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Insights into the management of pulmonary arterial hypertension patients in Spain

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ABSTRACT

Introduction and objectives: Accurate risk stratification is pivotal to tailor therapy according to the prognosis of pulmonary arterial hypertension (PAH) patients to positively impact the course of the disease. We conducted a nationwide study to assess how the current European Society of Cardiology/European Respiratory Society guidelines for risk assessment and management of PAH patients are followed in real-world practice in Spain.

Methods: Hospital-based physicians answered an online questionnaire describing their yearly caseload of PAH patients and their management of virtual cases scenarios for Word Health Organization functional class (FC) II–III PAH patients.

Results: The main tests requested for a regular risk assessment were echocardiography, 6-minute walk test, measurement of brain natriuretic peptide/N-terminal pro-B-type natriuretic peptide plasma levels and right heart catheterization. The main treatment prescribed was an oral double-combination therapy with an endothelin receptor antagonist (ERA) and a phosphodiesterase type 5 inhibitor (PDE5i) or guanylate cyclase stimulator. Around 20% of the clinicians would also add the selective prostacyclin-receptor agonist (selexipag) to ERA and PDE5i as initial therapy for FC III patients, and nearly all clinicians (99%) would add a prostacyclin pathway agent to FC III PAH patients presenting multiple new intermediate-risk parameters despite a 6-month dual therapy with ERA and PDE5i.

Conclusions: The main decisive factor for the management of PAH patients in Spanish hospitals is their functional class and intermediate-risk parameters. Selexipag was more frequently prescribed than parenteral prostacyclin-analogs in triple-combination therapy for FC II–III PAH patients presenting low-risk and intermediate-risk parameters.

Abbreviations: ERS, European Respiratory Society; ESC, European Society of Cardiology; FC, functional class; PAH, pulmonary arterial hypertension; PC, prostacyclin.

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Perspectivas sobre el tratamiento de la hipertensión arterial pulmonar en España

Palabras clave:
Hipertensión arterial pulmonar
Casos de pacientes virtuales
Estrategia de evaluación de riesgo
Terapia triple de combinación

RESUMEN

Introducción y objetivos: Una estratificación de riesgo precisa es fundamental para adaptar correctamente la terapia al pronóstico de los pacientes con hipertensión arterial pulmonar (HAP) de forma que se consiga un impacto positivo en el curso de la enfermedad. Se llevó a cabo un estudio a nivel nacional para evaluar el grado de seguimiento de las directrices actuales de la Sociedad Europea de Cardiología/Sociedad Respiratoria Europea en cuanto a la evaluación del riesgo y al tratamiento de pacientes con HAP en la práctica real en España.
Métodos: Médicos de centros hospitalarios respondieron a un cuestionario en línea que describía su número anual de pacientes con HAP vistos y su tratamiento de la enfermedad en distintos escenarios supuestos de pacientes de clase funcional (CF) II-III (definición de la Organización Mundial de la Salud).
Resultados: Las principales pruebas solicitadas para una evaluación periódica del riesgo fueron la ecocardiografía, la prueba de marcha de 6 minutos, la determinación de los niveles plasmáticos de péptido natriurético cerebral/fracción aminoterminal del propéptido natriurético cerebral (tipo B) y el cateterismo cardiaco derecho. El principal tratamiento prescrito fue terapia oral de doble combinación con un antagonista del receptor de la endotelina (ERA) y un inhibidor de la fosfodiesterasa tipo 5 (PDE5i) o estimulador de la guanilato ciclasa. Alrededor del 20% de los médicos también agregarían el agonista selectivo del receptor de prostaciclina (selexipag) a ERA y PDE5i como terapia inicial para pacientes CF III, y casi todos los médicos (99%) agregarían un agente de la vía de la prostaciclina a pacientes con HAP CF III que presenten múltiples parámetros nuevos de riesgo intermedio a pesar de una terapia dual de 6 meses con ERA y PDE5i.
Conclusiones: El principal factor determinante para el tratamiento de los pacientes con HAP en los hospitales españoles es su CF y los parámetros de riesgo intermedio. Selexipag se prescribió con más frecuencia que los análogos de prostaciclina parenterales en la terapia de combinación triple para pacientes con HAP CF II-III que presentaban parámetros de riesgo bajo e intermedio.

Introduction

Pulmonary arterial hypertension (PAH) is a specific form of pulmonary hypertension (PH); a life-threatening disease with progressive obstructive proliferative pathological changes of the distal pulmonary arteries, increasing pulmonary vascular resistance, and eventually leading to right-sided heart failure.[1] The survival rate of PAH patients 5 years from the time of diagnosis was estimated at around 60%.[2]

PAH is a rare disease. A systematic review of recent data from national centralized healthcare systems' online reports estimated PAH incidence at approximately 5.8 adults per million per year, and PAH prevalence between 47.6 and 54.7 adults per million.[3] In 2020, the Spanish Society of Cardiology (SEC) and the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) reported an estimated PAH incidence of 4.6 cases per million per year and a PAH prevalence of 19.2 cases per million in the adult population in Spain, based on data from the REHAP (Spanish Registry for pulmonary hypertension). These figures are on the rise since the initial REHAP investigators' report,[4] due to the growing awareness about PAH and the progress made on PAH diagnosis.

Both early diagnosis and stratification of patients according to their estimated 1-year prognosis assessed by a multiparametric risk stratification approach, are critical in assisting clinicians with their treatment strategy decision-making. The 2 main predictive models for survival of PAH patients were derived from the multivariable analysis of the FPHN[5] and REVEAL[6] registries, respectively.

In 2015, the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) issued risk assessment guidelines based on these 2 models.[7] The ESC/ERS guidelines recommend taking into account the WHO FC of the PAH patients, together with clinical signs of heart failure, progression of symptoms, cardiopulmonary exercise testing including multiple clinical variables, 6-minute walk test (6MWT), brain natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) plasma levels, echocardiography, and hemodynamic parameters (assessed by right heart catheterization [RHC]).

Advanced treatments for PAH include endothelin receptor antagonists (ERA), PDE5 inhibitors (PDE5i) or soluble GC stimulator (GCs), and PC pathway agents (PPA).[7,8] The main globally available PPA are parenteral PC analogs and one oral selec-

tive PC-receptor agonist, selexipag.[9,10] ERA and PDE5i/GCs are given either alone or in combination (dual therapy), and PPA are most frequently used as a third drug for treatment intensification.

