Use of Oral Anticoagulant Drugs in Patients with Pulmonary Hypertension

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DISCLOSURE STATEMENT

All the authors declare no significant disclosure to be declared.

KEY WORDS: Pulmonary Hypertension; Oral Anticoagulant Drugs; VKAs; DOACs.

KEY POINTS

- In patients with pulmonary hypertension, there is a significant burden of adverse outcomes and mortality
- Pathophysiological and clinical data support the use of oral anticoagulants (OAC) in pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH)
- Use of OAC appears to be able to mitigate this risk, even though supported mainly by observational data
- Most studies so far used vitamin K antagonists (VKAs), while data on direct oral anticoagulants (DOACs) still seem limited
- If use of OAC seems to be a mainstay in treatment of PAH and CTEPH, more data are still needed to support more solidly guidelines and evaluate use of DOACs

SYNOPSIS

Pulmonary hypertension (PH), in particular pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH), burdens patients

with relevant morbidity and mortality. Use of oral anticoagulants (OAC) seems able to mitigate the risk of adverse outcomes and death in these patients. Despite scarce evidence, use of OAC is recommended to treat PH patients, mainly based on observational data. So far data are still unclear about the impact of direct oral anticoagulant (DOACs), while vitamin K antagonists (VKAs) are the main drugs recommended. More data are needed to fully clarify the role of OAC and DOACs in PH patients.

INTRODUCTION

Pulmonary embolism (PE) and deep vein thrombosis are the main clinical manifestations of venous thromboembolism (VTE). Acute PE is the third most common acute cardiovascular condition. Acute PE is burdened by remarkable mortality, ranging from 7% (when correctly diagnosed and promptly treated) to 34% (in patients presenting with hemodynamic instability)[1]. Annual incidence rates for PE range from 39-115 per 100,000 population, and are increasing over time. Incomplete thrombus resolution occurs in 25–50% of patients after acute PE despite adequate anticoagulation but bears no clinical significance in most cases; therefore, no routine follow-up computed tomography pulmonary angiogram (CTPA) imaging is needed in such patients treated for PE[2].

The post-pulmonary embolism syndrome (PPES) occurs in up to 50% of PE survivors[3] and is defined as new or progressive dyspnoea, exercise intolerance, and/or impaired functional or mental status after at least 3 months of adequate anticoagulation following acute PE, which cannot be explained by other (pre-existing) comorbidities[4]. Chronic thromboembolic pulmonary hypertension (CTEPH) is the most severe clinical presentation of PPES.

On the other hand, pulmonary arterial hypertension (PAH) is a clinical condition characterized by the presence of pre-capillary PH and pulmonary vascular resistance >3 Wood units, in the absence of other causes of pre-capillary PH.

In this review, we disclose the role of oral anticoagulant (OAC) drugs for the main clinical presentations of pulmonary Hypertension, PAH and CTEPH, as well as the main guideline recommendations.

DEFINITIONS

Classification of Pulmonary Hypertension

Pulmonary hypertension (PH) is a haemodynamic and pathophysiological condition defined as an increase in mean pulmonary artery pressure (PAP) ≥25 mmHg at rest as assessed by right heart catheterization. PH can be found in multiple clinical conditions[5]. The clinical classification of PH includes five groups according to their similar clinical presentation, pathological findings, haemodynamic characteristics, and treatment strategy[6,7]:

- Pulmonary arterial hypertension (PAH, group 1) is a clinical condition characterized by the presence of pre-capillary PH and pulmonary vascular resistance >3 Wood units, in the absence of other causes of pre-capillary PH such as PH due to lung diseases, chronic thromboembolic PH, or other rare diseases. PAH includes different forms that share a similar clinical picture and virtually identical pathological changes of the lung microcirculation (i.e., idiopathic, heritable, drug induced, associated with connective tissue disease, etc.).
- Pulmonary hypertension due to left heart disease (group 2).
- Pulmonary hypertension due to lung diseases and/or hypoxia (group 3).
- Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions (group 4), includes CTEPH and other pulmonary artery obstructions (angiosarcoma, arteritis, congenital pulmonary arteries stenoses, hydatidosis).

