

## Early View

Review

# **ERS International Congress 2019 research highlights from Assembly 13 - A focus upon ESC/ERS guidance of acute PE, PH in relation to lung disease and PAH**

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**Manuscript title:**

ERS International Congress 2019 research highlights from Assembly 13 - A focus upon ESC/ERS guidance of acute PE, PH in relation to lung disease and PAH

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**Take home message:**

This article aims to summarise the research presented at last year's ERS congress:  
The new ESC/ERS guidance on acute PE diagnosis and management, PH in relation to  
chronic lung disease and advances in pulmonary arterial hypertension.

## **Abstract**

The European Respiratory Society's International Congress of 2019, held in Madrid, Spain had exciting sessions regarding the field of pulmonary vascular disease (PVD). The symposia related to the new ERS/ESC diagnosis and management of acute pulmonary embolism (PE) were well received, as were sessions of pulmonary hypertension (PH) related to lung disease, demonstrating the concept of PH not being the rarity that it was previously thought to be. The use of risk stratification in relation to pulmonary arterial hypertension (PAH) was heavily featured and the scientific sessions informing the respiratory community of potential biomarkers and targets for future therapies were thought provoking.

In preparation of the upcoming innovative ERS International Virtual Congress in the autumn of 2020 we wanted to prepare a highlights article of the 2019 PVD sessions as a summary of current knowledge and practise.

We have therefore, summarised the key points from the sessions pertaining to the new ERS/ESC guidance of the management of acute PE. We have also focused on prognostic factors and potential therapies in PH related to interstitial lung disease. Relating to PAH we have reviewed the symposia on risk stratification, along with the use on non-invasive measures and the sessions relating to biomarkers in PAH.

## **Acute Pulmonary Embolism**

### **The new ERS/ESC Guideline for the diagnosis and management of acute PE**

During the Congress there was a huge focus on pulmonary embolism sessions, which was well received by Congress delegates, as it coincided with the recent publication and update of the ERS/ESC Guidelines for the diagnosis and management of acute PE. In the following sections we will focus on the updated areas in the 2019 guidance in the acute management of PE.

Professor Konstantinides started the proceedings by reiterating the usefulness of a transthoracic echocardiography (TTE) to assess the right ventricle (RV) for signs of

dysfunction when faced with the haemodynamically unstable patient. In the new guidance the definition of haemodynamic instability has also altered to include 'obstructive shock' implying there is evidence of end-organ hypo-perfusion with a systolic blood pressure <90 mmHg (1).

Fortunately, however, many patients we assess are not unstable and Professor Konstantinides emphasised the importance of performing a Wells or Geneva score and only a D-dimer test if there is a low or intermediate probability of a venous thromboembolism (VTE) event (Figure 1).

Relating to the use of D-dimer, classically we would consider a level above 500 ng/mL as raised. Since the results of the ADJUST PE study in 2014, its use is advocated in those who are 50 years or older, e.g. in a 60 year old using a D-dimer cut off level of 600ng/mL (2).

The adapted D-dimer cut-off based on clinical probability as per the YEARS study group publication in 2017 has also been recommended in the current guidance. This simplified diagnostic tool utilises the 'YEARS' clinical decision rule of 1. Signs of DVT, 2. haemoptysis and 3. PE more likely than an alternative diagnosis with an adapted D-dimer cut off dependent on the answers to the 'rule'(3). E.g. no evidence of these points uses a D-dimer <1000ng/mL to exclude a PE, if however, there is a positive clinical point then a D-dimer level of <500ng/mL is used.

By utilising these methods, we are ensuring the judicious use computed tomography pulmonary angiography (CTPA) in our clinical environments. It was also highlighted that we must not overlook the role of ventilation/perfusion single-photon emission computed tomography (V/Q SPECT) in the diagnosis of PE. The new guidance also usefully illustrates the radiation of each imaging modality; this is especially relevant when considering female breast tissue (1).