Here, we conducted a nationwide study to analyze the management of PAH by hospital-based physicians in Spain, comparing their current practice for risk stratification and treatment decisions with the most recent ESC/ERS guidelines. Clinicians were asked to answer both a survey regarding their current practice and a questionnaire assessing their management of virtual case scenarios for FC II–III PAH patients in the absence of high-risk parameters.

Methods

Health care practitioner inclusion criteria and selection

Eighty participants were enrolled, all fully qualified senior physicians and decision-makers for initiating treatment of PAH patients. Since PAH is a complex disease impacting both the lung and the heart function, an equal number of pulmonologists (40) and cardiologists (40) was included, all working primarily in public hospitals. All participants were required to have a minimum caseload of 3 PAH patients per year (minimum to be considered a PAH treater, given the low national mean of 7.5 new patients per physician and year), and to dedicate at least 60% of their time to direct patient management (required to ensure respondents are only active clinical specialists, and dismiss healthcare professionals whose primary dedication is in research or academia). The geographic distribution of the participants was representative of the distribution of specialists across Spain, according to the latest report of the Spanish national institute of statistics (dated 31st December 2020). Around half of the clinicians were recruited in the Center and North-East of Spain (27% and 24%, respectively) and the other half were evenly distributed within the 3 other main areas (18% in the North/North-West, 16% in the South, and 15% in the East of Spain). The profile of all participants is summarized in Table 1.

Table 1 – Profile of the participating clinicians.

	% of clinicians
Hospital characteristics	
Public hospital	100%
University hospital	93%
Non-university hospital	8%
Capacity < 500 beds	39%
Capacity ≥ 500 beds	61%
Hospital with a PH unit	75%
Type of specialist	
Pneumologist	50%
Cardiologist	50%
Experience post-residency	
≤ 9 years	18%
10–20 years	63%
≥ 20 years	20%
Annual PAH caseload	
Lower (3–5 PAH patients/year)	39%
Intermediate (6–9 PAH patients/year)	29%
Higher (> 10 PAH patients/year)	33%
Initial treatment decided by	
The clinician alone	36%
Within a multidisciplinary committee	53%
Consulting with the specialized unit	11%

PAH: pulmonary arterial hypertension; PH: pulmonary hypertension.

Patient case scenarios

Two different clinical scenarios (prior to and after a 6-month treatment) were assessed on 4 virtual patients, all currently under double-combination therapy with ERA and PDE5i/GCs, as presented in Table 2. The survey focused on FC II and FC III PAH patients with 2 different etiologies, either idiopathic (IPAH) or connective tissue disorder (CTD-associated) PAH, which are the 2 most represented groups of PAH worldwide[3] and in Spain (together with congenital heart disease).[4]

Study design

Pilot interviews were carried out separately with one pulmonologist and one cardiologist by mean of a 60-minute videocall to assist in the design of an online survey investigating the management of PAH patients in Spain. These experts were selected using the same inclusion criteria as the main survey participating clinicians (Table 1). The aim of these interviews was to validate the pertinence of the survey with regards to PAH management and the terminology used by field experts.

Hospital-based physicians were asked to spend up to 45 minutes reviewing patient cases and answering an online questionnaire. All data were collected in a period of approximately 1 month, May 21st to June 24th, 2021. The data included the participating clinicians' profiles, caseloads (number and types of PH patients received in their clinical practice in an average year), and answers on their typical risk assessment strategy and management of mock cases scenarios based on the 4 virtual PAH patients as detailed in Table 2.

This research complied with the European general data protection regulation (GDPR).

All participating physicians signed informed consent form prior to participation, and the need for ethics approval was waived due to the study classification as Market Research and based on the Royal Decree 1090/2015 issued from the Spanish Ministry of Health, Social Services and Equality "BOE" (reference: BOE-A-2015-14082).

Statistical analysis

Statistical tests were carried out using the Gandia BarbWin analysis software (version 7.0.1614.3). Continuous variables were assessed using counts, standard deviation, and median values. Categorical variables were summarized using frequencies and percentages. Statistical tests were 2-sided, and *P*-values were calculated with a 95% confidence interval. *P*-values ≤.05 were considered statistically significant. For group comparisons, unpaired *t*-tests were used. Due to rounding and the multiple-choice nature of some of the retrieved results, the

Table 2 – Mock patient cases: main characteristics and clinical status.

Patient	1	2	3	4
PAH type	Idiopathic	Idiopathic	CTD	CTD
WHO FC	II	III	II	III
Age	43	60	48	53
Gender	Woman	Man	Woman	Man
Dyspnea	Yes, great efforts	Yes, small efforts	Yes, moderate-great efforts	Yes, small efforts
Hemodynamic variables	Low risk	Intermediate risk	Low risk	Intermediate risk
Prior clinical history	No clinical changes for 2 years	Diagnosed 6 months ago	Diagnosed with scleroderma 10 years ago	Diagnosed with scleroderma and recently diagnosed with group I PAH

CTD: connective tissue disease; FC: functional class; PAH: pulmonary arterial hypertension; WHO: Word Health Organization.

Table 3 – Caseload distribution and etiology of PH and PAH patients managed by the participants in an average year.

	Number of patients per year	
	Median value	Mean ± SD
Total (all PH patients)	46	59 ± 45
PH groups		
Group 1: PAH	7	9 ± 7
PAH subtypes		
Idiopathic/heritable	3	3 ± 2
CTD-PAH	2	3 ± 3
Associated with congenital heart disease	1	2 ± 2
Other type	1	1 ± 2
Group 2: PH due to left heart disease	14	25 ± 27
Group 3: PH due to respiratory disease and/or hypoxemia	10	16 ± 17
Group 4: CTEPH and other pulmonary obstructions	7	9 ± 6
Group 5: PH from unclear and/or multifactorial mechanisms	2	2 ± 2

PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; CTD: connective tissue disease; CTEPH: chronic thromboembolic; SD: standard deviation.

percentage totals on some tables and figures may not correspond to the sums of the separate percentages.

Data were compared between FC II and FC III PAH patients and between clinicians with different yearly caseloads. Three caseload categories were defined: low- (3–5 patients/year), intermediate- (6–9 patients/year) and high-caseload (over 10 patients/year).

