The 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: a practical chronicle of progress

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For the busy clinician, what is new in the 2015 ESC/ERS guidelines on pulmonary hypertension?
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The first World Health Organization (WHO) Symposium on Pulmonary Hypertension was held in 1973 in response to the sudden increase in the number of patients with primary pulmonary hypertension (PPH) [1]. This epidemic was related to the intake of appetite-suppressing drugs and only 17 clinicians and scientists convened at the landmark first WHO meeting. Back then, PPH was a mysterious condition without any known therapy. Two decades later, in 1993, the first consensus guideline on PPH endorsed by a specialist society was published [2]. The chairman of the 1993 consensus document, Lewis Rubin (University of California, San Diego, CA, USA), recognised the limited knowledge and science in the field at the time, and remarked some years later that "our task was relatively easy…since the published literature was fairly limited. Accordingly, our guidelines were largely driven by expert opinion" [3]. Since then, we have witnessed dramatic leaps in our knowledge of both the basic and clinical science of pulmonary hypertension. Intravenous epoprostenol, the first of many targeted pulmonary arterial hypertension (PAH) therapies that are currently available, gained US Food and Drug Administration approval in 1995. The turn of the 21st century saw the emergence of efficacious oral therapies that have altered the care of patients with PAH.

Numerous guidelines on pulmonary hypertension have since been developed by specialist societies across both the European and American continents as the science of pulmonary hypertension has evolved [3–8]. With time, the rigour and methodology of guideline development in clinical medicine have also improved. Practice guidelines are intended to provide clinicians with recommendations based on systematic review of the available evidence, and an assessment of the benefits and harms of care options, with the intention of optimising patient outcomes [9]. Expert opinion remains a major part of all practice guidelines, particularly when high-quality evidence is lacking. The last European Society of Cardiology (ESC)/European Respiratory Society (ERS) Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension were published back in 2009 [5, 6]. Pulmonary hypertension is a rapidly moving field and many new developments have since occurred in a relatively short space of time. Thus, the new 2015

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ESC/ERS guidelines [10] have been eagerly anticipated and will be welcomed by all professionals involved in the care of the pulmonary hypertension patient. In recognition that pulmonary hypertension can complicate a diverse range of medical conditions and is not the exclusive domain of any medical specialty, the 2015 ESC/ERS guidelines have been developed by an interdisciplinary panel of experts.

For the busy clinician, what is new in the 2015 ESC/ERS guidelines? The definitions and classification of pulmonary hypertension are now aligned with the recent recommendations of the fifth World Symposium on Pulmonary Hypertension [11, 12]. Haemodynamic criteria for the diagnosis of pulmonary hypertension are unaltered from previous guidelines, with the exception that a pulmonary vascular resistance >3 Wood units is now required to diagnose PAH. There remains no consensus definition for exercise pulmonary hypertension due to insufficient data, despite the growing interest and research in the role of exercise testing for the early detection of pulmonary vascular disease [13]. The clinical classification of pulmonary hypertension has been adapted from the fifth World Symposium but an expanded subclassfication for group 1′ pulmonary veno-occlusive disease (PVOD) is now proposed. Recently, biallelic mutations in the *EIF2AK4* gene were discovered to be the major genetic cause of PVOD [14] and it is increasingly acknowledged that PVOD can complicate systemic sclerosis or be induced by toxins such as chemotherapy agents [15–17]. Accordingly, a subclassification for PVOD is suggested to reflect our new knowledge of these distinct aetiologies.

The diagnostic algorithm for pulmonary hypertension has undergone some cosmetic changes but the general principles remain similar. A greater emphasis has been devoted to genetic testing in the 2015 ESC/ERS guidelines. Both PAH and PVOD have strong genetic predispositions, and patients with sporadic or heritable disease should be advised regarding the availability of genetic testing and counselling, given the possibility that many will carry a disease-causing mutation. Specific recommendations are also provided on the approach on how to test for the different genes implicated in PAH and PVOD.

One aspect of the 2015 ESC/ERS guidelines that might be of immense interest for clinicians is the new treatment algorithm for PAH. The expansion of the therapeutic armamentarium in PAH and recent trials focussing on combination therapy have meant that treatment strategies are now much more complex [18–21]. Many different combinations of PAH drugs from different classes are now possible to target the three main pathomechanistic pathways implicated in disease development (prostacyclin, endothelin-1 and nitric oxide pathways) [22]. In addition, combination therapy can be given with an upfront approach or sequentially if treatment targets are not met.