Professor Konstantinides discussed the importance of examining for right ventricular dysfunction, even in those with a Simplified Pulmonary Embolism Severity Index (sPESI) score of 0. This stems from a meta-analysis by Barco et al in 3000 patients with a low

PESI/sPESI=0. The investigators discovered the acute mortality was 2-4% in those with evidence of RV dysfunction. This dysfunction can initially be assessed by biomarkers such as troponin or N-terminal proB Natriuremic Peptide (NT-proBNP), right to left ventricular diameter ratio at end-systole (RV/LV ratio) on CTPA and clearly by TTE (4).

The role of precise risk stratification is vital to identify those patients with low-risk PE (Figure 25). Patients, therefore with a Pulmonary Embolism Severity Index (PESI) class I or II, sPESI score 0, or meeting no Hestia criteria (with no evidence of RV dysfunction) are considered to have a low-risk PE and are eligible for safe early discharge with careful outpatient management (5). In Barco et al's 2019 study this represented 15% of their cohort (4).

Patients with haemodynamic instability, i.e. high-risk PE, should be strongly considered for thrombolysis. With reference to intermediate-risk PE the PEITHO investigators demonstrated no benefit from thrombolysis in the long-term, in the immediate setting it does reduce haemodynamic instability but with an increased major bleed risk (6). There has been much attention given to the use of 'reduced dose' thrombolysis (7,8), the 2019 Guidelines however, still recommend only standard dosing regimens.

In patients with contraindications for thrombolytic therapy, surgical pulmonary embolectomy is still preferred above percutaneous interventional procedures (1). Professor Konstantinides was also very clear that extracorporeal membrane oxygenation (ECMO) should only be utilised as a bridge to therapy i.e. surgical embolectomy or catheter directed therapy.

The new guidance also states that inferior vena cava (IVC) filters should only be utilised in two groups of patients: patients with acute PE and an absolute contraindications to anticoagulation therapy and for patients with well-managed anticoagulation therapy and recurrent PE (1,9).

### Pulmonary embolism in pregnancy

A new section of the guidance, which has been especially well received, is that of PE in relation to pregnancy, as it is the highest cause of maternal death in high-income country. VTE risk factors in the specific context of pregnancy were underlined, and especially the increased risk linked to in vitro fertilization, particularly in the first trimester (10).

At the Congress the assessment of suspected PE in pregnancy was explained by Professor Meyer (Figure 3). By utilising the outcomes of two prospective multi-centre studies, a combination of a pregnancy-adapted YEARS algorithm with D-dimer levels, substantially increases the probability of safely excluding PE without CTPA (11,12).

Local radiology experience and chest radiogram results should aid the decision as to whether to perform a CTPA or scintigraphy scan. The radiation exposure to the foetus is minimal but is high to female breast tissue particularly with a CTPA (13).

Those with a proven PE should be managed in a centre with experience of managing PE in pregnancy. Low-molecular weight heparin (LMWH) remains the treatment of choice and the dosing regimen should be based on an early pregnancy weight. Also, Fondaparinux could be considered if there is an allergy to LMWH. Finally, amniotic fluid embolism should be excluded in case of severe cardiac or respiratory impairment, especially in the context of disseminated intravascular coagulation.

### Cancer and Direct oral anticoagulants

Professor Meyer underlined the role of direct oral anticoagulants (DOAC) in the treatment and secondary prevention of PE in patients with cancer (14,15). In patients with non gastrointestinal cancer and a low risk of bleeding, edoxaban and rivaroxaban can be safely used. For those with active gastrointestinal or genitourinary cancer, LMWH remains the recommended treatment (1).

Extension treatment after 6 months should be strongly considered especially in those with active cancer. The risk of recurrence of PE in cancer patients was also assessed using a score incorporating factors such as breast or lung cancer, involvement of lymphatic node, female

sex and previous VTE (16). A noteworthy point is that in patients with cancer and an incidental PEs should be managed as one would for a symptomatic PE if involving segmental, proximal, multiple subsegmental or a single subsegmental branch in association with a proven deep venous thrombosis (DVT).