Results

Characteristics of PH and PAH patients received in clinical practices

In total, the clinicians declared receiving a median of 46 PH patients for management or consultation within their average year (Table 3). The median number of PAH patients (group 1 PH) was 7 and represented the third most frequent type of PH cases, following group 2 (PH due to left heart disease; 14 cases/year) and group 3 PH (due to respiratory disease and/or hypoxemia; 10 cases/year).

The 2 main types of PAH among their received PAH patients were idiopathic (IPAH) and/or heritable PAH, and CTD-associated PAH (CTD-PAH) with, respectively, 3 and 2 cases/year.

Clinical practice for risk assessment

A poorer functional class of PAH (FC III or FC IV) was the most frequent clinical factor for drug intensification, considered by 88% of the clinicians. The 2 succeeding main criteria associated with worse prognosis and therefore pointing to treatment intensification, were hospitalization for PAH decompensation within the past 6 months and intermediate- or high-risk hemodynamic parameters (from 79% and 76% of the clinicians, respectively). In other criteria, 40% of clinicians took into account the age of the patients for patients over 65 years, 35% considered any relevant comorbidities, and 29% the male gender.

For initial risk assessment, Fig. 1A shows that most clinicians requested an echocardiography (93%), a 6MWT (85%), a BNP/NT-proBNP testing (79%), and an RHC (78%). Interestingly, clinicians from all 3 caseload categories ranked echocardiography, BNP/NT-proBNP test, 6MWT and RHC as the 4 most decisive tests for determining the risk status of PAH patients (data not shown).

Before considering treatment intensification for FC II and FC III PAH patients currently under oral double combination therapy (ERA and PDE5i/GCs), clinicians again agreed that the echocardiography, 6MWT, BNP/NT-proBNP blood tests and RHC were the main intermediate-risk criteria to be considered,

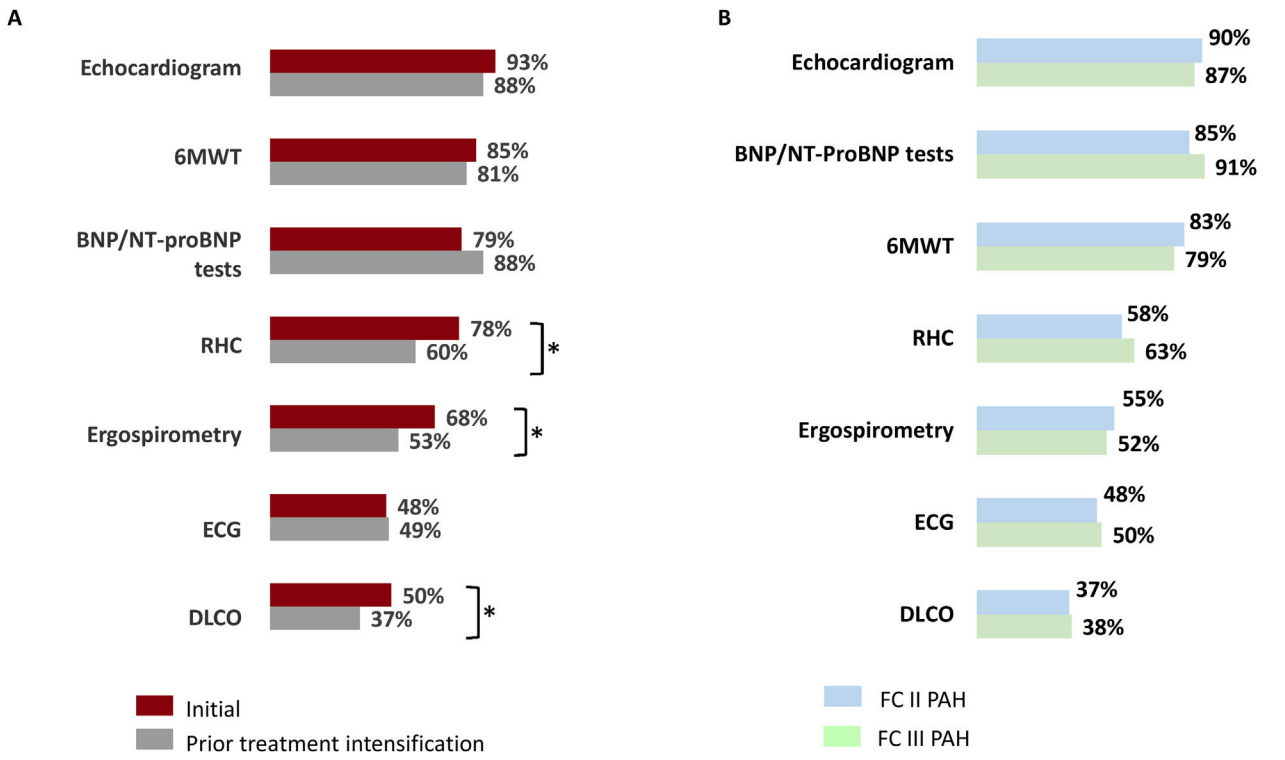

Fig. 1 – Intermediate-risk parameters ranked as very and/or extremely important. (A) For initial assessment or before considering treatment intensification (*N* = 80). (B) For risk-assessment before treatment intensification for FC II (*n* = 160) and FC III (*n* = 160) PAH patients (*N* = 80). Data are given as percentage of clinicians who ranked each of the risk parameters as very and/or extremely important. 6MWT: 6-minute walk test; BNP: brain natriuretic peptide; DLCO: diffusion lung capacity for carbon monoxide; ECG: electrocardiogram; *N*: number of clinicians; *n*: total number of answers collected for each of the PAH patients; NT-proBNP: N-terminal pro-B-type natriuretic peptide; RHC: right heart catheterization. *$P \leq .05$ with 95% confidence interval.

although they tended to use ergospirometry and diffusing capacity for carbon monoxide less frequently (Fig. 1A). These ratings were similar for FC II and FC III PAH patients (Fig. 1B).

Risk score calculators

Our data showed that ESC/ERS color coding is by far the most commonly used tool for risk stratification (68% of clinicians) regardless of the clinician caseload, followed by REVEAL 2.0 (Fig. 2). REVEAL 2.0 was used by around a quarter of clinicians with lower (3–5 PAH patients/year) and intermediate (6–9 PAH patients/year) caseloads. Clinicians with the highest caseload (over 10 PAH patients/year) used REVEAL 2.0 and REVEAL lite 2 at similar levels, closely followed by the FPHN registry (simplified model) (Fig. 2).