- Pulmonary hypertension with unclear and/or multifactorial mechanisms (group 5).

Pulmonary Artery Hypertension

PAH is a proliferative vasculopathy characterized by vasoconstriction, cell proliferation, fibrosis, and thrombosis. Pathologic findings include intimal hyperplasia and fibrosis, medial hypertrophy and in situ thrombi of the small pulmonary arteries and arterioles[8,9]. The small pulmonary arteries and arterioles seem qualitatively similar in the pathologic studies in all patients with PAH. It is unclear whether these mechanisms are shared with most other types of PH. A previous pathophysiologic review suggested that abnormalities of both coagulation and the fibrinolytic system lead a prothrombotic state in patients with idiopathic PAH[10]. Patients with PH are at increased risk for intrapulmonary thrombosis and thromboembolism due to sluggish pulmonary blood flow, dilated right heart chambers, venous stasis, and immobility. Even a small thrombus can produce haemodynamic deterioration in a patient with a compromised pulmonary vascular bed[9]. There is a high prevalence of vascular thrombotic lesions at post-mortem examination in patients with PAH[6].

Chronic Thromboembolic Pulmonary Hypertension

Approximately 40% of PE survivors have persistent perfusion defects. Despite that, the diagnosis of CTEPH is rare, presenting with a prevalence in PE survivors of 2–3%, and 5–8% in PE survivors with persistent dyspnea[4,11].

CTEPH is a disease caused by the persistent obstruction of pulmonary arteries by fibrotic organized thrombi causing fixed mechanical obstruction that leads to overflow of the open pulmonary arteries and remodelling of the pulmonary microvascular bed,

that leads to a progressive increase in pulmonary vascular resistance (PVR)[12]. Interestingly, there is no clear correlation between the degree of mechanical obstruction found at imaging and hemodynamics. Most patients diagnosed with CTEPH are derived from cohorts with acute PE[13].

Associated conditions include thrombophilia disorders, particularly antiphospholipid antibody syndrome and high coagulation factor VIII levels, cancer, a history of splenectomy, inflammatory bowel disease, ventricular-atrial shunts, and infection of chronic intravenous lines and devices such as implantable pacemakers. Median age at diagnosis of CTEPH is 63 years and both sexes are equally affected. Clinical symptoms and signs are non-specific or absent in early stages, thus early diagnosis remains a challenge. When present, the clinical symptoms of CTEPH may resemble those of acute PE or of pulmonary arterial hypertension. Scores for predicting or ruling out CTEPH are limited by a lack of specificity[14,15].

The diagnosis of CTEPH requires a mean PAP of ≥25 mmHg along with a pulmonary arterial wedge pressure of ≤15mmHg, documented at right heart catheterization in a patient with mismatched perfusion defects on ventilation/perfusion lung scan, performed after at least 3 months of adequate anticoagulation (to distinguish this condition from acute PE). Specific diagnostic signs for CTEPH on CTPA include ring-like stenoses, webs, slits, and chronic total occlusions[6]. Of note, a change to decrease mean PAP to ≥20 mmHg to define PH has been proposed but is not yet incorporated into diagnostic criteria of CTEPH[11].

CTEPH is defined as chronic pulmonary vascular obstruction with normal mean PAP pressure at rest, but with limited exercise tolerance, which is attributed, at least in part, to an increased slope of the PAP–flow relationship (>3mmHg/L/min) during exercise or dead space ventilation[16]. Dead space fraction is decreased with exercise, while ventilatory efficiency, measured by the ventilatory equivalent for carbon dioxide slope, is decreased[17,18]. Currently, there is no sufficient data to support the definition of 'PH on exercise'[6].

Based on the elements described above, both PAH and CTEPH receive a direct indication to be prescribed with OAC in European Society of Cardiology and other international guidelines[6,19].

ADVERSE OUTCOMES IN PATIENTS WITH PULMONARY HYPERTENSION

Irrespective of its relatively low prevalence and incidence, the presence of PH is burdened by significant morbidity and mortality[6,20]. Indeed, PH and the consequential right heart failure, can often lead to complications affecting every organ and system, from those more commonly known as consequences on left heart side function, kidney function and cognitive function, to the less known as those affecting endocrine system, gut and liver function, immune system, and others[20].