### PE Terminology

The new guideline advises the clinician to avoid terms such as 'provoked', 'unprovoked' and 'idiopathic'. The rationale is to prevent potentially erroneous decisions regarding the duration of anticoagulation therapy (1). The guidance is very clear that the duration of anticoagulation therapy is based on the risk of recurrence of PE and risk of bleeding.

The estimated risk for long-term PE recurrence is divided into three groups: low risk (<3% per year), intermediate risk (3-8% per year) and high risk (>8% per year). Low risk group encompasses major transient or reversible factors e.g. surgery with a general anaesthetic which lasted >30 minutes. The intermediate risk group, comprising of minor transient or reversible factors, such as non-malignant persistent factors and cases in whom the index PE event occurred in the absence of any identifiable risk factors, and the high risk group where risk factors persist e.g. active cancer (1).

### Duration of anti-coagulation

Professor Meyer echoed the importance of re-assessing patients at three months. The minimum duration of anticoagulation recommended for patients with PE related to major reversible risk factors. One should consider extension if there is evidence of recurrent VTEs not related to a major transient or reversible risk factor, if there is no identifiable risk factor or a persistent risk factor. As well as in patients with a minor transient or reversible risk factor for the index PE event.

When considering extended therapy after 6 months of therapeutic anticoagulation, it is feasible to consider reduced dose rivaroxaban and apixaban. It is however important to re-assess the tolerance of the anticoagulant, with monitoring of renal and liver function as well as assessing the bleed risk.



### Follow-up

The guideline recommends a follow up visit at 3-6 months. If there is persistent dyspnoea and/or functional limitation a TTE should be organised, with a cardiopulmonary exercise testing (CPET) also being useful. It is also important to consider risk factors for possible chronic thromboembolic pulmonary hypertension (CTEPH) or chronic thromboembolic disease (CTED) in both the symptomatic and asymptomatic patient, which are helpfully listed in the new guidance (17–19). If there is a high probability of pulmonary hypertension (PH) on TTE or evidence of functional limitation it is recommended to obtain a V/Q scan and to refer the patient to an expert pulmonary vascular disease institute (Figure 4).

The recommended CTEPH treatment for proximal disease remains pulmonary endarterectomy (PEA). Medical therapy (specifically Riociguat), and balloon pulmonary angioplasty (BPA) are additional therapeutic options for patients with inoperable disease or persistent pulmonary hypertension after PEA (20,21).

### **Pulmonary hypertension in interstitial lung disease**

Pulmonary hypertension frequently affects those with chronic lung disease (CLD). Commonly there are patients with evidence of mild elevation of pulmonary artery pressures when measured at echocardiography but there is also a cohort with indicators of severe pulmonary hypertension, which may appear out of proportion to the degree of their CLD. Unsurprisingly the development of PH in this cohort of patients is associated with a poorer life expectancy, increased symptom burden including worse functional capacity, increased oxygen requirements and more frequent acute exacerbations (22).

### Prognostic factors

Kapasi et al presented a large retrospective study whereby over a 9 year period they identified 5890 patients with idiopathic pulmonary fibrosis (IPF) from their Scientific Registry of Transplant Recipients. These patients were classified into 6 groups using mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) measured in millimetres of mercury (mmHg) and wood units (WU) respectively: 1. PH absent (mPAP<21mmHg); 2. Borderline PH, preserved PVR (mPAP 21-24mmHg), PVR <3wu); 3. Borderline PH, high PVR (PVR≥3WU); 4. PH, preserved PVR (mPAP25-34mmHG, PVR<3WU);

5. PH, high PVR ( $PVR \geq 3WU$ ); 6. Severe PH ( $mPAP \geq 35mmHg$ ). Of their 5890 patients with IPF – 48% had evidence of PH and 921(16%) had severe PH. Groups 3, 5 and 6 demonstrated that those with a high PVR had an increased risk of death when compared to those with a preserved PVR. Suggesting that in IPF patients increased PVR appears to predict poorer survival regardless of the mPAP (23).