Initial combination therapies for PAH patient case scenarios

Overall, for FC II–III PAH patients, double-combination therapy (ERA and PDE5i/GCs) was the preferred initial treatment (Fig. 3). The addition of a third drug (either PC-receptor agonist or PC analog) was more frequently prescribed to FC III PAH patients with at least one intermediate-risk hemodynamic parameter, compared to FC II patients who presented only low-risk parameters (Fig. 3), indicating that a more severe functional class and intermediate-risk parameters advocated for a more aggressive therapy. When considering initial triple-combination therapy, the oral selective PC-receptor agonist was chosen by most clinicians. In particular for initial treatment of FC III PAH patients, around 20% of the clinicians would directly add the PC-receptor agonist to ERA and PDE5i/GCs (Fig. 3).

Choice of a third drug for intensification

Most of the clinicians (85%) chose to prescribe a PC-receptor agonist as a first choice for intensification to triple-combination therapy, for FC II–III PAH patients in absence of high-risk parameters (Fig. 4A). The choice of a third drug for intensification slightly varied according to the functional class of PAH patients, with 91% of clinicians prescribing the oral PC-receptor agonist to FC II patients compared to 79% to FC III PAH patients ($P \leq .05$). Parenteral PC analogs were prescribed more frequently to FC III PAH patients (21% versus 9% for FC II PAH patients; $P \leq .05$) (Fig. 4A). The clinicians rated both comfort and efficacy as the 2 main reasons for selecting either PPA as their first choice for a third additional drug (Fig. 4B), closely followed by the drug safety for PAH patients (Fig. 4B). Another reason for prescribing a PPA for around

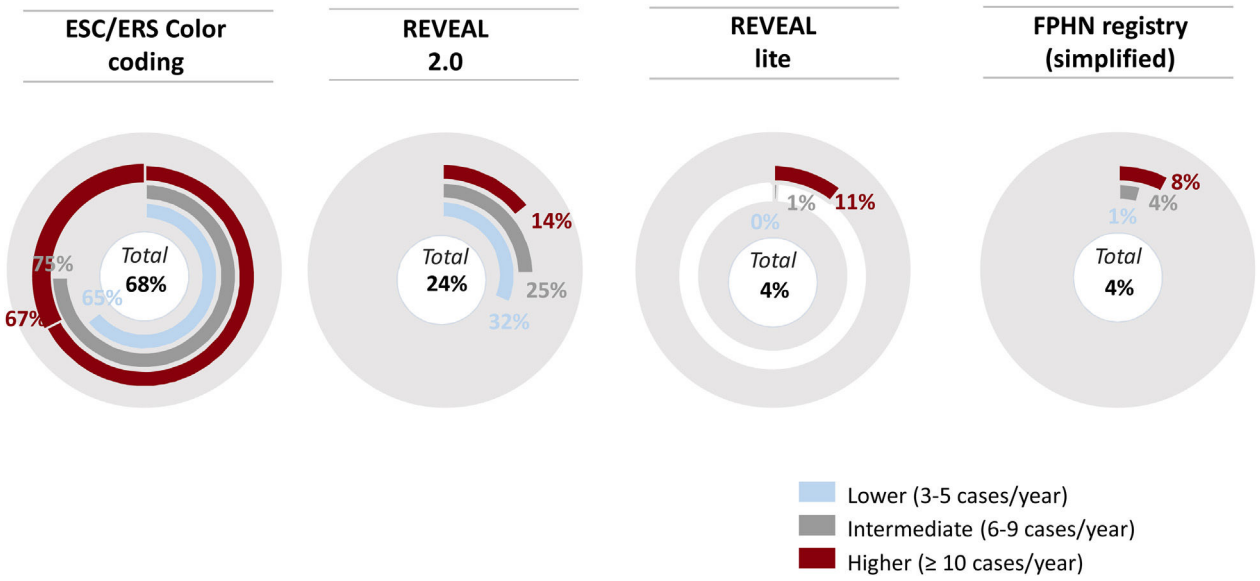

Fig. 2 – Risk stratification tools used by the clinicians overall and according to their PAH caseload. The overall percentage of clinicians using each tool is shown in the center of each panel (*N* = 80 participants). Data are presented for each stratification tool for clinicians with lower (3–5 cases/year) *N* = 31, intermediate (6–9 cases/year) *N* = 23 and higher caseload (≥10 cases/year) *N* = 31. ESC/ERS: European Society of Cardiology/European Respiratory Society; FPHN: French Pulmonary Hypertension Network; *N*: number of clinicians.

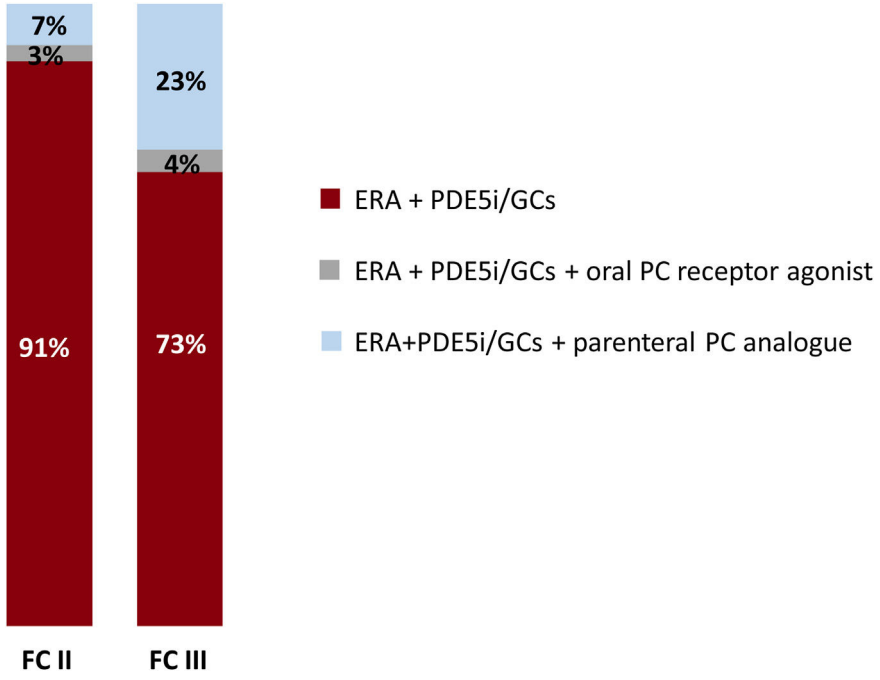

Fig. 3 – Initial combination therapies given in PAH mock case scenarios according to functional class. Percentage of clinicians who would prescribe double-combination therapy (ERA and PDE5i/GCs) or triple-combination therapy (adding either an oral PC-receptor agonist or a parenteral PC analog). Data are presented for FC II (*n* = 160) and FC III (*n* = 160) PAH patients. *N* = 80 clinicians. *n* = total number of answers collected for each of the PAH patients. ERA: endothelin receptor antagonists; FC: functional class; GCs: guanylate cyclase stimulator; PAH: pulmonary arterial hypertension; PC: prostacyclin; PDE5i: phosphodiesterase type 5 inhibitors.

