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# Outcome of adults with Eisenmenger syndrome treated with drugs specific to pulmonary arterial hypertension: A French multicentre study

*Devenir des adultes avec syndrome d'Eisenmenger traités par médicaments spécifiques anti-hypertenseur pulmonaire : données d'une étude multicentrique française*

Sebastien Hascoet<sup>a,b,\*</sup>, Emmanuelle Fournier<sup>a,b,c</sup>,  
Xavier Jaïs<sup>d,e</sup>, Lauriane Le Gloan<sup>f</sup>, Claire Dauphin<sup>g</sup>,  
Ali Houeijeh<sup>h</sup>, Francois Godart<sup>h</sup>, Xavier Iriart<sup>c</sup>,  
Adelaïde Richard<sup>i</sup>, Jelena Radojevic<sup>j</sup>,  
Pascal Amedro<sup>k</sup>, Gilles Bosser<sup>l</sup>, Nathalie Souletie<sup>m</sup>,  
Yvette Bernard<sup>n</sup>, Pamela Mocerio<sup>o</sup>, Hélène Bouvaist<sup>p</sup>,  
Pierre Mauran<sup>q</sup>, Elise Barre<sup>r</sup>, Adeline Basquin<sup>s</sup>,  
Clement Karsenty<sup>m,t,u</sup>, Damien Bonnet<sup>v</sup>,  
Laurence Iserin<sup>t,u</sup>, Olivier Sitbon<sup>d,e</sup>, Jérôme Petit<sup>a,b</sup>,  
Elie Fadel<sup>e,w,x</sup>, Marc Humbert<sup>d,e</sup>,  
Magalie Ladouceur<sup>t,u,v</sup>

<sup>a</sup> Department of congenital heart diseases, centre de référence malformations cardiaques congénitales complexes M3C, hôpital Marie-Lannelongue, 133, avenue de la Résistance, 92350 Le Plessis-Robinson, France

<sup>b</sup> Faculté de médecine Paris-Sud, université Paris-Sud, université Paris-Saclay, Paris, France

<sup>c</sup> Department of congenital heart diseases, centre de compétence M3C, CHU de Bordeaux, Bordeaux, France

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*Abbreviations:* CHD, Congenital heart disease; ERA, Endothelin receptor antagonist; ES, Eisenmenger syndrome; MCE, Major clinical event; NYHA/WHO FC, New York Heart Association/World Health Organization functional class; PAH, Pulmonary arterial hypertension; PAH-SDT, Pulmonary arterial hypertension-specific drug therapy; SaO<sub>2</sub>, Peripheral arterial oxygen saturation.

\* Corresponding author. Department of congenital heart diseases, centre de référence malformations cardiaques congénitales complexes M3C, hôpital Marie-Lannelongue, 133, avenue de la Résistance, 92350 Le Plessis-Robinson, France.

E-mail address: [s.hascoet@ccml.fr](mailto:s.hascoet@ccml.fr) (S. Hascoet).



- <sup>d</sup> Service de pneumologie, centre de référence de l'hypertension pulmonaire sévère, DHU thorax innovation, hôpital Bicêtre, Le Kremlin-Bicêtre, France
- <sup>e</sup> UMR-S 999, Inserm, hôpital Marie-Lannelongue, université Paris-Sud, université Paris-Saclay, Paris, France
- <sup>f</sup> Department of cardiology, centre de compétence M3C, CHU de Nantes, Nantes, France
- <sup>g</sup> Department of cardiology, centre de compétence M3C, CHU de Clermont-Ferrand, Clermont-Ferrand, France
- <sup>h</sup> Department of paediatric cardiology, centre de compétence M3C, CHRU de Lille, Lille, France
- <sup>i</sup> Paediatric and adult congenital heart diseases centre, cabinet Intercard Vendôme, Lille, France
- <sup>j</sup> Fetal, paediatric and congenital cardiology, clinique de l'Orangerie, Strasbourg, France
- <sup>k</sup> Paediatric and congenital cardiology department, M3C regional reference centre, university hospital, physiology and experimental biology of heart and muscles laboratory, PHYMEDEXP, UMR CNRS 9214–Inserm U1046, university of Montpellier, Montpellier, France
- <sup>l</sup> Department of congenital heart diseases and paediatric cardiology, centre de compétence M3C, CHRU de Nancy, Nancy, France
- <sup>m</sup> Department of cardiology, centre de compétence M3C, CHU de Toulouse, Toulouse, France
- <sup>n</sup> Department of cardiology, centre de compétence M3C, CHU de Besançon, Besançon, France
- <sup>o</sup> Department of cardiology, centre de compétence M3C, CHU de Nice, Nice, France
- <sup>p</sup> Department of cardiology, centre de compétence M3C, CHU de Grenoble, Grenoble, France
- <sup>q</sup> Department of paediatric and congenital cardiology, centre de compétence M3C, American memorial hospital, CHU de Reims, Reims, France
- <sup>r</sup> Department of paediatric and congenital cardiology, centre de compétence M3C, CHU de Rouen, Rouen, France
- <sup>s</sup> Department of cardiology, centre de compétence M3C, CHU de Rennes, Rennes, France
- <sup>t</sup> Adult congenital heart diseases unit, department of cardiology, centre de référence M3C, hôpital européen Georges-Pompidou, Assistance publique–Hôpitaux de Paris, Paris, France
- <sup>u</sup> Paris cardiovascular research centre (PARCC), Inserm U970, Paris Descartes University, Paris, France
- <sup>v</sup> Centre de référence malformations cardiaques congénitales complexes M3C, hôpital universitaire Necker-Enfants-Malades, Assistance publique–Hôpitaux de Paris, université Paris Descartes, Sorbonne Paris Cité, Paris, France
- <sup>w</sup> Department of thoracic surgery, hôpital Marie-Lannelongue, Plessis-Robinson, France
- <sup>x</sup> Faculté de médecine Paris-Sud, université Paris Sud, université Paris-Saclay, Paris, France

## KEYWORDS

Eisenmenger syndrome;  
Drug therapy;  
Outcome;  
Pulmonary arterial hypertension;  
Congenital heart diseases

## Summary

**Background.** – The relationship between pulmonary arterial hypertension-specific drug therapy (PAH-SDT) and mortality in Eisenmenger syndrome (ES) is controversial.

**Aims.** – To investigate outcomes in patients with ES, and their relationship with PAH-SDT.

**Methods.** – Retrospective, observational, nationwide, multicentre cohort study.

**Results.** – We included 340 patients with ES: genetic syndrome ( $n=119$ ; 35.3%); pretricuspid defect ( $n=75$ ; 22.1%). Overall, 276 (81.2%) patients received PAH-SDT: monotherapy (endothelin receptor antagonist [ERA] or phosphodiesterase 5 inhibitor [PDE5I]) 46.7%; dual therapy (ERA + PDE5I) 40.9%; triple therapy (ERA + PDE5I + prostanoid) 9.1%. Median PAH-SDT duration was 5.5 years [3.0–9.1 years]. Events (death, lung or heart-lung transplantation) occurred in 95 (27.9%) patients at a median age of 40.5 years [29.4–47.6]. The cumulative occurrence of events was 16.7% [95% confidence interval 12.8–21.6%] and 46.4% [95% confidence interval 38.2–55.4%] at age 40 and 60 years, respectively. With age at evaluation or time since PAH diagnosis as time scales, cumulative occurrence of events was lower in patients taking one or two PAH-SDTs ( $P=0.0001$  and  $P=0.004$ , respectively), with the largest differences in the post-tricuspid defect subgroup ( $P<0.001$  and  $P<0.02$ , respectively) versus patients without PAH-SDT. By multivariable Cox analysis, with time since PAH diagnosis as time scale, New York Heart Association/World Health Organization functional class III/IV, lower peripheral arterial oxygen saturation and pretricuspid defect were associated with a higher risk of events ( $P=0.002$ ,  $P=0.01$  and  $P=0.04$ , respectively), and one or two PAH-SDTs with a lower risk of events ( $P=0.009$ ).

*Conclusions.* – Outcomes are poor in ES, but seem better with PAH-SDT. ES with pretricuspid defects has worse outcomes despite the delayed disease onset.

