diseases.^{5,12–17} In addition, our study was performed in selected centers with expertise in pulmonary vascular medicine and may therefore focus on a subset of patients with severe disease. Because PAH care in France is performed by a network of selected sites associated with the French national referral center, our results presumably represent the current status of PAH management and outcomes in the modern management era in France.²⁹ Because this is a real-world observational study, therapies were used as considered appropriate at each center in accordance with national recommendations for PAH treatment.³³ The selection of a hard outcome measure (survival) in a population with no comorbid conditions is a strength of this multicenter nationwide study.

Conclusions

This contemporary study provides novel information on PAH in the era of modern management. Although current survival in idiopathic, familial, and anorexigen-associated PAH is better than in historical series, this condition still remains a progressive fatal disease, especially when one analyzes an incident population. Mortality was most closely associated with male gender, right ventricular hemodynamic function,

and exercise limitation in idiopathic, familial, and anorexigen-associated PAH.

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CLINICAL PERSPECTIVE

The management of pulmonary arterial hypertension has advanced significantly since the publication of the National Institutes of Health–supported 1980s registry, which established a prognostic benchmark for survival that is still used today. The present article reports results from the French Network on Pulmonary Hypertension national prospective registry, which investigated contemporary, “real-world” survival during a 3-year follow-up of consecutive adult patients with idiopathic, familial, or anorexigen-associated pulmonary arterial hypertension. Patients were enrolled between October 2002 and October 2003 and received treatment according to recommendations and availability. Kaplan-Meier survival estimates at 1, 2, and 3 years were 85.7%, 69.6%, and 54.9%, respectively, in incident cases, and 82.9%, 67.1%, and 58.2%, respectively, in a combined incident and prevalent population. With the use of the modeling approach of the original National Institutes of Health registry, observed survival in the current management era was improved by $\approx 10\%$ versus estimates. Mortality was most closely associated with male gender, right ventricular hemodynamic function, and exercise limitation. In summary, although survival among patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension has improved compared with historical estimates, it is clear that pulmonary arterial hypertension remains a progressive, fatal disease. Continued efforts are required to improve the management of patients with pulmonary arterial hypertension.