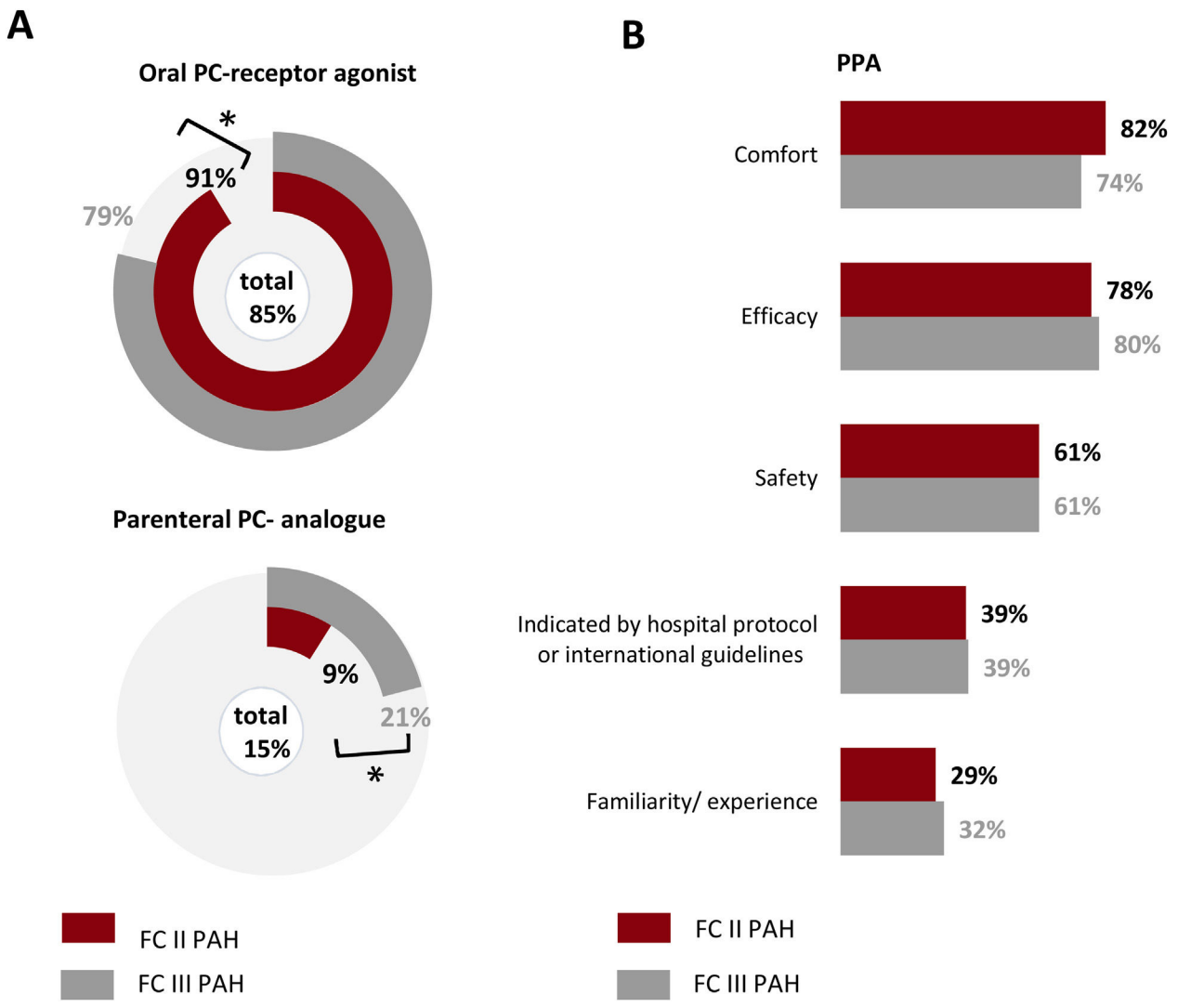

Fig. 4 – Prescription of PPA. (A) Percentage of clinicians who would prescribe either an oral selective PC-receptor agonist or a parenteral PC analog for treatment intensification overall and according to functional class for patients presenting intermediate-risk parameters. The total percentage of clinicians using each type of PPA is shown in the center (N = 80). (B) Reasons for choosing either an oral PC-receptor agonist or a parenteral PC analog according to the functional class (FC) (II or III) of the PAH patients. N: number of clinicians; FC: functional class; PAH: pulmonary arterial hypertension; PC: prostacyclin; PPA: prostacyclin pathway agents. *P ≤ .05 with 95% confidence interval.

one third of clinicians was to follow the international clinical guidelines and/or their hospital's protocol (Fig. 4B).

Pharmacological treatments typically used in clinical practice

Overall, bosentan and macitentan were the most frequently prescribed ERA (86% and 80% of the clinicians, respectively) compared to ambrisentan which is used by 70% of the clinicians (Fig. 5A). The GCs riociguat was shown to be currently used by 79% of specialists (Fig. 5A). Selexipag, approved by the European Medicines Agency in 2016, was known to nearly all physicians and had already been prescribed by two-thirds (66%) of them. All physicians knew the ERA bosentan. Only 1% of the clinicians were not familiar with the ERA macitentan or the GCs riociguat and 3% with the ERA ambrisentan or the PPA selexipag (not shown). Of note, Fig. 5B shows that management of PAH patients under selexipag was rated easy or very easy by 53% of the clinicians.