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## MOTS CLÉS

Syndrome d'Eisenmenger ;  
Médicament ;  
Pronostic ;  
Cardiopathies congénitales ;  
Hypertension artérielle pulmonaire

## Résumé

*Contexte.* – L'intérêt du traitement médical spécifique (TMS) de l'hypertension artérielle pulmonaire (HTAP) dans le syndrome d'Eisenmenger (SE) est controversé.

*Objectifs.* – Étudier le pronostic à long terme des patients ayant un SE et la relation avec le TMS.

*Méthodes.* – Une cohorte observationnelle longitudinale multicentrique rétrospective historique française de 340 SE a été constituée.

*Résultats.* – Le shunt était prétricuspidé dans 75 cas (22,1 %). Au total, 276 (81,2 %) patients étaient sous TMS (monothérapie 46,7 % ; bi-thérapie 40,9 % ; tri-thérapie 9,1 %). La durée médiane de TMS était de 5,5 ans [3,0–9,1]. Un événement clinique majeur (ECM : décès, transplantation cardiopulmonaire ou bipulmonaire) a été observé dans 95 (27,9 %) cas à un âge médian de 40,5 [29,4–47,6] ans. La survenue cumulée d'un ECM était de 16,7 % [IC 95 % 12,8–21,6 %] et 46,4 % [IC 95 % 38,2–55,4 %] à l'âge de 40 et 60 ans. Avec l'âge ou le délai depuis le premier examen comme échelle temporelle, la survenue cumulée des ECM était moindre chez les patients sous un ou deux TMS ( $p=0,0001$  et  $p=0,004$ ), en particulier chez les patients avec un shunt post-tricuspidé ( $p<0,001$  et  $p<0,02$ ) comparée aux patients sans TMS. Une analyse multivariée de Cox avec le délai depuis le diagnostic de l'HTAP comme échelle temporelle a montré qu'une classe fonctionnelle III ou IV de la NYHA/WHO, une saturation périphérique en oxygène basse (en variable continue), un shunt pré-tricuspidé et l'absence de TMS étaient associés à un risque augmenté d'ECM ( $p=0,002$  ;  $p=0,01$  ;  $p=0,04$  and  $p=0,009$ , respectivement).

*Conclusions.* – Le TMS dans le SE semble associé à un meilleur pronostic. Néanmoins, même avec un traitement médical palliatif, le pronostic du SE reste altéré. Les patients avec un shunt prétricuspidé ont un profil clinique et un pronostic plus sombre malgré une survenue plus tardive de l'HTAP.

## Background

Eisenmenger syndrome (ES) develops when pulmonary arterial hypertension (PAH) caused by an unrepaired congenital left-to-right shunt becomes sufficiently severe to reverse the direction of the shunt, resulting in cyanosis [1]. ES is present in 3.5–12.0% of adults with congenital heart disease (CHD) [2].

PAH-specific drug therapies (PAH-SDTs) are mainly designed to induce vasodilation and diminish pulmonary microvascular remodelling [3,4]. Moderate beneficial effects of PAH-SDTs on New York Heart Association/World Health Organization functional class (NYHA/WHO FC) have been reported in patients with ES [5,6]. The PAH-SDT bosentan, a dual endothelin receptor antagonist (ERA), is approved in Europe for patients who are NYHA/WHO FC III or IV [7]. Evidence supporting the use of other PAH-SDTs in ES is scantier [7]. Indeed, survival is better in ES than in idiopathic PAH, and the long-term effects of PAH-SDTs on hard outcomes, such as death and lung transplantation, remain unclear [6,8–12].

We conducted a large, multicentre, retrospective, cohort study of patients with ES to assess the relationships linking PAH-SDT to death and lung transplantation.

## Methods

This retrospective, longitudinal, cohort study included all patients with ES followed in French tertiary care centres (university hospitals, the M3C Network for Complex CHD, the French Community of CHD Specialists [filiale de cardiologie pédiatrique et congénitale de la Société française de cardiologie] and the French referral centre for severe pulmonary hypertension). This study was compliant with the requirements of the Commission nationale de l'informatique et des libertés, and all patients provided informed consent to participate [13].

ES was defined as PAH (as demonstrated by right-heart catheterization, showing a mean pulmonary pressure of  $\geq 25$  mmHg, a normal pulmonary capillary wedge pressure of  $\leq 15$  mmHg and pulmonary vascular resistance  $> 3$  Wood units) in the presence of a large, non-restrictive, intracardiac or extracardiac shunt, according to the Nice classification [7,14]. Patients with other patterns of PAH associated with CHD were not included: PAH with coincidental small cardiac defect or patent foramen ovale, or correctable or non-correctable prevalent systemic-to-pulmonary shunt; patients who had previously undergone corrective surgery or interventions and did not present with



an unrestrictive residual shunt; patients with Glenn-type physiology; and those with segmental pulmonary hypertension (e.g. pulmonary atresia with ventricular septal defects). The diagnosis of CHD was based on echocardiography and/or cardiac catheterization findings.

For each patient, the following data were retrieved from the medical files: age; sex; cardiac and extracardiac diagnoses, including genetic syndromes; NYHA/WHO FC; resting peripheral arterial oxygen saturation (SaO<sub>2</sub>), 6-minute walking test results; and medications (PAH-SDTs, heart-failure medications, oral anticoagulation and aspirin). For each patient on PAH-SDTs, we collected clinical data for three time points: PAH diagnosis; PAH-SDT initiation; and most recent evaluation. For each patient without PAH-SDT, there were only two data-collection time points: PAH diagnosis; and most recent evaluation. Data for the earliest time point were not collected when the PAH diagnosis data were unclear.

Follow-up data were obtained from the medical files and by telephone calls to patients, relatives, general practitioners and/or cardiologists. The following clinical events were recorded: heart failure; severe infection; arrhythmias; stroke; haemoptysis; other bleeding events; lung or heart-lung transplantation; and death. Selection for transplantation was based on an assessment of each individual patient during a multidisciplinary discussion that focused on functional class and right-heart-failure variables [15].

## Statistical methods

Statistical analyses were performed using Stata<sup>®</sup> 11.2 software (StataCorp, College Station, TX, USA). Data are described as mean ± standard deviation for normally distributed variables, median [interquartile range] for skewed continuous variables and number (%) for categorical variables. Categorical variables were compared with the  $\chi^2$  statistic or Fisher's exact statistic. Comparisons of continuous variables were done with Student's *t* test for independent samples, if its basic assumptions were satisfied (Shapiro-Wilks and Levene tests), and the Wilcoxon-Mann-Whitney U test otherwise. When continuous variables were distributed among more than two groups, the Kruskal-Wallis test was applied. Within-patient comparisons of continuous variables at different time points were made with the Wilcoxon matched-pairs signed-rank test. In patients taking PAH-SDT, changes in clinical variables from PAH-SDT initiation to the most recent evaluation were assessed, regardless of the number of drugs. Reported *P*-values are two-sided. *P*-values < 0.05 were considered statistically significant.

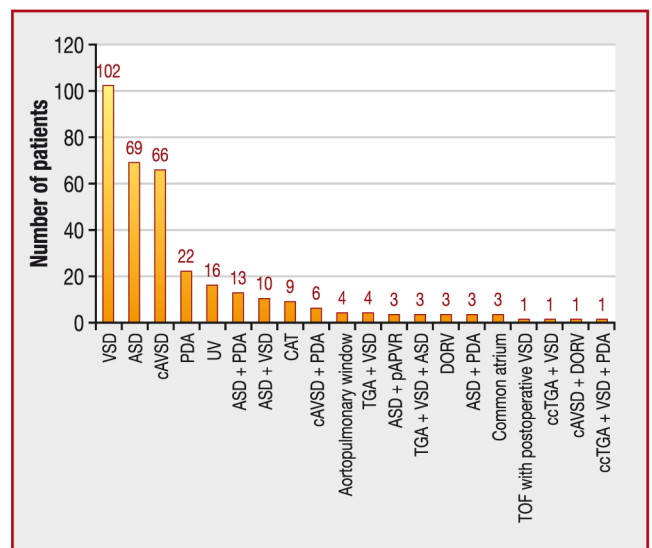
Kaplan–Meier curves of time to major clinical events (MCEs) (i.e. death, heart-lung transplantation and lung transplantation) were plotted using two different time scales: age at last follow-up, with the scale starting at 18 years, as the study was confined to adults; and years since PAH diagnosis. Differences between event-free times for each PAH-SDT and clinical data were assessed using the log-rank test. Patients with pretricuspid defects were divided into two groups according to age at PAH diagnosis. The cut-off value for age was determined by receiver operating characteristic curve analysis. Associations between baseline variables and outcomes were assessed in a Cox proportional

hazards model with stepwise backward regression, including all variables associated with MCEs ( $P \leq 0.1$ ). Proportionality of hazards was evaluated by applying a test for correlation between the scaled Schoenfeld residuals and the logarithmic transformation of time. A first model was built using clinical data at PAH diagnosis and age as the time scale. Defect location, PAH-SDT, CHD complexity, sex and genetic syndrome were forced into the model at the start of the regression process. A second model was built using clinical data at PAH diagnosis, and time since PAH diagnosis as the time scale. Defect location, PAH-SDT, CHD complexity, sex and genetic syndrome were also forced into the model at the start of the regression process.