This reinforces the study by Awerbach et al, who showed in ILD related PH,  $PVR > 7WU$  was associated with 3-fold higher mortality than  $PVR < 7$ . Awerbach et al also demonstrated that ILD related PH patients at right heart catheterization (RHC), had lower mean pulmonary arterial pressures (mPAP) and pulmonary vascular resistance (PVR) when compared to their idiopathic PAH cohort, despite these findings, mortality was high in both groups (24).

Another area of interest is that of pulmonary artery compliance and its changes during exercise. Panagiotidou et al presented that of 16 patients with either IPF or ILD related to connective tissue disease. Pulmonary arterial compliance at rest and exercise correlated well with diffusion capacity of carbon monoxide (DLCO), 6-minute walking distance (6MWD), and New York Heart Association functional class (NYHA FC). The decrease in pulmonary arterial compliance may represent a valuable factor in the symptoms and prognosis of ILD-PH and further exploration of this is warranted (25).

An important non-invasive measure which has previously been reported by Bax et al is that of right ventricular: left ventricular diameter of  $>1$  at CTPA. It is a significantly prognostic indicator of mortality at a multivariate level and appears to be superior to haemodynamic data in this cohort of patients (26).

#### Treatment strategies

The INSTAGE trial disappointingly showed no additional benefit of nintedanib plus sildenafil compared with nintedanib plus placebo in patients with IPF and a DLCO of  $<35\%$ . Its primary endpoint was of a change in score from baseline in the St. George's respiratory questionnaire (SGRQ) over a 24-week period. It did however show a numerically lower decline in forced vital capacity in the nintedanib plus sildenafil group (27).

A further sub-analysis of this cohort compared those IPF patients with evidence of right heart dysfunction (RHD) to those without RHD as demonstrated by echocardiography. The investigators found that the IPF group with RHD on nintedanib and sildenafil showed stabilization of their BNP levels ( $p < 0.01$ ) when compared to the IPF group with no RHD - 119.9 ng/L (95% CI: -171.3, -68.5) and 3.6 ng/L (95% CI: -47.2, 40.0) respectively (28).

Further to this at the ERS Congress, the INSTAGE researchers presented data pertaining to biomarkers relevant to the pathophysiology of IPF. Namely biomarkers of inflammation, lung cell damage and extracellular matrix damage. Of the 273 patients treated with nintedanib plus sildenafil there was an association with statistically significant reductions in collagen 6 degraded by MMP-2/9 (C6M) and citrullinated vimentin degraded by MMP-2/8 (VICM) vs nintedanib alone (29).

During the same session, Chandran et al presented their study findings of the effect of nintedanib on the pulmonary vasculature in a murine model. By utilizing Fra2 overexpressing mice (a propensity to develop spontaneous ILD and pH) and wild type mice. They were able to ascertain the effects of nintedanib on the pulmonary vasculature by employing wire myography. Nintedanib was shown to induce significant pulmonary artery relaxation, which was endothelium independent, and more pronounced in the Fra2 mice (30). This noteworthy finding certainly warrants further investigation.

According to the preliminary data of the recently completed INCREASE trial of inhaled treprostinil in 326 Group 3 PH patients has met its primary endpoint of an improvement in 6MWD and all its secondary endpoints, thus substantiating the careful use of pulmonary vasodilators in appropriate patients with ILD related PH under the care of expert PVD centres.

Nathan et al have provided an useful algorithm (Figure 5) to aid the pulmonologist when deciding which CLD patient should be further assessed at an expert pulmonary vascular disease centre for consideration of PAH therapy on an individualized basis (31).