Decisive parameters and reasons to intensify treatment

Next, we investigated the decision-making process for treatment intensification with a third drug (either parenteral PC analog or oral selective PC-receptor agonist) for FC II and III PAH patients who were receiving the double-combination therapy ERA and PDE5i/GCs for a period of 6 months (Fig. 6). For FC II PAH patients who initially presented only low-risk hemodynamic parameters, the actual decision depended on the presence of one or more new intermediate-risk parameters. We found that for FC II patients who presented only one intermediate-risk parameter, 83% of the clinicians con-

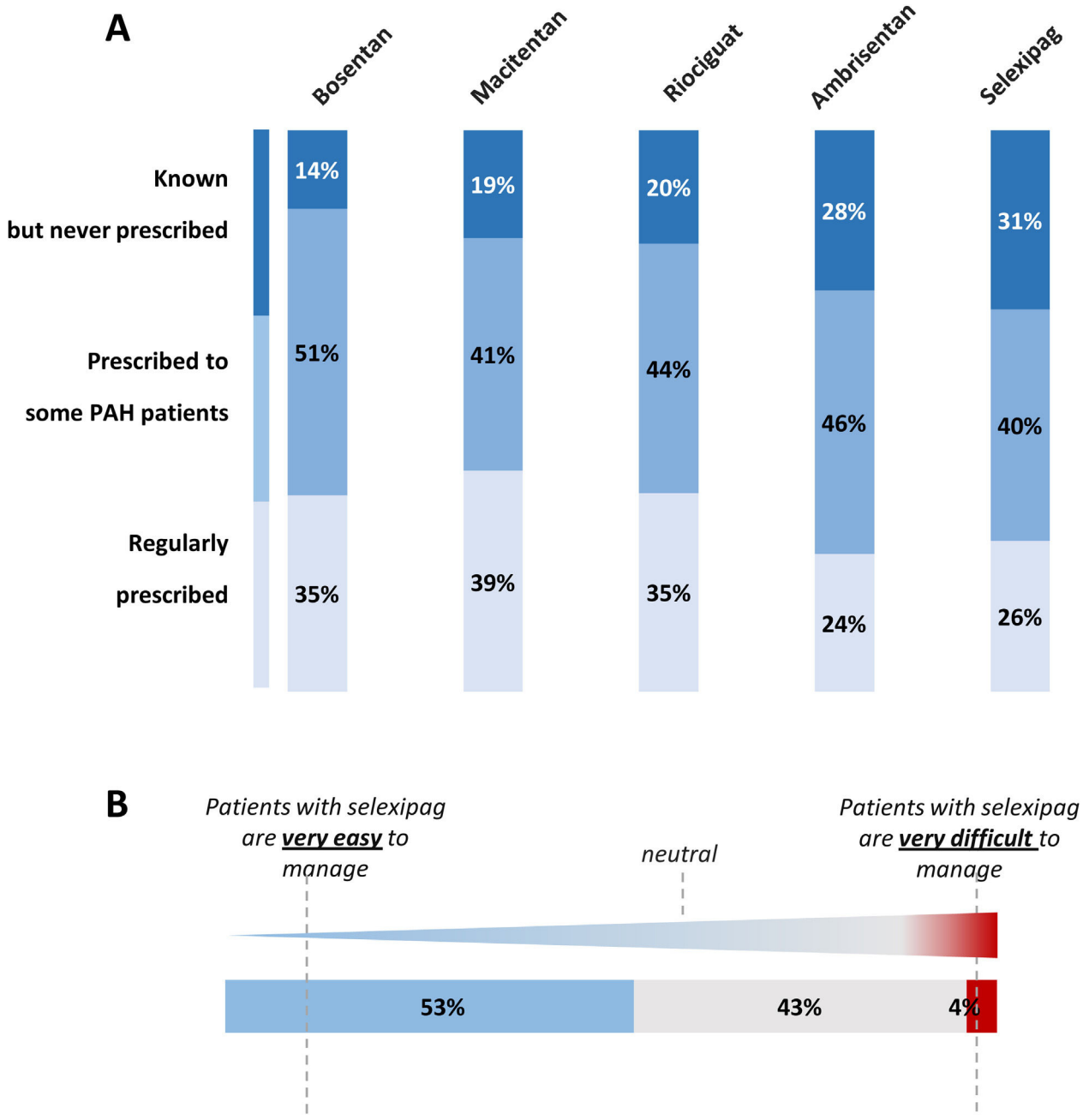

Fig. 5 – Pharmacological treatments typically used in clinical practice. (A) Percentage of clinicians who regularly, occasionally, or never prescribed bosentan, ambrisentan, macitentan, riociguat, and selexipag. N = 80. (B) Rating of PAH patients management under selexipag. N = 80. N: number of clinicians; PAH: pulmonary arterial hypertension.

sidered intensifying treatment with a PPA, and 92% were inclined to prescribe PPA upon the occurrence of multiple new intermediate-risk parameters (Fig. 6).

For FC III patients who initially presented at least one intermediate-risk parameter and maintained the same risk status despite a 6-month treatment with ERA and PDE5i/GCs, 93% of the clinicians would consider prescribing PPA, and nearly all clinicians would add a PPA in sequential triple-combination therapy to FC III PAH patients with one or several new intermediate-risk parameters (97% and 99%, respectively; Fig. 6).

Discussion

In this Spanish nationwide study, we investigated both the risk-assessment procedures and decision-making processes for treatment of PAH patients that are followed by hospital-based physicians. We found that for both initial risk stratification and assessment prior to treatment intensification, an echocardiogram was requested by nearly all clinicians, closely followed by 6MWT, BNP/NT-proBNP tests and RHC. ESC/ERS color coding was the most frequently used