## Results

### Study population

We included 340 patients at 20 French centres, six to 99 per centre (online-only [Appendix 1](#)). The percentage of patients taking PAH-SDT ranged across centres from 41.7% to 100.0%. Data at PAH diagnosis were available for 298 (87.6%) patients overall, 73 of 75 (97.3%) with pretricuspid shunt and 225 of 265 (84.9%) with posttricuspid defects. [Table 1](#) reports the demographic and clinical data in the overall population and in the two subgroups defined by defect location. A post-tricuspid defect (isolated or with another defect) was diagnosed in 265 (77.9%) patients. [Fig. 1](#) reports the distribution of diagnoses. Ventricular septal defect predominated ( $n=102$ ; 30.0%), followed by atrial septal defect ( $n=69$ ; 20.3%), complete



**Figure 1.** Distribution of diagnoses in the study patients. The numbers at the top of the bars are the numbers of patients with the relevant diagnosis. ASD: atrial septal defect; CAT: common arterial trunk; cAVSD: complete atrioventricular septal defect; ccTGA: congenitally corrected transposition of the great arteries; DORV: double outlet right ventricle; PAPVR: partial anomalous pulmonary venous return; PDA: patent ductus arteriosus; TGA: transposition of the great arteries; TOF: tetralogy of Fallot; UV: univentricular heart; VSD: ventricular septal defect.

**Table 1** Demographic and clinical data for the whole population, and divided in two subgroups according to shunt position.

|                                     | Total population<br>(n = 340) | Pretricuspid shunt<br>(n = 75; 22.1%) | Mixed or post-tricuspid shunt<br>(n = 265; 77.9%) | P        |
|-------------------------------------|-------------------------------|---------------------------------------|---|----------|
| Female sex                          | 236 (69.4)                    | 63 (84.0)                             | 173 (65.3)  | 0.002    |
| Genetic syndrome                    | 119 (35.0)                    | 2 (2.7)                               | 117 (44.2)  | < 0.0001 |
| <i>First exam (n = 299; 87.4%)</i>  |                               |                                       |   |          |
| Age (years) (n = 299)               | 26.5 [11.9–39.7]              | 37.7 [26.7–52.4]                      | 20.6 [8.4–35.1]                                   | < 0.0001 |
| SaO <sub>2</sub> (%) (n = 185)      | 85 [81–90]                    | 90 [84–93]                            | 85 [80–90]  | 0.02     |
| 6-minute walking test (m) (n = 68)  | 348 [231–385]                 | 371 [276–461]                         | 331 [180–375]                                     | 0.04     |
| NYHA/WHO FC (n = 231)               |                               |                                       |   | 0.04     |
| 1                                   | 27 (11.7)                     | 4 (7.8)                               | 23 (12.8)   |          |
| 2                                   | 115 (49.8)                    | 19 (37.3)                             | 96 (53.3)   |          |
| 3                                   | 85 (36.8)                     | 26 (51.0)                             | 59 (32.8)   |          |
| 4                                   | 4 (1.7)                       | 2 (3.9)                               | 2 (1.1)   |          |
| <i>Last exam (n = 327; 96.2%)</i>   |                               |                                       |   |          |
| Age (years) (n = 327)               | 41.7 [32.0–52.0]              | 49.6 [40.0–60.2]                      | 40.0 [30.1–49.6]                                  | < 0.0001 |
| SaO <sub>2</sub> (%) (n = 275)      | 85 [79–89]                    | 90 [82–92]                            | 84 [78–88]  | < 0.0001 |
| 6-minute walking test (m) (n = 166) | 358 [280–446]                 | 410 [330–483]                         | 342 [266–432]                                     | 0.01     |
| NYHA/WHO FC (n = 285)               |                               |                                       |   | 0.2      |
| 1                                   | 17 (6.0)                      | 3 (4.9)                               | 14 (6.3)  |          |
| 2                                   | 140 (49.1)                    | 25 (41.0)                             | 115 (51.3)  |          |
| 3                                   | 96 (33.7)                     | 22 (36.1)                             | 74 (33.0)   |          |
| 4                                   | 32 (11.2)                     | 11 (18.0)                             | 21 (9.4)  |          |
| PAH-SDT                             | 276 (81.2)                    | 69 (92.0)                             | 207 (78.1)  | 0.007    |
| Single therapy                      | 129 (39.0)                    | 24 (32.4)                             | 105 (40.9)  | < 0.0001 |
| Double therapy                      | 113 (34.1)                    | 30 (40.5)                             | 83 (32.3)   |          |
| Triple therapy                      | 25 (7.6)                      | 14 (18.9)                             | 11 (4.3)  |          |
| Complications                       | 194 (57.1)                    | 46 (61.3)                             | 148 (55.9)  | 0.5      |
| Heart failure                       | 73 (21.5)                     | 23 (30.7)                             | 50 (18.9)   | 0.03     |

Data are expressed as number (%) for qualitative variables and median [interquartile range] for quantitative variables. PAH-SDT: pulmonary arterial hypertension-specific drug therapy; SaO<sub>2</sub>: peripheral arterial oxygen saturation; NYHA/WHO FC: New York Heart Association/World Health Organization functional class.

atrioventricular septal defect (n = 66; 19.4%), patent ductus arteriosus (n = 22; 6.5%), univentricular heart (n = 16; 4.7%) and ventricular septal defect + patent ductus arteriosus (n = 13; 3.8%). Other defects were less common.

Comparing the two defect-location subgroups showed a higher proportion of women in the pretricuspid group (P = 0.002) and patients with genetic syndromes (chiefly Down syndrome, n = 111/117; 94.9%) in the post-tricuspid group (P < 0.0001) (Table 1). Median age at PAH diagnosis in the pretricuspid group was 37.7 years (range: 3.0–82.7 years). At PAH diagnosis, patients with pretricuspid defects were older (P < 0.0001), had a higher resting SaO<sub>2</sub> (P = 0.02) and 6-minute walking test distance (P = 0.04), and a lower NYHA/WHO FC (P = 0.04). At last evaluation, resting SaO<sub>2</sub> and 6-minute walking test distance remained higher in the pretricuspid group (P < 0.0001 and P = 0.01, respectively), which had higher proportions of patients taking oral anticoagulation (P < 0.0001) and PAH-SDT (P = 0.007). PAH-SDT was more intensive in the pretricuspid than the post-tricuspid group; thus, 40.5% of patients with pretricuspid defects were taking two drugs, and 18.9% were taking three drugs (P < 0.0001).

## PAH-SDT

Table 2 reports the demographic and clinical data in PAH-SDT users and non-users at the last evaluation. Of the 340 patients, (81.2%), 276 took PAH-SDTs. The 64 non-users were younger and predominantly had post-tricuspid or combined defects. The proportion of PAH-SDT users was non-significantly lower in the group with genetic syndromes (76.5%; P = 0.1).

Clinical data at PAH-SDT initiation were available for 259 (93.8%) of the 276 users. The median age was 41.0 years [32.4–56.0 years] in the pretricuspid group and 34.4 years [26.0–44.9 years] in the post-tricuspid/combined group (P < 0.0001). NYHA/WHO FC was III or IV in 62.7% of patients at PAH-SDT initiation, whereas 6 (2.9%) patients were class I. Median follow-up after PAH-SDT initiation was 5.5 years [3.0–9.1 years].