The new treatment algorithm suggests that when considering initial or *de novo* therapy in PAH, patients should first undergo risk stratification into either the low/intermediate- or high-risk group. Although the low/intermediate- and high-risk groups correspond broadly to those in WHO functional class II–III and IV, respectively, it is acknowledged that some patients in WHO functional class III will be classified as high-risk when other prognostic parameters such as 6-min walk distance, brain natriuretic peptides, right ventricular function and haemodynamics are considered. For those stratified as high-risk, upfront combination therapy is advocated and should include *i.v.* epoprostenol, given the fact that *i.v.* epoprostenol remains the only drug to have demonstrated a survival benefit over 3 months in PAH. A recent open-label study [23] demonstrated that upfront triple combination therapy in very severe PAH was associated with impressive haemodynamic and functional responses that were sustained at long-term follow-up, providing proof of the concept of a more aggressive treatment approach in this population.

Perhaps the biggest change comes with the recommendation that low/intermediate-risk patients should also be offered upfront combination therapy. This recommendation comes from the recently published AMBITION study [24], demonstrating that upfront combination with ambrisentan and tadalafil was associated with a 50% reduction in the primary composite morbidity/mortality end-point, as compared with ambrisentan or tadalafil alone. Despite the compelling results of the AMBITION study, the new treatment algorithm has adopted a sensible approach and has recommended that initial monotherapy remains an equally acceptable alternative for low/intermediate-risk patients. At an individual-patient level, clinical experience indicates that there are many patients who achieve treatment targets on monotherapy and do well over the long term. Furthermore, what remains unknown is whether upfront combination therapy is superior to an optimised sequential combination therapy strategy. In other words, upfront combination therapy has never been properly tested against an aggressive sequential strategy where additional therapy is added if treatment targets are not met at early review following initiation of monotherapy.

In terms of sequential combination therapy, the broad principles recommended by the new guidelines are preserved from the previous guidelines. The aim is to set high treatment goals that will place patients into a low-risk category, essentially translating to good exercise capacity, the absence of clinical right heart failure and good right ventricular function. If treatment goals are not met, additional therapy should be

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introduced at early follow-up. However, with the many PAH drugs that are now available, are there any drug combinations that are considered ideal?

There remain no head-to-head randomised controlled trials (RCTs) that have evaluated the outcomes of different combination therapies in PAH. Furthermore, such trials are unlikely to be performed in the near future. However, sequential combination therapy trials have not yielded consistently positive results and the current guidelines have attempted to stratify the level of evidence according to the results obtained from these studies. Specific combinations of PAH drugs that have yielded positive primary end-points from RCTs have been given a higher level of recommendation accordingly.

Since the last guidelines, there have also been significant advances in pharmacological and interventional approaches to the management of chronic thromboembolic pulmonary hypertension (CTEPH). Pulmonary endarterectomy remains the treatment of choice for those with operable disease. For those with inoperable CTEPH or persistent/recurrent CTEPH following surgery, targeted therapy with the soluble guanylate stimulator riociguat is recommended, which has been demonstrated to improve haemodynamics and functional capacity [25]. Balloon pulmonary angioplasty is gaining momentum worldwide and experienced centres are now offering this percutaneous intervention alone or in combination with targeted therapy for inoperable disease. An updated treatment algorithm for CTEPH is proposed in the new guidelines that incorporates these new treatment options for inoperable disease.

Despite their wide promulgation, the effect of guidelines on changing physician behaviour can be variable [26]. As evidenced by a recent study on real-life physician adherence to guidelines, only 6% of patients with a diagnosis of PAH underwent all of the recommended tests that should be performed as part of the diagnostic workup [27]. Although guidelines are not intended to provide a "cookbook" that is universally applicable to all patients with complex disorders such as PAH, significant gaps exist between guidelines recommendations and clinical practice. Thus, it is equally important to identify barriers that prevent adoption of guidelines, and guidelines have been shown to be more effective in changing practice patterns when they are accompanied by active implementation strategies such as standing orders, reminder systems, clinical audit and feedback [28].

Finally, pulmonary hypertension is a global health issue but regional differences are present with regards to healthcare resources, healthcare priorities and access to high-cost medications. Thus, international guidelines are not necessarily applicable to all regions of the world. Such disparities are not confined to the developing countries; for example, subsidised combination therapy for PAH is still not available in Australia. In countries where medication access remains limited, the 2015 ESC/ERS guidelines should provide further support for clinicians and stakeholders to lobby for wider medication access that are in line with world's best practice.

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