Despite the significant advances in the specific clinical and pharmacological management achieved in the last years[6,21,22], the most concerning effect of PH is the increased medium- and long-term risk of mortality[23]. Even though several specific pharmacological treatments are currently available[21,22], and despite the diffusion of pulmonary endarterectomy as treatment of choice for CTEPH[6], data coming from

observational registries did not show significant improvement in the risk of death in long-term follow-up (Table 1)[13,23–27]. Indeed, the data coming from a French nationwide registry including 674 patients with PH in 2006 documented an overall mortality rate of almost 12% in incident PH patients at 1 year of follow-up[24], Ling and colleagues in 2012 reported an overall mortality rate of almost 27% over a 5-year follow-up time also in incident PH patients[25], and Kerr and colleagues reported an overall mortality rate of 6.53%, which increases up to 11.5% in inoperable patients, in a registry of CTEPH only patients[27]. Evidence coming from the observational registries also confirmed that over time, PH patients report a significant clinical deterioration and worsening, both the general PH cohorts[26] and those with CTEPH only[27].

Significant evidence of an important burden of adverse outcomes comes also from other clinical scenarios. In a large systematic review and meta-analysis including more than 16,000 patients, Kolte and colleagues reported that even patients with mild PH (defined as pulmonary artery pressure <25 mmHg) show a significant increase in the risk of all-cause death (risk ratio [R+R 1.52, 95% confidence interval [CI] 1.32-1.74), over a long-term follow-up observation[28]. Similar data were also reported in specific clinical populations. Indeed, Covic et al. reported a 2-fold increased risk of death in PH patients receiving a kidney transplant[29] and Liu et al. reported a more than 3-fold increased risk of death in systemic sclerosis-associated PH[30].

IMPACT OF OAC ON ADVERSE OUTCOMES IN PH PATIENTS

As reported above, both PAH and CTEPH recognize a specific indication for treatment with OAC[6]. The importance of OAC in both patients with PAH and CTEPH has been clear since the earlier paper studying the various forms of PH, underlining the role of thrombotic mechanisms in the developing of both conditions[31]. While nowadays the advances of specific pharmacological therapy for PAH reduced the importance of OAC in those patients, it remains a mainstay for treatment of patients with CTEPH[31]. Since the earlier studies reporting specific data about the use of vitamin K antagonists (VKAs) in PH patients, it became clear how the use of OAC would have been useful to reduce the risk of death on long-term follow-up[32].

In a systemic review and meta-analysis published in 2018, Khan and colleagues aimed to summarize the evidence available about the effectiveness of OAC in PAH[33]. In this study, which included data about more than 2,500 patients, OAC was associated with a significant reduction in risk of death (hazard ratio [HR] 0.72, 95% CI 0.57-0.93), particularly in patients with idiopathic PAH[33]. Importantly, in the 12 studies included in the meta-analysis, in almost all of them VKAs were the only OAC used. Furthermore, modelling data seem to confirm the beneficial effect of OAC in idiopathic PAH patients, with a significant improvement in risk of outcomes and gain in terms of quality of life[34].

The use of OAC in CTEPH is pivotally indicated by its thromboembolic origin, even though this indication has not been supported by specific studies and the specific evidence is substantially scarce[2]. Since their introduction, the direct oral anticoagulants (DOACs), have become an attracting treatment option for patients with CTEPH, and generally for PH patients[31]. Notwithstanding, so far only very few