SaO<sub>2</sub> did not change significantly from PAH-SDT initiation to the last evaluation (P = 1.0). The 6-minute walking test distance increased (364 vs 330 m; P = 0.0003). NYHA/WHO FC improved in 69 (35.6%) users, remained unchanged in 89 (45.9%) and deteriorated in 36 (18.6%). In PAH-SDT

**Table 2** Demographic and clinical data in two subgroups according to pulmonary arterial hypertension-specific drug therapy.

|  | PAH-SDT<br>(n = 276; 81.2%) | No PAH-SDT<br>(n = 64; 18.8%) | P            |
|--|-----------------------------|-------------------------------|--------------|
| <i>Genetic syndrome</i>                                | 91 (33.0)                   | 28 (43.8)                     | 0.07         |
| <i>Pretricuspid shunt</i>                              | 69 (25.0)                   | 6 (9.4)                       | 0.007        |
| <i>First exam (n = 299, 87.4%)</i>                     |                             |                               |              |
| Age (years) (n = 299)                                  | 27.8 [12.8–41.0]            | 18.6 [7.2–29.7]               | 0.02         |
| SaO <sub>2</sub> (%) (n = 185)                         | 85 [81–90]                  | 86 [80–91]                    | 0.7          |
| 6-minute walking test (m) (n = 68)                     | 350 [239–387]               | 180 [150–372]                 | <sup>a</sup> |
| NYHA/WHO FC (n = 231)                                  |                             |                               | 0.6          |
| 1  | 21 (11.4)                   | 6 (12.8)                      |              |
| 2  | 88 (47.8)                   | 27 (57.5)                     |              |
| 3  | 71 (38.6)                   | 14 (29.8)                     |              |
| 4  | 4 (2.2)                     | 0 (0.0)                       |              |
| <i>Exam before PAH-SDT initiation (n = 259; 93.8%)</i> |                             |                               |              |
| Age (years) (n = 259)                                  | 36.7 [27.6–47.0]            |                               |              |
| SaO <sub>2</sub> (%) (n = 196)                         | 84 [80–89]                  |                               |              |
| 6-minute walking test (m) (n = 142)                    | 330 [230–396]               |                               |              |
| NYHA/WHO FC (n = 209)                                  |                             |                               |              |
| 1  | 6 (2.9)                     |                               |              |
| 2  | 72 (34.5)                   |                               |              |
| 3  | 118 (56.5)                  |                               |              |
| 4  | 13 (6.2)                    |                               |              |
| <i>Last exam (n = 327; 96.2%)</i>                      |                             |                               |              |
| Age (years) (n = 327)                                  | 43.0 [33.0–52.3]            | 38.4 [28.9–46.9]              | 0.006        |
| SaO <sub>2</sub> (%) (n = 275)                         | 85 [80–90]                  | 83 [74–88]                    | 0.2          |
| 6-minute walking test (m) (n = 166)                    | 364 [285–450]               | 315 [228–432]                 | 0.2          |
| NYHA/WHO FC (n = 285)                                  |                             |                               | 0.8          |
| 1  | 13 (5.6)                    | 4 (7.7)                       |              |
| 2  | 117 (50.2)                  | 23 (44.3)                     |              |
| 3  | 77 (33.0)                   | 19 (36.5)                     |              |
| 4  | 26 (11.2)                   | 6 (11.5)                      |              |
| <i>Complications</i>                                   | 152 (55.1)                  | 42 (65.6)                     | 0.2          |
| Heart failure  | 60 (21.7)                   | 13 (20.3)                     | 1.0          |
| Severe infectious syndrome                             | 21 (7.6)                    | 5 (7.8)                       | 1.0          |
| Arrhythmias  | 43 (15.6)                   | 10 (15.6)                     | 1.0          |
| Haemoptysis  | 32 (11.6)                   | 11 (17.2)                     | 0.2          |
| Stroke   | 17 (6.2)                    | 0 (0.0)                       | 0.05         |
| Bleeding   | 10 (3.6)                    | 3 (4.7)                       | 0.7          |

Data are expressed as number (%) for qualitative variables and median [interquartile range] for quantitative variables. PAH-SDT: pulmonary arterial hypertension-specific drug therapy; SaO<sub>2</sub>: peripheral arterial oxygen saturation; NYHA/WHO FC: New York Heart Association/World Health Organization functional class.

<sup>a</sup> No comparison was done as there were only three patients in the no PAH-SDT group.

non-users, neither SaO<sub>2</sub> nor the 6-minute walking test distance changed significantly from PAH diagnosis to the last evaluation (45.3% and 65.6% with available data,  $P=0.1$  and  $P=0.3$ , respectively). NYHA/WHO FC improved in five (11.9%) non-users, remained unchanged in 19 (45.2%) and deteriorated in 18 (42.9%). The NYHA/WHO FC improved more in the users than in the non-users ( $P<0.001$ ).

Table 3 compares clinical data in users according to intensity of PAH-SDT. The triple-therapy subgroup had a longer PAH-SDT duration compared with patients taking one or two PAH-SDTs ( $P<0.0001$ ), a higher proportion of pretricuspid defects ( $P<0.0001$ ), a lower proportion of genetic

syndromes ( $P<0.0001$ ) and worse NYHA/WHO FC at PAH-SDT initiation ( $P<0.001$ ) and at the last evaluation ( $P=0.02$ ). ES-related complications, particularly haemoptysis and heart failure, were more common in the triple-therapy group. Most transplantations were performed in this group. Mortality was not significantly different across the three treatment-intensity groups.

Details of PAH-SDT regimens are provided in the online-only Appendix 2. The most common regimen was monotherapy ( $n=129$ ; 46.7%), usually with bosentan ( $n=83/129$ ; 64.3%). Dual therapy ( $n=113$ ; 40.9%) usually consisted of bosentan and sildenafil ( $n=65/276$  users;



**Table 3** Demographic and clinical data in two subgroups according to pulmonary arterial hypertension-specific drug therapy.

|                                       | Monotherapy<br>(n = 129; 46.7%) | Dual therapy<br>(n = 113; 40.9%) | Triple therapy<br>(n = 25; 9.1%) | P        |
|---------------------------------------|---------------------------------|----------------------------------|----------------------------------|----------|
| <i>Genetic syndrome</i>               | 58 (45.0)                       | 30 (26.5)                        | 2 (8.0)                          | < 0.0001 |
| <i>Pretricuspid shunt</i>             | 24 (18.6)                       | 30 (26.6)                        | 14 (56.0)                        | < 0.0001 |
| <i>Exam before PAH-SDT initiation</i> |                                 |                                  |                                  |          |
| Age (years) (n = 259)                 | 34.9 [26.1–46.7]                | 38.5 [28.8–47.8]                 | 34.8 [24.4–45.9]                 | 0.6      |
| SaO <sub>2</sub> (%) (n = 196)        | 84 [80–89]                      | 85 [80–88]                       | 82 [74–89]                       | 0.8      |
| 6-minute walking test (m) (n = 142)   | 333 [220–413]                   | 309 [230–382]                    | 310 [120–316]                    | 0.3      |
| NYHA/WHO FC (n = 209)                 |                                 |                                  |                                  | < 0.001  |
| 1                                     | 2 (1.9)                         | 4 (4.7)                          | 0 (0.0)                          |          |
| 2                                     | 48 (44.4)                       | 20 (23.5)                        | 0 (0.0)                          |          |
| 3                                     | 51 (47.2)                       | 58 (68.2)                        | 7 (70.0)                         |          |
| 4                                     | 7 (6.5)                         | 3 (3.5)                          | 3 (30.0)                         |          |
| <i>Last exam</i>                      |                                 |                                  |                                  |          |
| Age (years) (n = 327)                 | 40.4 [31.6–50.6]                | 44.9 [35.2–55.1]                 | 46.9 [33.9–53.2]                 | 0.08     |
| SaO <sub>2</sub> (%) (n = 275)        | 47 [14–77]                      | 83 [49–121]                      | 118 [59–138]                     | 0.0001   |
| 6-minute walking test (m) (n = 166)   | 84 [79–89]                      | 85 [80–90]                       | 89 [84–91]                       | 0.1      |
| NYHA/WHO FC (n = 285)                 | 350 [272–446]                   | 379 [305–467]                    | 303 [180–420]                    | 0.2      |
| 1                                     | 7 (6.1)                         | 6 (6.5)                          | 0 (0.0)                          | 0.02     |
| 2                                     | 61 (53.5)                       | 47 (50.5)                        | 3 (16.7)                         |          |
| 3                                     | 37 (32.5)                       | 29 (31.2)                        | 9 (50.0)                         |          |
| 4                                     | 9 (7.9)                         | 11 (11.8)                        | 6 (33.3)                         |          |
| Complications                         | 65 (50.4)                       | 63 (55.8)                        | 20 (80.0)                        | 0.03     |
| Heart failure                         | 22 (17.1)                       | 29 (25.7)                        | 9 (36.0)                         | 0.07     |
| Severe infectious syndrome            | 11 (8.5)                        | 8 (7.1)                          | 2 (8.0)                          | 0.9      |
| Arrhythmias                           | 19 (14.7)                       | 20 (17.7)                        | 3 (12.0)                         | 0.8      |
| Haemoptysis                           | 8 (6.2)                         | 14 (12.4)                        | 8 (32.0)                         | 0.02     |
| Stroke                                | 6 (4.7)                         | 11 (9.7)                         | 0 (0.0)                          | 0.1      |
| Bleeding                              | 7 (5.4)                         | 2 (1.8)                          | 1 (4.0)                          | 0.3      |
| <i>Death/transplantation</i>          | 30 (23.3)                       | 25 (22.1)                        | 11 (44.0)                        | 0.08     |
| Death                                 | 29 (22.5)                       | 13 (11.5)                        | 3 (12.0)                         | 0.07     |
| Transplantation                       | 1 (0.8)                         | 12 (10.6)                        | 8 (32.0)                         | < 0.001  |