## **Pulmonary arterial hypertension**

### **Risk stratification**

Risk assessment and prognostication in PAH has been a hot topic in recent years, with many new studies were presented at ERS 2019. The updated REVEAL 2.0 Risk Score was published in 2019, which includes revised cut-points for some variables (e.g. pulmonary vascular resistance  $< 5$  instead of  $> 32$  Wood units) from the original REVEAL score and now includes the presence of all-cause hospitalization within the previous 6 months (32). An external validation of the REVEAL 2.0 was presented using a retrospective cohort of 1011 patients from the Australian and New Zealand PH Registry (PHSANZ) for which at least 7 variables were available (33). Although lacking information for renal function and NT-proBNP or BNP, REVEAL 2.0 discriminated short term (12-month) and long-term (60-month) survival in the PHSANZ cohort. There was overlap in survival estimates according to the 8-tier risk strata but excellent discrimination (C-statistic 0.74, 95% CI 0.72-0.78) using 3-tier risk strata (low, intermediate, high).

The EFORT study (NCT01185730) which was a prospective, modern cohort of treatment naïve patients with idiopathic, heritable or drug-induced PAH. The aim of EFORT was to determine transplant-free survival, prognostic factors, and treatment goal cut-offs using a dynamic survival-prediction model. For 146 patients enrolled between 2012-2013, the 1-, 3-, and 5-year rates for transplant-free survival were 97%, 83%, and 71%, respectively. Increasing age was the only baseline variable independently associated with death or transplantation. Using Cox models with time-dependent variables, optimal treatment goal thresholds identified in this study were: NYHA FC 1 or 2 (HR 0.19, 95%CI 0.089-0.42), 6MWD  $> 400$ m (HR 0.16, 95% CI 0.089-0.42), Cardiac index (CI) goal of  $\geq 2.4$  L/min/m<sup>2</sup> (0.16, 95%CI 0.052-0.48), and either BNP  $\leq 150$  or NT-proBNP  $\leq 700$  ng/L (HR 0.035, 95%CI 0.010-0.12). Achievement of at least 2 of these goals decreases the instantaneous risk of death or lung transplant whereas achievement of 0 or 1 of these goals was associated with higher instantaneous risk (34).

There has been limited study on risk stratification in congenital heart disease-associated PAH (CHD-PAH). Ramjug et al analyzed survival in CHD-PAH patients according to the

number of low-risk factors present: NYHA/WHO functional class I/II, ISWT > 420 metres, presence of a post-tricuspid defect, and a diffusion capacity for carbon monoxide > 60%. The vast majority of patients had 0 or 1 low-risk feature. In the overall CHD-PAH population (n=240), survival was lowest for patients without any low-risk factors, slightly better for those with 1 low-risk factors and similar long-term survival in those with 2-4 risk low-risk factors (35).

#### Non-invasive parameters in PAH

Swift et al presented a prospective study that evaluated the reproducibility and sensitivity to change of non-invasive endpoints in PAH. They compared changes in biomarkers, 6MWD and the incremental shuttle walk test (ISWT) on repeat tests within 48 hours and at 4-6 months between healthy volunteers and PAH patients. Intraclass correlation (ICC) was excellent (>0.74) for the 6MWD and ISWT as well as for NT-pro-BNP and almost all MRI-derived volumes and flow measures. For sensitivity to change, the MRI-derived right ventricular ejection fraction (RVEF) had the largest Cohen's D change whereas 6MWT and NT-pro-BNP had only fair change, indicating less sensitivity to change. RVEF on MRI may be the most suitable non-invasive end-point for PAH due to its excellent repeatability and large change in PAH patients undergoing treatment initiation or escalation (36).