observational studies have addressed this issue[35]. Recently, two systematic reviews emerged from the literature[36,37]. In the paper by Sedhom and colleagues, 6 cohorts were included in the systematic review, for a total of 2145 patients. In this study, the authors underlined a trend in lower risk of major bleeding in patients treated with DOACs, with a still contradictory impact in terms of thrombotic event recurrence[37]. In another systematic review and meta-analysis, presented during the latest American College of Cardiology meeting, the authors included 4 observational studies with a total of 1750 patients with CTEPH, showing a safety advantage of DOACs treatment[36]. Indeed, while there was no significant difference in terms thrombotic event recurrence (odds ratio [OR] 2.07, 95% CI 0.65-6.65), the risk of major bleeding was significantly lower with DOACs than VKAs (OR 0.51, 95% CI 0.28-0.93)[36], also with no relevant heterogeneity regarding this pooled outcome data (I^2 0%). Interestingly, the authors also reported a strong trend in reduction of risk of death (OR 0.45, 95% CI 0.20-1.01, p=0.05), despite a moderate-to-high heterogeneity (I^2 66%). Clearly, these data need to be further confirmed in larger cohorts, hopefully in a randomized controlled trial.

CHOICE OF OAC DRUGS

VKAs are a group of oral anticoagulants that act by antagonizing the effect of vitamin K and thus decreasing the levels of vitamin K-dependent coagulation factors (II, VII, IX and X). VKA are drugs with a large body of clinical experience, low cost and widely available. The main disadvantages of VKA are the requirement for frequent monitoring and the several food and drug interactions. VKA have been for decades the treatment of choice in patients with atrial fibrillation and venous thromboembolism[38,39].

On the other hand, DOACs, are oral anticoagulants introduced more than a decade ago, indicated as first option in patients with atrial fibrillation and venous thromboembolism[39,40]. Their mechanism of action consists in inhibiting factor Xa (rivaroxaban, apixaban and edoxaban) or thrombin (dabigatran). They do not require regular monitoring of levels and have less drug-to-drug interactions than VKAs[38–41].

Choice of OAC in patients with PAH

Interruption and consequent modulation of the coagulation cascade should theoretically improve survival in patients with PAH. This presents a plausible rationale for the use of OAC in PAH. However, because of the non-existence of randomized controlled trials on anticoagulation versus placebo for the treatment of pulmonary hypertension, effectiveness, and benefits of OAC therapy in these patients is confined to observational data[6,9].

Hence, the evidence regarding the use of anticoagulation in patients with idiopathic PAH is mostly based in small series and retrospective studies[32,42,43]. As already reported, Khan and colleagues, performed a systematic review, which reported a moderate risk of bias, to examine the impact of adjunctive OAC in patients with PAH. In 11 of the 12 studies included, patients received warfarin as anticoagulant therapy[33]. In the remaining study, 93% patients received warfarin, 6% heparins and only 1% were treated with DOACs[42]. Thus, warfarin has been the treatment of choice when anticoagulation is considered in patients with PAH, based on the available experience. Interestingly, international normalized ratio (INR) is targeted at 1.5-2.5 in many centres in the United States and Japan[19,44], while many European centres

target INR at 2-3. Based on the aforementioned studies, guidelines recommend the use of warfarin in patients with PAH when anticoagulation is considered[6,19,45].

Currently, there is no evidence to support the use of DOACs in patients with PAH. There is no published study regarding the use of DOAC in these patients[29]. Several factors may limit the use of DOACs in patients with PAH. Renal and hepatic failure is frequent in patients with PAH, and this may limit the use of DOACs and might increase the risk of bleeding and decrease the efficacy of the drug[46]. Also, DOACs may present drug-drug interactions with PH targeted therapies. DOACs bioavailability might be increased by P-gp or CYP3A4 inhibition, thus increasing the risk of bleeding. Type 5 phosphodiesterase inhibitors (sildenafil, tadalafil and vardenafil) are P-gp inhibitors, while other therapies such as prostanoid receptor agonist (selexipag), guanylate cyclase stimulator (riociguat) or endothelin antagonist (ambrisentan) are P-gp substrates[47].

Choice of OAC in patients with CTEPH

Use of OAC is considered the first step and the cornerstone in the management of CTEPH. In fact, the diagnosis of CTEPH is based on findings obtained after at least 3 months of effective anticoagulation[6]. There is a general agreement that therapeutic OAC should be continued indefinitely, regardless of the surgical or medical treatment of CTEPH, although as already reported this recommendation has not been validated in a clinical trial[7]. Guidelines recommend the use of VKAs as the treatment of choice, given the scarce evidence of DOACs in this setting[2,6].