Data are expressed as number (%) for qualitative variables and median [interquartile range] for quantitative variables. PAH-SDT: pulmonary arterial hypertension-specific drug therapy; SaO<sub>2</sub>: peripheral arterial oxygen saturation; NYHA/WHO FC: New York Heart Association/World Health Organization functional class. The number of PAH-SDTs was unknown for nine patients (3.3%).

23.6%). Of the 276 users, 82.6% took ERAs, 63.0% took phosphodiesterase type 5 inhibitors and 15.0% took prostacyclin. Median time from PAH diagnosis to PAH-SDT initiation was 9.1 months [0.3–45.9 months] in the pretricuspid group and 67.0 months [7.2–234.6 months] in the post-tricuspid group ( $P < 0.0001$ ).

## MCEs

Five patients (1.5%) were lost to follow-up. Median age at follow-up completion in patients without MCEs was 41.7 years [32.7–52.2 years] (range: 18.1–85.8 years). MCEs occurred in 95 (27.9%) patients. Table 4 reports the results of the bivariate analysis comparing patients with and without MCEs.

During follow-up, 67 (19.7%) patients died. Median age at death was 41.8 years [30.9–49.0 years] (range: 19.0–76.4 years). Age at death was not significantly different in patients with pretricuspid versus post-tricuspid

defects (46.2 vs 39.5 years;  $P = 0.1$ ). Causes of death were heart failure (25.4%), infection (17.6%) (pulmonary infection,  $n = 6$ ; gastrointestinal infection,  $n = 2$ ; septic shock,  $n = 2$ ; cerebral abscesses,  $n = 2$ ), sudden death (10.5%), non-cardiac surgery (6.0%), thromboembolic events (3%) (stroke,  $n = 1$ ; leg ischaemia,  $n = 1$ ) and one postpartum complication (1.5%; [16]). PAH was the only identified cause of death in 32.8% of the patients.

Transplantation was performed in 28 (8.2%) patients, usually (26/28 patients) at the national referral centre (Hôpital Marie-Lannelongue). Heart-lung transplantation was done in 24 patients, and double-lung transplantation was done in the remaining four patients, two of whom also underwent percutaneous atrial septal defect closure.

## Risk of MCEs according to patient age

Fig. 2 shows the Kaplan–Meier MCE-free curves by defect location and PAH-SDT, with age as the time scale.

**Table 4** Demographic and clinical data according to outcome.

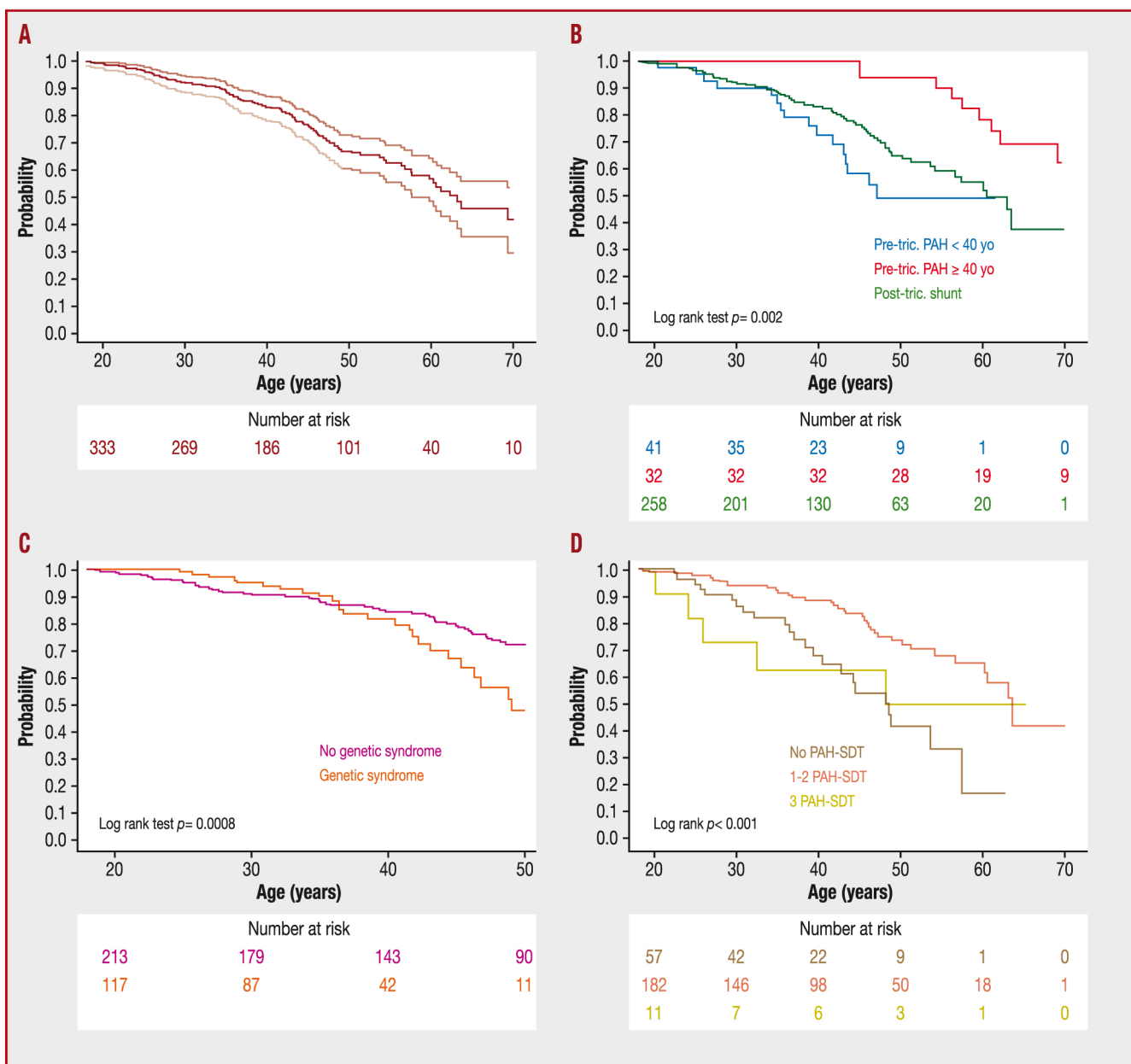
|  | Events (transplantation, death)<br>(n = 95; 27.9%) | No event<br>(n = 245; 72.1%) | P        |
|--|--|------------------------------|----------|
| <i>Female</i>                            | 67 (70.5)  | 169 (69.0)                   | 0.8      |
| <i>Genetic syndrome</i>                  | 28 (30.4)  | 91 (37.1)                    | 0.3      |
| <i>Pretricuspid shunt</i>                | 27 (28.4)  | 48 (19.6)                    | 0.08     |
| <i>Complex CHD</i>                       | 37 (39.0)  | 107 (43.7)                   | 0.4      |
| <i>First exam</i>                        |  |                              |          |
| Age (years) (n = 299)                    | 27.5 [13.5–38.2]                                   | 26.0 [11.3–40.3]             | 0.9      |
| SaO <sub>2</sub> (%) (n = 185)           | 85 [80–90]   | 85 [82–90]                   | 0.1      |
| 6-minute walking test (m) (n = 68)       | 330 [245–406]                                      | 348 [227–385]                | 0.8      |
| NYHA/WHO FC (n = 231)                    |  |                              | 0.5      |
| 1  | 7 (13.0)   | 20 (11.3)                    |          |
| 2  | 24 (44.4)  | 91 (51.4)                    |          |
| 3  | 21 (38.9)  | 64 (36.2)                    |          |
| 4  | 2 (3.7)  | 2 (1.1)                      |          |
| Oral anticoagulation therapy (n = 224)   | 5 (10.4)   | 21 (11.9)                    | 1.0      |
| Aspirin (n = 224)                        | 5 (10.4)   | 21 (11.9)                    | 1.0      |
| Antithrombotic therapy (n = 224)         | 10 (20.8)  | 41 (23.3)                    | 0.7      |
| Diuretics (n = 223)                      | 12 (25.0)  | 33 (18.9)                    | 0.3      |
| <i>Last exam</i>                         |  |                              |          |
| Age (years) (n = 327)                    | 41.8 [30.2–48.2]                                   | 41.8 [32.3–52.2]             | 0.2      |
| SaO <sub>2</sub> (%) (n = 275)           | 79 [71–85]   | 86 [80–90]                   | < 0.0001 |
| 6-minute walking test (m) (n = 166)      | 298 [185–338]                                      | 377 [300–460]                | 0.0004   |
| NYHA/WHO FC (n = 285)                    |  |                              | < 0.0001 |
| 1  | 1 (1.5)  | 16 (7.4)                     |          |
| 2  | 13 (18.8)  | 127 (58.8)                   |          |
| 3  | 28 (40.6)  | 68 (31.5)                    |          |
| 4  | 27 (39.1)  | 5 (2.3)                      |          |
| Oral anticoagulation therapy (n = 301)   | 32 (46.4)  | 73 (31.2)                    | 0.02     |
| Aspirin (n = 299)                        | 15 (22.1)  | 44 (18.9)                    | 0.6      |
| Diuretics (n = 302)                      | 42 (59.2)  | 94 (40.3)                    | 0.005    |
| PAH-SDT                                  | 68 (71.6)  | 208 (84.9)                   | 0.005    |
| None                                     | 27 (29.0)  | 37 (15.6)                    | 0.006    |
| Single therapy                           | 30 (32.3)  | 99 (41.6)                    |          |
| Double therapy                           | 25 (26.9)  | 88 (37.0)                    |          |
| Triple therapy                           | 11 (11.8)  | 14 (5.9)                     |          |
| Heart failure                            | 49 (51.6)  | 24 (9.8)                     | < 0.0001 |
| Severe infectious syndrome               | 14 (14.7)  | 12 (4.9)                     | 0.002    |
| Arrhythmias                              | 20 (21.1)  | 33 (13.5)                    | 0.08     |
| Haemoptysis                              | 14 (14.7)  | 29 (11.8)                    | 0.5      |
| Stroke                                   | 6 (6.3)  | 11 (4.5)                     | 0.6      |
| Bleeding                                 | 6 (6.3)  | 7 (2.9)                      | 0.2      |
| Age at event or end of follow-up (years) | 40.5 [29.4–47.6]                                   | 41.7 [32.7–52.2]             | 0.09     |