#### Use of intravenous prostanoid

In a retrospective study of 126 PAH patients not at treatment goal with oral therapies, Olsson et al evaluated the effect of add-on IV treprostinil on transplant-free survival and risk strata (37). Their risk assessment was based on 6 variables which were given an integer risk score (1, 2, or 3) if the variable was in the low, intermediate, or high-risk range. The majority (79%) were intermediate risk at baseline and 78% were on double combination therapy. The median treprostinil dose achieved at follow-up was 35 ng/kg/min. Long-term transplant-free survival was markedly better for the minority of patients (19%) who achieved a low-risk status by 6-12 months. However, lack of response within 6-12 months was associated with an approximately 50% risk of death or transplant in the subsequent 2 years. Haemodynamics did not differ between responders and non-responders. In a multivariable analysis, only 6MWD and DLCO predicted a good treatment response. This study suggests that add-on IV treprostinil can 'rescue' about 20% of PAH patients but the majority do not

obtain treatment targets within 6-12 months and these patients should be considered for lung transplantation, if eligible.

### Biomarkers in PAH

Endostatin is an angiogenic peptide derived from Collagen XVIII alpha 1 (*Col18a1*), an extracellular matrix protein. In recent reports it is correlated with invasive haemodynamics and is shown to be elevated in PAH as compared to healthy individuals (38). Furthermore, a genetic variant in *Col18a1* has been associated with differences in serum endostatin levels and outcomes in PAH (39).

At the ERS Congress, Simpson C et al hypothesized that endostatin is a mechanistic biomarker of disease severity and survival in PAH (40). They performed whole genome genotyping and ELISA measurements on 2017 patients with PAH. The investigators found that a higher level of circulating endostatin correlated with higher invasive haemodynamics and lower 6MWD. Additionally, high endostatin levels were independently associated with a poorer prognosis. Based on the sequencing data the team were also able to demonstrate that serum endostatin levels are influenced by genetic variants in *Col18a1* which are consequently associated with phenotypes and outcomes. Hence suggesting that endostatin may serve as a biomarker of disease severity in PAH.

Another promising biomarker is asymmetric dimethylarginine (ADMA) which has been shown to be of relevance in different forms of PH (41–45). Skoro-Sajer et al (Vienna) aimed to validate ADMA as a biomarker to monitor disease progression in PAH and CTEPH patients on targeted PAH therapy or undergoing balloon pulmonary angioplasty (46). ADMA levels were measured in 47 patients (34 PAH, 13 CTEPH). The patients were stratified into risk groups (low, intermediate, high) according to ERS/ESC 2015 Guidelines (47). ADMA did not change significantly between the therapy groups, however at follow-up in those patients who improved it correlates with follow-up BNP and risk assessment scores ( $r^2 = 0.328$ ).

Blood count with its broad availability is receiving more attention in the field of biomarker research. Red cell distribution width for example has been shown to be prognostic for PAH (48). The mechanisms, which determine the levels of these markers, are unclear, however a

study presented at the Congress highlighted the importance of cell free haemoglobin as a source of oxidative stress (49).

In vitro data on human pulmonary endothelial cells treated with methaemoglobin (metHb) showed that reactive oxygen species (ROS) production and IL-6 secretion is increased. This finding implies a strong relationship between metHb-induced oxidated damage and further amplification of endothelial dysfunction through overproduction of cellular ROS.

The prostacyclin pathway is implicated in PAH, it includes prostacyclin, which is associated with vasodilation, and thromboxane, which promotes vasoconstriction. Thromboxane is mainly excreted by platelets, therefore Oliveira et al retrospectively analysed 243 patients with PAH at baseline with RHC haemodynamics, platelet count and mean platelet volume (MPV). When comparing a subset of this cohort to 79 healthy volunteers they found that PAH individuals had a lower platelet count. Subsequently platelet count was correlated with an improved survival in the PAH cohort (50). Conversely the same Brazilian group demonstrated that in 88 CTEPH patients, they had similar platelet count as controls but they showed lower platelet volume. Platelet count or volume was not different between patients who underwent pulmonary endarterectomy and those who were treated conservatively (51).