As addressed above, the currently available evidence comes exclusively from observational studies, also with conflicting results. A recent study compared consecutive CTEPH patients undergoing pulmonary endarterectomy between 2007 and 2018 (794 treated with VKAs and 206 with DOACs). Hemodynamic outcomes, bleeding events and mortality were similar in both groups, but VTE recurrence was higher with DOACs (0.76% vs 4.62% person-year, p=0.008)[48]. However, another study including 501 CTEPH patients between 2011 and 2018 (312 treated with warfarin and 134 with rivaroxaban) found that major bleeding was significantly higher with warfarin (HR 1.94, 95% CI 1.05-3.62), with no difference in the rates of VTE recurrence (HR 1.21, 95% CI 0.64-2.23)[49]. Hayashi et al. compared 120 CTEPH patients (70 treated with VKA and 50 treated with DOACs), and they found no significant differences in the risk of bleeding or VTE recurrence[50].

Results coming from single studies, as well as the pooled data coming from the recent systematic reviews and meta-analyses [36,37], suggest that DOACs represent a safe alternative to VKAs, and also underline the need for more solid and well-conducted studies to elucidate the actual impact of DOACs vs VKAs in patients with CTEPH and PAH, also taking proper account of issues regarding bioaccumulation and drug-drug interactions[51].

GUIDELINES RECOMMENDATIONS

The ESC and the European Respiratory Society (ERS) published their last guidelines on diagnosis and treatment of pulmonary hypertension back in 2015[6] (Table 2). The experts recommended the use of OAC in patients with idiopathic PAH, hereditary PAH and PAH due to anorexigens (Recommendation Class IIb,

Level of Evidence C). This recommendation was based on single-centre experience and retrospective studies. However, ESC/ERS guidelines did not give recommendations regarding the type of oral anticoagulant to be used, indicating that the role of DOACs was still unclear[6]. There is less evidence regarding the use of oral anticoagulation in patients with Eissenmenger syndrome, due to the high risk of thrombosis and bleeding. In these patients, oral anticoagulation should only be considered in cases of PA thrombosis, signs of heart failure and absent or mild haemoptysis (Recommendation Class IIb, Level of Evidence C). In patients with PAH associated with connective tissue disease, OAC may be considered on an individual basis and in the presence of thrombophilia predisposition (Recommendation Class IIb, Level of Evidence C) according to ESC/ERS guidelines. In patients with PAH associated with portal hypertension, OAC is not recommended due to high risk of bleeding (Recommendation Class III, Level of Evidence C)[6]. In patients with PAH associated with HIV infection, OAC is also not recommended due to high bleeding risk and the lack of data on the efficacy/risk ratio (Recommendation Class III, Level of Evidence C). In patients with CTEPH, lifelong anticoagulation is recommended (Recommendation Class I, Level of Evidence C), even after pulmonary endarterectomy (PEA). Again, experts indicated the absence of data on the efficacy and safety of DOACs in these patients.

The Spanish Society of Pulmonology and Thoracic Surgery Guidelines, published in 2018, give similar recommendations, including OAC for patients with idiopathic PAH, heritable PAH and PAH caused by anorexigens. OAC is also recommended for patients with CTEPH, and the experts recommend the use of VKAs, since there is no evidence with sufficient strength to support the use of DOACs[45].

Interestingly, the CHEST Guideline and Expert Panel Report on Therapy for Pulmonary Hypertension in Adults, published in 2019, chose not to make any recommendations regarding the use of OAC in patients with PAH. The experts found that studies addressing anticoagulation in PAH patients could not be included in meta-analysis due to the small sample, different interventions, and different subpopulations[52].

SUMMARY AND CONCLUSIONS

In this narrative we summarized the evidence regarding the use of OAC in patients with PH, specifically those with PAH and CTEPH. The presence of both conditions entails an increased risk for adverse outcomes, particularly an increased risk of all-cause death. Even though coming exclusively from observational studies, current evidence underlines a beneficial effect of OAC therapy in these patients, beyond the other pharmacological therapy. Despite appearing as a promising alternative to VKAs, use of DOACs in these patients is still debated and demands more evidence [Figure 1].