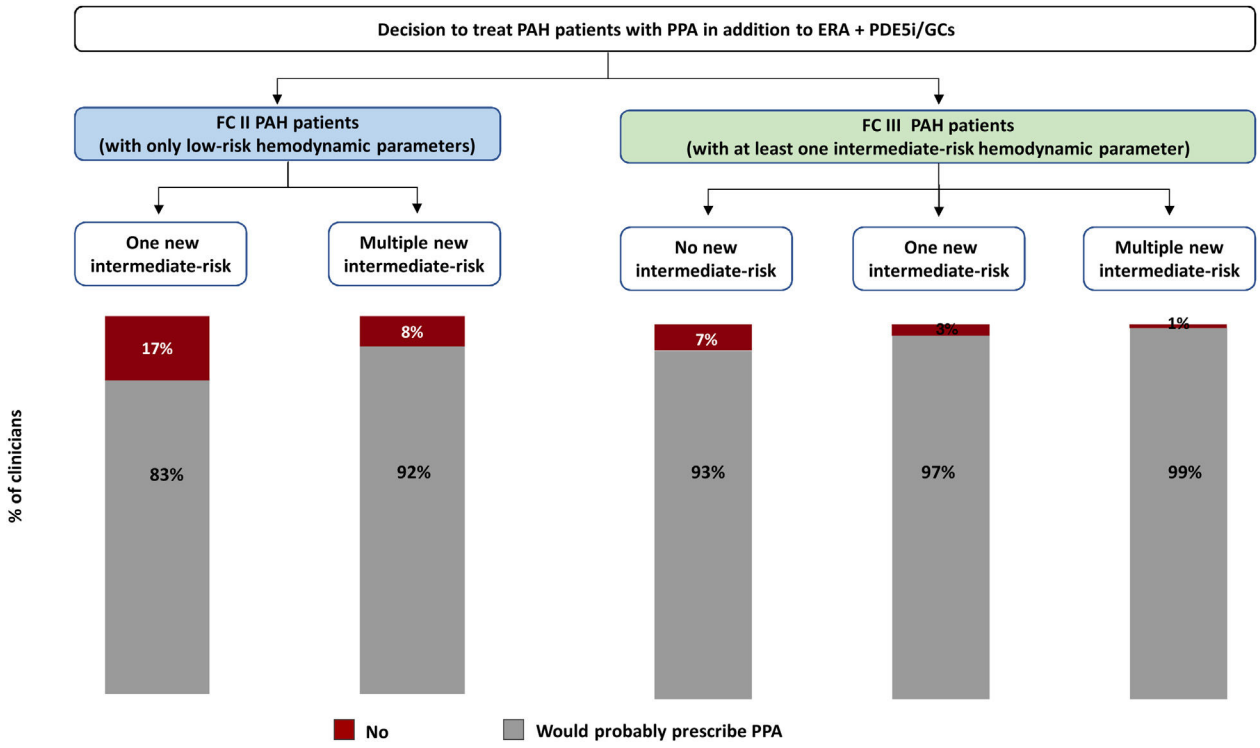

Fig. 6 – Decision pathway for triple therapy. Percentage of clinicians who would add a PPA (either an oral PC-receptor agonist or a parenteral PC analog) to ERA and PDE5i/GCs combination therapy according to functional class and new intermediate-risk parameters; N = 80 clinicians. ERA: endothelin receptor antagonists; FC: functional class; GCs: guanylate cyclase stimulator; PAH: pulmonary arterial hypertension; PC: prostacyclin; PDE5i: phosphodiesterase type 5 inhibitors; PPA: parenteral or oral prostacyclin pathway agents (either PC-receptor agonist or PC analogs).

risk stratification tool globally, followed by REVEAL 2.0 and REVEAL Lite which were mostly used by specialists with the highest caseload. In line with current ESC/ERS guidelines, we found that functional class and intermediate-risk parameters were the most determinant criteria for the prescription of initial and sequential triple-combination therapy, with nearly all specialists considering adding a PPA for the more advanced stage FC III patients. Another important finding of our study was that most clinicians seem to have adopted in their current practice the use of the oral PC-receptor agonist selexipag as a third oral drug for initial treatment of FC II–III PAH patients, in the absence of high-risk parameters. One major facilitator was the oral mode of administration of selexipag which is more comfortable for PAH patients than parenteral PC analogs.

Intermediate-risk parameters and decision to treat

Risk stratification is primordial to tailor the treatment strategy according to the risk of adverse outcomes for PAH patients.[7,8] We found that the hospital-based clinicians of our study mostly requested echocardiography, 6MWT, BNP-pro-NT-BNP levels and, although to a lower extent, RHC. RHC was most often used for initial risk stratification and slightly less requested for re-evaluating the patients before treatment intensification. RHC is necessary to diagnose PAH as per the European ESC/ERS guidelines.[7] However, whether RHC should be used to monitor PAH patients after initial diagnosis is controversial when all other risk parameters are low or intermediate,[7,11] which is the case in all the mock scenarios evaluated in our study. In addition, the clinicians may base their decision on their experience of alternative tests being more easily accepted by patients than RHC.[12] The ESC/ERS guidelines advise that risk assessment should include the determination of WHO FC, at least one exercise capacity evaluation such as 6MWT, and some indication of RV function. Most of these parameters can be measured in a non-invasive and cost-effective manner. Indeed, several critical hemodynamic parameters were shown to be reliably measured by transthoracic echography and to strongly correlate with RHC results. These included right atrial pressure[13] and pulmonary arterial systolic pressure.[14] A retrospective analysis (from January 2001 to December 2012) showed that right ventricular systolic pressure estimated by echocardiography also reflected RHC results.[14] In addition, Boucly et al.[15] reported that non-invasive 6MWT and BNP/NT-proBNP plasma levels were reliable indicators of 1-year survival, together with functional class, potentially precluding the need for RHC for FC II PAH patients after initial diagnosis. More recently, Helgeson et al.[16]. suggested that BNP and NT-proBNP levels could also be used as an alternative to right atrial pressure for risk stratification. Accordingly, we observed a tendency to request slightly more often BNP/NT-proBNP testing than 6MWT, for risk-assessment prior to escalation to triple-combination therapy for FC II–III PAH patients. This finding was also in line with the CHEST expert consensus survey.[17] Altogether, our results reflect the current trend in follow-up risk assessments to favor

less invasive procedures which are shown to offer powerful and reliable prognostic value.

Risk stratification tools

We found that, in addition to ESC/ERS risk assessment strategy defined in the European clinical guidelines, the American registry-based REVEAL 2.0 risk calculator was often used by the Spanish clinicians, whereas the FPHN registry was the least used model. This is in line with findings from Benza et al.[18] who reported that REVEAL 2.0 showed greater risk discrimination compared to FPHN and COMPERA registry-based models, in patients enrolled in the REVEAL registry. REVEAL lite was also used, though mostly by clinicians with higher caseloads.