Data are expressed as number (%) for qualitative variables and median [interquartile range] for quantitative variables. CHD: congenital heart disease; PAH-SDT: pulmonary arterial hypertension-specific drug therapy; SaO<sub>2</sub>: peripheral arterial oxygen saturation; NYHA/WHO FC: New York Heart Association/World Health Organization functional class.

Overall, the cumulative occurrence of MCEs at 30, 40, 50 and 60 years of age was 7.6% (95% confidence interval [CI]: 5.2–11.1%), 16.7% (95% CI: 12.8–21.6%), 33.7% (95% CI: 27.7–40.6%) and 46.4% (95% CI: 38.2–55.4%), respectively (Fig. 2A). The cumulative incidence of MCEs was lower in patients taking one or two PAH-SDTs compared with non-users and patients taking three PAH-SDTs ( $P=0.0001$ ). In the post-tricuspid group, the cumulative occurrence of MCEs in the patients aged 30, 40, 50 and 60 years was 8.8% (95%

CI: 5.8–13.2%), 17.7% (95% CI: 13.1–23.8%), 36.3% (95% CI: 28.8–44.9%) and 50.7% (95% CI: 39.7–62.9%), respectively; these percentages were not significantly different from those in the pretricuspid group. However, the cumulative occurrence of MCEs was higher in patients with pretricuspid defects who were younger than 40 years at PAH diagnosis compared with patients with pretricuspid defects who were older at PAH diagnosis and patients with post-tricuspid defects ( $P=0.002$ ) (Fig. 2B). When stopping Kaplan–Meier



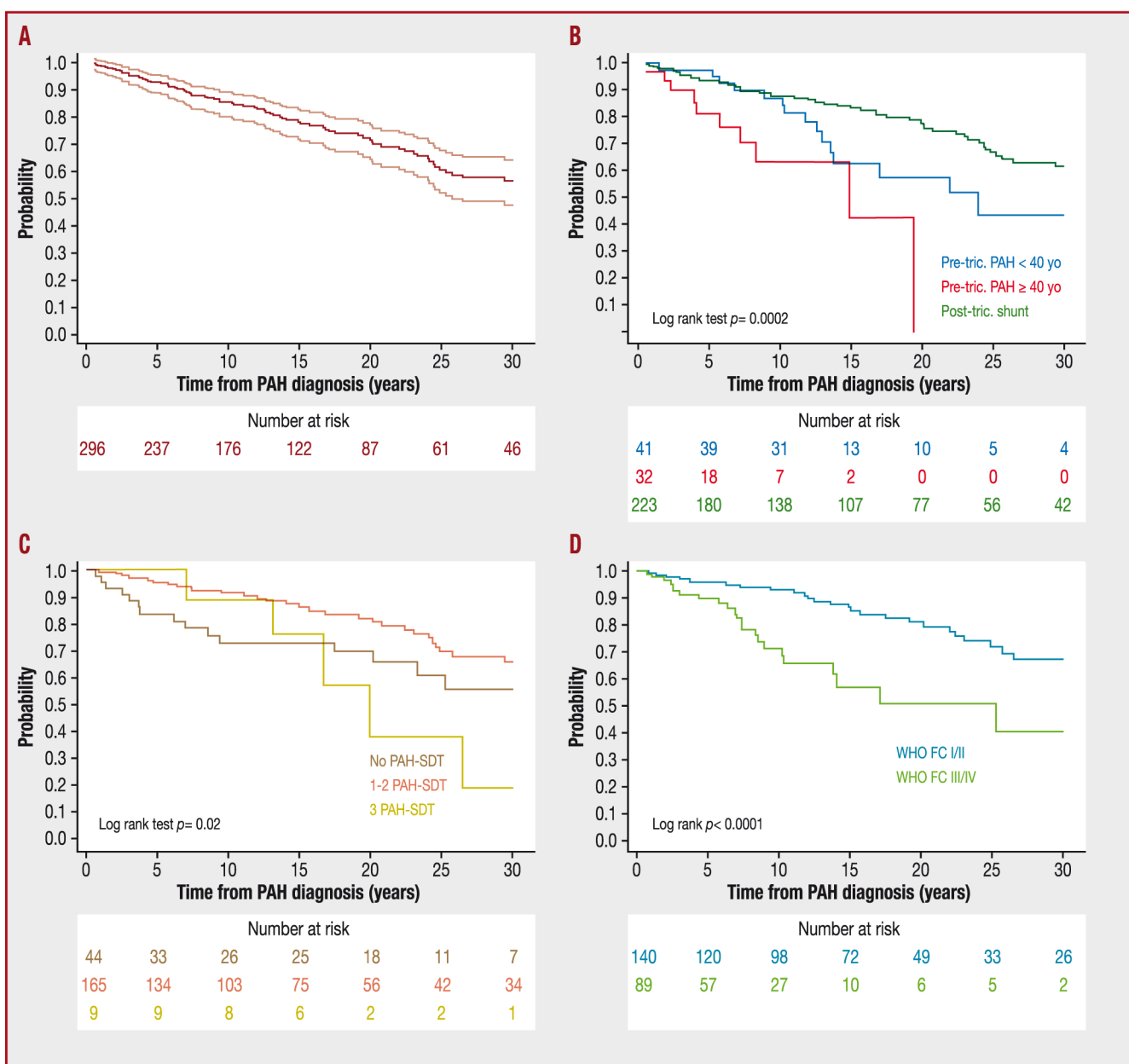


**Figure 2.** Kaplan–Meier curves showing survival without major clinical events (death or transplantation) according to age at follow-up, overall and in subgroups defined by defect location, presence or absence of genetic syndrome and pulmonary arterial hypertension-specific drug therapy (PAH-SDT). A, B and C. Event-free survival. D. Event-free survival in patients with post-tricuspid (post-tric.) or combined defects. PAH < 40 yo: pulmonary arterial hypertension diagnosis before 40 years of age; pre-tric.: pre-tricuspid.