Our manuscript clearly underlines how, in the context of a now advanced clinical management and pharmacotherapy[16] patients with both PAH and CTEPH are still burdened by significant morbidity and mortality[6,20]. Thus, irrespective of the overall low prevalence and incidence of this condition, figures regarding the risk of adverse outcomes, in particular mortality, appear to be still unacceptably high. In this light, the use of OAC seems to remain an important and pivotal mainstay of the overall treatment of these patients. This is certainly true even when considering the general

evidence about the effectiveness of OAC in reducing mortality also in other clinical scenarios[53].

Standing on these premises appears important to obtain more solid and clear evidence about the impact of OAC in PH patients. Indeed, as underlined, if the international guidelines now recommend the use of OAC with substantially high degree of recommendation, this evidence is basically supported by a limited number of observational studies, weakening the strength of evidence[6]. Such lack of a strong scientific background could appear in some way unacceptable, considering the important clinical impact of this condition. Moreover, more studies are strongly needed to understand whether the use of DOACs could significantly reduce the risk of adverse outcomes without any relevant safety concern. Given the availability of these drugs, that surely made possible an important implementation of OAC therapy in other conditions, as atrial fibrillation, it appears pivotal to clarify their possible role in managing PH patients[31].

Moreover, given the important impact of PH on patients' health, we can underline how the use of OAC and of specific pharmacological therapy are important cornerstones of a clinical management that should be more comprehensive and holistic, to address the many clinical consequences of PH presence[20]. This aligns with a more modern approach that is now suggested for several cardiovascular conditions[40,54,55].

In conclusion, use of OAC, particularly VKAs is substantially recommended in patients with PAH and CTEPH, given the important risk of adverse outcomes they

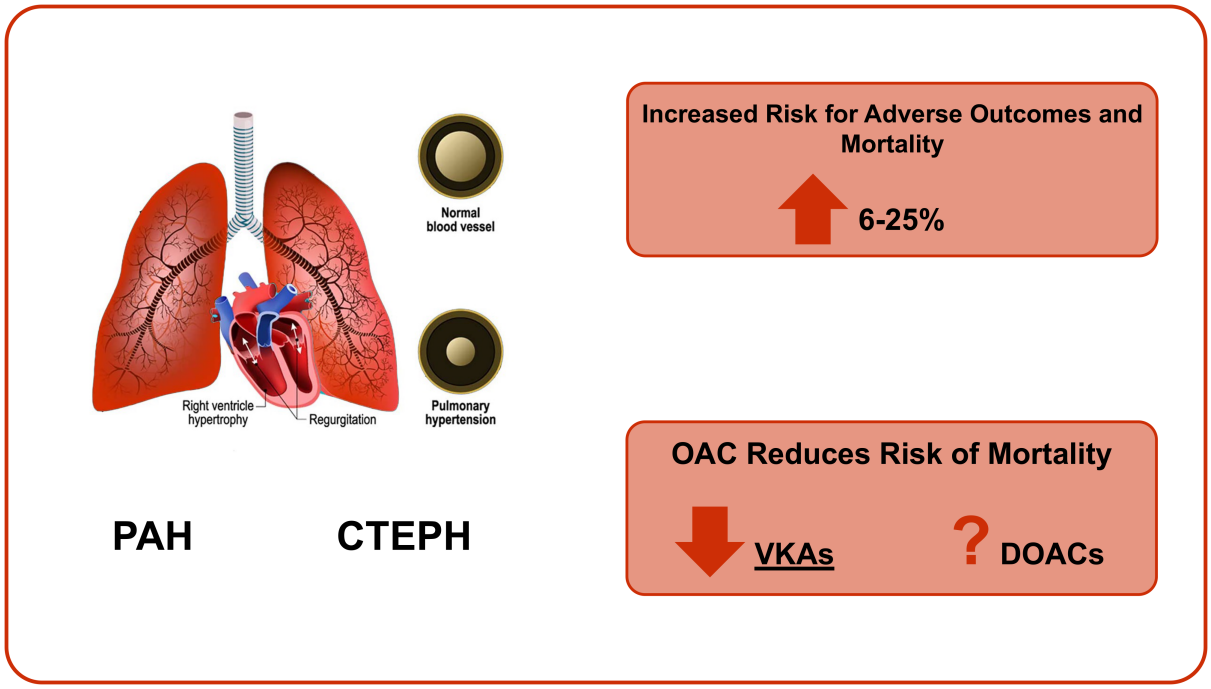
could experience and the positive impact of these drugs on this risk. Notwithstanding, given the substantial lack of solid evidence, more studies are needed to better substantiate guidelines recommendations. This is particularly needed to clarify the possible utility of DOACs in this clinical scenario, which still demand more evidence.