Of note, our study highlighted that the recently developed REVEAL Lite calculator was used mostly by clinicians who manage over 10 PAH patients/year, indicating that these specialists are more prone to consider the new tools available and to integrate them quickly into their current practice. This result may also be explained by their individual experience and, for those who are practicing in specialized PH units, the combined knowledge and expertise of their colleagues, further advocating for the referral of PAH patients to specialized PH centers.[11,19]

Therapeutic strategy

We found that dual therapy with ERA and PDE5i/GCs was prescribed by most clinicians for FC II–III patients in the absence of high-risk parameters. Indeed, initial double-combination therapy with ERA and PDE5i was shown to delay the progression of PAH[20,21] and is recommended for newly diagnosed FC II–III PAH patients with intermediate-risk status.[7,8,22]

The decision of the Spanish clinicians to add PPA to ERA and PDE5i/GCs for FC III patients whose intermediate-risk status did not improve, and FC II–III PAH patients whose condition worsened despite 6 months dual oral therapy, follows the current guidelines. Indeed, the ESC/ERS experts advise to intensify treatment to lower risk parameters, for intermediate-risk FC II, III and IV PAH patients,[7] with the objective to achieve or maintain low-risk status.[22] The addition of parenteral PC analogs is the recommended strategy for high-risk FC III and IV PAH patients,[7,8] whilst the selective PC-receptor agonist selexipag is recommended for treatment intensification of FC II PAH patients with intermediate-risk parameters and FC III PAH patients in the absence of high-risk parameters.[8] Selexipag may also be prescribed to FC IV patients who severely suffer from side effects resulting from the implanted device administering PC analogs subcutaneously.[12,20] Selexipag may be prescribed to FC II PAH patients as either mono-, double- or triple-combination therapy with ERA and/or PDE5i.[7]

The recommendation for selexipag in triple-combination therapy for FC II and III PAH patients whose risk status remains intermediate while receiving double-combination therapy[9] was based on several clinical trials. Firstly, the GRIPHON clinical trial showed a benefit of the oral PC-receptor agonist selexipag, when added to the ERA and PDE5i combination, for FC II–III PAH patients.[10,23] Comparatively, the American guidelines were not able to make a definitive recommendation on when to add selexipag to dual ERA and PDE5i therapy, because of a higher cut-off value for 6MWT set by the CHEST experts.[24] Most recently, the TRITON study suggested that there was a positive trend over time to fewer morbidity and mortality events in newly diagnosed/treatment naive patients with PAH treated with initial triple oral therapy (ERA macitentan, PDE5i tadalafil, and selexipag) versus initial double oral combination therapy (macitentan and tadalafil), and both strategies showed a marked reduction of pulmonary vascular resistance. The benefit of selexipag as a third drug for treatment intensification was supported by a pooled post hoc analysis of adverse clinical outcomes in PAH patients enrolled in the GRIPHON and the TRITON clinical trials. In this latest study, Coghlan et al.[25] showed that initial and early sequential (less than 6 months after diagnosis) treatment with selexipag, in addition to double-combination therapy (ERA and PDE5i), decreased the risk of disease progression by 48% compared to double-combination therapy only.

Strengths and limitations

The major strengths in the design of our study interrogating clinicians on their management of virtual PAH patients, is that their decisions on risk assessment and treatment could reliably be compared, without the bias of individual variations specific to any patient, and that all answers could be collected without any missing data. Another advantage, compared to retrospective studies, was the ability to analyze the rationale behind these choices. However, we recognize that this design has several limitations. Firstly, the mock case scenarios do not represent all PAH patients received by the participants in their real-world practice, and therefore do not address all possible clinical situations. One other limitation of our survey regarding typical practice is that it did not include details on the clinical profile of the patients, such as age and comorbidities. Besides, we did not interrogate the clinicians on the type of ERA, PDE5i or PC analogs they would prescribe to the virtual patients. Finally, the interpretation of some subgroup analyses was limited by their small size.

Conclusions

Our study showed that the ESC/ERS guidelines play a major role in the management of PAH patients by Spanish hospital-based clinicians, together with clinical experience for specialists with the highest caseload. In agreement with the recent validation of simplified risk stratification tools, we noted a tendency for non-invasive testing of FC II–III patients with low- or intermediate-risk parameters. Our study showed that selexipag was more often prescribed in initial and sequential triple-combination therapy than PC analogs to FC II–III PAH patients with low- or intermediate-risk status. The main reasons given by the clinicians for this decision were the efficacy and safety of selexipag, together with its oral mode of administration, which renders it more comfortable to the patients.

What is known about the subject?

- Despite PAH being a rare disease, both its incidence and prevalence are on the rise in the Spanish population.
- Both early diagnosis and stratification of patients, according to their estimated 1-year prognosis assessed by a multiparametric risk stratification approach, are critical in assisting clinicians with their treatment strategy decision-making.
- The main therapeutic objective is to decrease the risk profile to low risk and/or maintain it.

Does it contribute anything new?

- Nearly all clinicians requested an echocardiogram, closely followed by 6MWT, BNP/NT-proBNP tests and RHC for both initial risk stratification and assessment prior to treatment intensification.
- The most frequently used risk stratification tool globally was ESC/ERS color coding, followed by REVEAL 2.0 and REVEAL Lite which were mostly used by specialists with the highest caseload.
- The efficacy and safety of selexipag, together with its oral mode of administration, made it more often prescribed in initial and sequential triple-combination therapy than PC analogs to FC II–III PAH patients with low- or intermediate-risk status.

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Authors' contributions

A. García, M. Lázaro, R. Utande, and V. Cuenca analyzed and interpreted the data regarding the PAH patients' risk assessment and therapeutic preferences in intensification. All the authors were involved in writing this manuscript. All authors read and approved the final manuscript.

Conflicts of interest

M. Lázaro has received funds or compensation of any kind from Janssen, MSD, AstraZeneca, Bayer; Coordinator Pulmonary Circulation Group-IC-SEC Association. A. García has received funds or compensation of some kind from Janssen, MSD, Bial, Menarini, Chiesi; is a member of the Board of Directors of the Spanish Society of Pulmonology and Thoracic Surgery. R. Utande is an employee at Janssen Spain, Medical Affairs department. V. Cuenca is an employee at Janssen Spain, Medical Affairs Department, and a member of the Spanish Society of Cardiology and the Spanish Society of Pediatric Cardiology and Congenital Heart Disease.

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