Iron deficiency is common in those with PH and conveys a worse prognosis (52–54). At the Congress, Campean et al revealed that there was a high prevalence of iron deficiency in 109 CTEPH patients (74%). Defined by ferritin  $<100\mu\text{g/L}$  or ferritin between  $100\text{--}299\mu\text{g/L}$ , transferrin saturation  $<20\%$  and raised levels of soluble transferrin receptor ( $>4.5\text{nmol/L}$  for females, and  $>5.0\text{nmol/L}$  for males). This correlated with lower exercise capacity but not with haemodynamics or survival (55).

### Non-coding RNA

Non-coding RNA molecules have gained attention over the last decade as mediators of PH pathogenesis. It has been postulated that they even may become effective targets for future PH therapies (56,57). The non-coding transcriptome can be classified into small non-coding

RNAs (sncRNAs, < 200 nt), including the microRNAs (miRNAs), and long non-coding RNAs (lncRNAs, > 200 nt).

Little is known about their role in right ventricular failure. Utilising a rodent model with monocrotaline treatment to induce pulmonary hypertension, Connolly et al, (58) studied miR-1, which has been shown to be down-regulated in hypertrophying rodent hearts. They were able to clearly demonstrate that TGF- $\beta$ 1 (ALK5) is targeted by miR-1 and miR-1 reduced TGF- $\beta$  activation and its downstream SMAD2/3, proposing that it may regulate cardiac hypertrophy.

A study presented by Omura et al (59) utilising RV biopsies from donors with compensated RV hypertrophy (CRVH, cardiac index >2.2) and decompensated RV hypertrophy (DRVH, PAH patients who died of PAH) compared to controls, showed that H19 and miR-675 was up-regulated in DRVH. This was also displayed in a monocrotaline rat model. The team also found that the up-regulation of H19/miR-675 was specific to the right ventricle in both rats and humans as no change was seen in either the left ventricle or lungs of DRVH subjects. They also found in 70 patients with PAH that H19 was up-regulated in plasma and correlated with haemodynamics and prognosis.

Plasma also contains microparticles (MPs), which are phospholipid rich, submicron particles are released from the membranes of endothelial cells, platelets, leucocytes and erythrocyte. MicroRNAs were isolated from microparticles by Oto et al (60), in control subjects, PAH, operable CTEPH and non-operable CTEPH. MicroRNAs differential expression in MPs and plasma differed between the 4 groups. It was noted that miR-133a-3p was found to be dysregulated in both MPs and plasma signifying it may play an important role in PH.

### **Looking to the future**

In the current pandemic of coronavirus-19 much attention has been given to the topic of the prevention and management of venous thromboembolism in patients infected with the virus. We are all soon to see if there are any sequelae related to this and we will be sure to hear more on topic at the Virtual ERS Congress, 2020.



It is hoped that the new ERS/ESC guidance related to the definitions, diagnosis and management of PH will be realised in 2021. In the meantime, the update articles from the 6<sup>th</sup> PH World Symposium in Nice, France, has provided us with helpful suggestions. As an Assembly, we aspire in the near future with the advent of PHAROS to be better placed to phenotype our PH patients in order to offer them more personalized and holistic care.

Ultimately as a community we have all found innovative ways to connect with one another across Europe and the World. Barriers to progressing with research both at the bedside and bench side appeared to have reduced in an attempt to work together as a respiratory community with a common goal. May this ethos continue.

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**Figures titles:**

**Figure 1:** Diagnostic algorithm for patients with suspected pulmonary embolism without haemodynamic instability

**Figure 2:** Risk adjusted management strategy for acute pulmonary embolism

**Figure 3:** Diagnostic work-up and management of suspected pulmonary embolism during pregnancy and up to 6 weeks post-partum

**Figure 4:** Follow-up strategy and diagnostic work up for long-term sequelae of pulmonary embolism

**Figure 5:** Evaluation of pulmonary hypertension in chronic lung disease