free curves when patients reached 40 years, the cumulative occurrence of MCEs was similar in the groups with and without genetic syndromes. Among patients who lived for more than 40 years, the cumulative occurrence of MCEs was higher in the group with genetic syndromes ( $P=0.0008$ ) (Fig. 2C). Among patients with post-tricuspid defects, those using one or two PAH-SDTs had a lower cumulative occurrence of MCEs compared with non-users or users of three PAH-SDTs ( $P<0.001$ ) (Fig. 2D). In the group with post-tricuspid defects and no genetic syndrome, the cumulative occurrence of MCEs was also lower in users of one or two PAH-SDTs compared with non-users or users of three PAH-SDTs ( $P=0.0004$ ).

### Risk of MCEs by time since PAH diagnosis

Fig. 3 shows the Kaplan-Meier MCE-free curves according to defect location and PAH-SDT, with time since PAH diagnosis as the time scale. Overall, the cumulative occurrence of MCEs 10, 20 and 30 years after PAH diagnosis was 14.5% (95% CI: 10.7–19.5%), 28.4% (95% CI: 22.5–35.6%) and 43.6% (95% CI: 35.7–52.5%), respectively (Fig. 3A). In the pre-tricuspid group, corresponding values were 21.2% (95% CI: 12.8–33.8%), 51.6% (95% CI: 35.9–69.3%) and 72.8% (95% CI: 50.9–90.7%), respectively. The cumulative occurrence of MCEs was higher in patients with pretricuspid defects whose PAH was diagnosed after 40 years of age compared with



**Figure 3.** Kaplan–Meier curves showing survival without major clinical events (death or transplantation) according to time since the diagnosis of pulmonary artery hypertension, overall and in subgroups defined by defect location, pulmonary arterial hypertension-specific drug therapy (PAH-SDT) and functional class. A, B and D. Event-free survival. C. Event-free survival in patients with post-tricuspid (post-tric.) or combined defects. PAH < 40 yo: pulmonary arterial hypertension diagnosis before 40 years of age; pre-tric.: pre-tricuspid; NYHA/WHO FC, New York Heart Association/World Health Organization functional class.

patients with pretricuspid defects and PAH diagnosed before 40 years and patients with post-tricuspid defects ( $P=0.0002$ , log-rank test) (Fig. 3B). Overall, the cumulative occurrence of MCEs was lower in users of one or two PAH-SDTs compared with non-users or users of three PAH-SDTs ( $P=0.004$ ). In the post-tricuspid group, the cumulative occurrence of MCEs was also lower in users of one or two PAH-SDTs ( $P<0.04$ , log-rank test; Fig. 3C) compared with non-users and users of three PAH-SDTs, and was also lower in patients with a lower NYHA/WHO FC ( $P<0.0001$ , log-rank test; Fig. 3D). In the pretricuspid group, the number of non-users ( $n=6$ ) was too

small for an analysis of the cumulative occurrence of MCEs according to PAH-SDT intensity.

### Variables associated with MCEs

Table 5 lists the variables associated with MCEs. In the Cox model, with age as the time scale and MCE as the censored variable, using one or two PAH-SDTs and pretricuspid defect diagnosed after 40 years were negatively associated with MCEs ( $P=0.001$  and  $P=0.04$ , respectively), whereas genetic syndrome and pretricuspid defect diagnosed before 40 years

**Table 5** Association between variables and death or transplantation.

|  | HR (95% CI)      | P       |
|--|------------------|---------|
| <i>Age as time scale</i>                         |                  |         |
| Univariate analysis                              |                  |         |
| Genetic syndrome                                 | 1.8 (1.1–3.0)    | 0.01    |
| Post-tricuspid shunt                             | Reference        |         |
| Pretricuspid shunt diagnosed before age 40 years | 1.6 (0.9–2.7)    | 0.1     |
| Pretricuspid shunt diagnosed after age 40 years  | 0.4 (0.2–0.8)    | 0.007   |
| No PAH-SDTs                                      | Reference        |         |
| 1–2 PAH-SDTs                                     | 0.4 (0.2–0.6)    | < 0.001 |
| Multivariable analysis: model 1                  |                  |         |
| No PAH-SDTs                                      | Reference        |         |
| 1–2 PAH-SDTs                                     | 0.4 (0.3–0.7)    | 0.001   |
| Genetic syndrome                                 | 1.8 (1.0–3.0)    | 0.03    |
| Post-tricuspid shunt                             | Reference        |         |
| Pretricuspid shunt diagnosed before age 40 years | 2.0 (1.1–3.7)    | 0.03    |
| Pretricuspid shunt diagnosed after age 40 years  | 0.5 (0.2–1.0)    | 0.04    |
| Delay since PAH diagnosis as time scale          |                  |         |
| Univariate analysis                              |                  |         |
| Post-tricuspid shunt                             | Reference        |         |
| Pretricuspid shunt diagnosed before age 40 years | 1.9 (1.1–3.3)    | 0.03    |
| Pretricuspid shunt diagnosed after age 40 years  | 3.9 (1.9–7.9)    | < 0.001 |
| NYHA/WHO FC III/IV at PAH diagnosis              | 2.8 (1.6–5.0)    | < 0.001 |
| SpO <sub>2</sub> per each % increase             | 0.95 (0.91–0.99) | 0.02    |
| No PAH-SDTs                                      | Reference        |         |
| 1–2 PAH-SDTs                                     | 0.5 (0.3–0.8)    | 0.007   |
| Multivariable analysis: model 2                  |                  |         |
| Post-tricuspid shunt                             | Reference        |         |
| Pretricuspid shunt                               | 2.4 (1.0–5.4)    | 0.04    |
| NYHA/WHO FC III/IV at PAH diagnosis              | 3.0 (1.5–6.0)    | 0.002   |
| SpO <sub>2</sub> per each % increase             | 0.95 (0.92–0.99) | 0.01    |
| No PAH-SDTs                                      | Reference        |         |
| 1–2 PAH-SDTs                                     | 0.4 (0.2–0.8)    | 0.009   |

CI: confidence interval; HR: hazard ratio; PAH: pulmonary arterial hypertension; PAH-SDT: pulmonary arterial hypertension-specific drug therapy; SpO<sub>2</sub>: peripheral capillary oxygen saturation; NYHA/WHO FC, New York Heart Association/World Health Organization functional class.

were positively associated with MCE ( $P=0.03$  and  $P=0.03$ , respectively). In the Cox model, with time since PAH diagnosis as the time scale and MCE as the failure variable, variables positively associated with MCE were NYHA/WHO FC III/IV ( $P=0.002$ ), decreasing SpO<sub>2</sub> ( $P=0.01$ ) and pretricuspid defect ( $P=0.04$ ); the only variable negatively associated with MCE was use of one or two PAH-SDTs ( $P=0.009$ ).

## Discussion

In this large, multicentre, nationwide, retrospective, cohort study of 340 adults with ES, single or dual PAH-SDT was associated with a better outcome. Furthermore, outcomes varied with defect location.