CLINICS CARE POINTS

- Patients with Pulmonary Hypertension (PH) are burdened with relevant morbidity and mortality
- Use of Oral Anticoagulant (OAC) drugs mitigate the risk of adverse outcomes in PH patients, particularly those with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH)
- Data so far support the use of vitamin K antagonists (VKAs), even though based on observational studies
- So far is still unclear the role of direct oral anticoagulants (DOACs) in these patients
- More data are needed to better substantiate guidelines in the future

FIGURE LEGENDS

Figure 1: Impact and Use of OAC in Patients with Pulmonary Hypertension



Legend: CTEPH= Chronic Thromboembolic Pulmonary Hypertension; DOACs= Direct Oral Anticoagulants; OAC= Oral Anticoagulant; PAH= Pulmonary Artery Hypertension; VKAs= Vitamin K Antagonists.

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Table 1: Main Outcome Data Coming from Observational Registries in Patients with Pulmonary Hypertension

Study	Year	Geographic Location	Patients	FU	Outcomes
Humbert et al.[24]	2006	France	674 *Prevalent: 553* *Incident: 121*	1 year	Mortality in Incident Group: 11.6%
Pepke-Zaba et al.[13]	2011	Europe/Canada	679	NR	Overall Mortality: 9.9%
Ling et al.[25]	2012	UK/Ireland	482	5 years	Overall Mortality: 26.8% 1-year Survival: 92.7% 2-year Survival: 84% 3-year Survival: 73.3% 5-year Survival: 61.1%
Frost et al.[26]	2013	US	3001	2 years	Overall Survival: 80.2% ± 0.7% Overall Survival-Free from Major Events: 78.9% ± 0.8% Clinically Worsened: 1340 (44.6%)
Kerr et al.[27]	2021	US	750 *Operated: 566* *Operable/No Surgery: 88* *Inoperable: 96*	1 year	Overall Mortality: 6.53% *<u>WHO Functional Classes:</u>* *Operated: I/II 82.9%* *Operable/No Surgery: I/II 56%* *Inoperable: I/II 48.2%*

Chang et al.[23]	2022	US	935	496 days*	Overall Mortality: 12.9% 1-year Mortality: 8% 2-year Mortality: 16% 3-year Mortality: 21%

Legend: *median follow-up; FU= Follow-Up; NR= Not Reported; UK= United Kingdom; US= United States; WHO= World Health Organization.

Table 2: ESC Guidelines Recommendations Regarding OAC in Patients with Pulmonary Hypertension

Type of PH	OAC Recommended	Choice of OAC	Class of Recommendation	Level of Evidence
Idiopathic PAH	Yes	VKAs	IIb	C
Hereditary PAH	Yes	VKAs	IIb	C
PAH due to Anorexigens	Yes	VKAs	IIb	C
PAH due to Congenital Heart Disease	No (consider if pulmonary artery thrombosis or signs of heart failure)	-	IIb	C
PAH with Connective Tissue Disease	No (consider if thrombophilia predisposition)	-	IIb	C
PAH Associated with Portal Hypertension	No	-	III	C
PAH associated with HIV	No	-	III	C
Chronic Thromboembolic Pulmonary Hypertension	Yes	VKA	I	C

Legend: HIV= Human Immunodeficiency Virus; OAC= Oral Anticoagulant; PAH= Pulmonary Artery Hypertension; VKAs= Vitamin K Antagonists.