### Relationship between PAH-SDT and outcome

PAH-SDT is the standard of care for various types of PAH [7]. Compared with idiopathic PAH, ES has a different haemodynamic pattern and better survival. Data on

mortality in patients with ES given PAH-SDT are scant. The randomized, placebo-controlled trial BREATHE-5 demonstrated a moderate improvement in functional capacity with bosentan compared with placebo in patients with ES and NYHA/WHO FC III or IV [5,6]. Based on this study, bosentan was licensed in France for ES in NYHA/WHO FC III–IV patients. In an extrapolation of guidelines for PAH, some teams also use PAH-SDT in NYHA/WHO FC II patients [7]. Our cohort study shows that PAH-SDT is widely used to treat ES in everyday practice in France. The proportion of treated patients was 80.9% overall, and was higher in patients with pretricuspid defects, with variations from 41.7% to 100% across centres. The ability to conduct large, placebo-controlled trials to assess effects of PAH-SDT on mortality is limited by the slow pace of disease progression and the low incidence of ES in our country. Thus, only 340 patients were included by 20 tertiary-care centres. Therefore, although subject to selection bias, cohort studies such as ours are of value in the assessment of associations between PAH-SDT and mortality. To date, two cohort studies have suggested a beneficial effect of PAH-SDT in



CHD [10,11]. In a single-centre study including 229 patients, the group taking PAH-SDT had a significantly lower mortality rate by unadjusted analysis, and after propensity score regression adjustment for baseline clinical differences [10]. In 153 patients with ES included in the German CHD registry, survival rates in treatment-naive patients were 86%, 60% and 34% after 1, 5 and 10 years, and were lower than in patients taking PAH-SDT [11]. In a multicentre, retrospective, international cohort including 1098 patients with ES, PAH-SDT was associated with a better outcome in the univariate analysis, but the association was lost in the multivariable model [12]. In our multicentre, nationwide cohort, we observed a relationship between PAH-SDT and outcome. As the aim of our study was to assess outcomes of adults with ES, only patients aged > 18 years were included. Therefore, immortal time bias occurred, and life expectancy was overestimated, particularly in patients with post-tricuspid defects. Despite this bias and the use of PAH-SDT in four-fifths of patients, the prognosis was severe: death or transplantation occurred in half of the patients with post-tricuspid defects by 50 years of age, and in half of the patients with pretricuspid defects within 20 years after PAH diagnosis [17]. Nearly all deaths were related to ES. These findings also serve as a reminder that PAH-SDT has only palliative effects. Despite substantial advances in drug development over the past two decades, with up to seven drugs used in this cohort, responses to medical therapy remain incomplete and unsatisfactory [4].

## Relationship between defect location and outcome

An original feature of our work is that 22.1% of patients had pretricuspid defects, compared with 3.2% in the German registry and 12.7% in the international cohort [12]. The clinical phenotype, haemodynamics and outcomes of ES differ according to defect location [18–20]. PAH develops in early life in patients with post-tricuspid defects, and later in those with pretricuspid defects. Thus, PAH was diagnosed at a median age of 37.7 years in our pretricuspid group, which had a predominance of women and few patients with genetic syndromes. This late age at diagnosis is unlikely to be related to a long time from disease onset to diagnosis, as overall life expectancy remained better in patients diagnosed after 40 years of age. Age at PAH diagnosis in patients with pretricuspid defects is often clearly recorded, and varies widely among patients. Time from PAH diagnosis may therefore be the best time scale in these patients. On the other hand, in patients with post-tricuspid defects, the date of PAH diagnosis is often difficult to determine in a retrospective study; in our cohort, it was available for 84.9% of patients. Life expectancy may be a useful surrogate time scale for assessing outcomes in this group. Using these two time-scales for the survival analysis, we found a lower cumulative occurrence of death and transplantation in patients with pretricuspid defects and ES diagnosed before 40 years of age than in patients with post-tricuspid defects. In the post-tricuspid group, these MCEs were less common in patients with single or dual PAH-SDT than in untreated patients. Comparisons were not performed in the pretricuspid group because only six patients did not take PAH-SDT. Furthermore, whereas in the pretricuspid group,

patients diagnosed after 40 years of age had better outcomes compared with those diagnosed at younger ages when age was the time scale, the opposite was found with time from PAH diagnosis as the time scale. Together, these data suggest that despite a delayed onset, the pace of disease progression is faster in patients with pretricuspid compared with post-tricuspid defects [12]. Right ventricular function is a key prognostic factor in patients with ES [21]. In our study, heart failure was more common in the pretricuspid group. PAH-SDT and diuretic therapy were more intensive in the pretricuspid than in the post-tricuspid group. A possible explanation is that pretricuspid defects may fail to offer sufficient release of right ventricular pressure overload. These results agree with a recent longitudinal cohort study [22]. Right ventricular function was impaired in patients with atrial septal defect, who had larger right ventricles and impairments in systolic function and adaptation. There was a trend toward lower mortality in patients with post-tricuspid versus pretricuspid defects overall, and a significant difference in the subgroup of patients older than 48 years [22]. In an echocardiographic study, patients with post-tricuspid defects also had lower global left ventricular longitudinal strain, but greater right ventricular transverse strain, compared with patients with pretricuspid defects [23]. Our study emphasizes the differences in physiology and outcomes between patients with pretricuspid compared with post-tricuspid defects.

## Combination therapy in ES

PAH-SDT is used according to a stepwise intensification strategy when treatment goals are not met after initial therapy [7]. Data on combination therapy in ES are scant. More than a third of our patients were treated with two or three drugs. The cumulative occurrence of MCEs was not significantly different between the groups given one or two drugs, as suggested by the German registry, although the study was not designed to analyse this point [11]. Adding sildenafil to bosentan failed to improve haemodynamic and functional variables in a randomized, placebo-controlled, double-blind trial in patients with ES [24]. However, sildenafil was added routinely after 3 months on bosentan [24]. Stepwise treatment intensification with addition of a PAH drug when the previous treatment becomes inadequately effective seems to be associated with improvements in haemodynamics and functional capacity [8,18]. Initiating PAH-SDT with two drugs in combination may even provide greater haemodynamic improvements than a single initial drug. Triple therapy including prostacyclin, which is more complex to manage, was used mostly in patients with pretricuspid shunt, worse functional status and more complications. Despite this intensive medical therapy, these patients had the worst outcomes. Overall, whether multiple drug therapy is better than monotherapy remains unclear.

## Study limitations

The data collected in this study did not allow assessments of long-term quality of life, echocardiographic variables or haemodynamic variables in patients taking PAH-SDT. In a recent, prospective, cross-sectional study, quality of life was impaired, and was closely related to functional status

and to anxiety and depression scores [25]. As observed in our study, NYHA/WHO FC is also a robust predictor of outcome [17]. In a 20-year study of ES patients who received regular follow-up by standardized catheterization, we recently found that PAH-SDT initiation or intensification was associated with early haemodynamic improvements. Nevertheless, these effects varied across patients and declined over time [18]. Furthermore, they occurred in only about two-thirds of patients. This study also showed interindividual variations in treatment response. Thus, we need to devise methods of identifying those patients most likely to benefit from PAH-SDT.

The retrospective design limited the availability of investigations performed early in the study period, as well as the accuracy of the date of PAH diagnosis. Nevertheless, the availability of follow-up information for up to 98.5% of patients allowed a reliable assessment of survival. To our knowledge, this historical cohort is one of the largest to date, and included sufficient patients to explore subgroup specificities, as analysed above. Our study population was heterogeneous in terms of both defect location and calendar years of diagnosis and management. Nearly one-third of the patients had genetic syndromes, for which transplantation is generally not an option. There was a trend toward less PAH-SDT use in these patients. PAH-SDT remains controversial in patients with genetic syndromes, whose inclusion in our study may have resulted in bias. However, quality of life and functional status can be improved in these patients, despite their short life expectancy [26]. Another potential source of bias in our study is that medical management varied across centres, with differences in the proportions of patients given PAH-SDT, and nearly all transplantations being done in a single centre. In the international cohort, only six (0.6%) patients underwent transplantation versus 28 (8.2%) in our cohort [12]. The place and results of transplantation in these patients need to be better defined [17,27]. Nevertheless, our cohort study reflects daily practice. The discrepancies among physicians in the care of ES patients indicates a need for additional research to develop specific guidelines.

## Conclusions

In patients with ES, PAH-SDT seems to be associated with a lower risk of transplantation and mortality. However, PAH-SDT is palliative, and the outcome of ES remains poor. ES caused by pretricuspid shunting has distinctive characteristics, with a worse outcome despite the delayed onset of the disease. Whether stepwise PAH-SDT intensification is better than monotherapy remains to be demonstrated.

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