What do the "new" Pulmonary Hypertension Guidelines tell us: should we change our practice?

The 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) Pulmonary Hypertension (PH) Guidelines have been developed by a Task Force Committee reflecting on the multidisciplinary nature of PH (1). The recommendations of the new guidelines were presented and discussed by Cihangir Kaymaz, MD, National Reviewer of 2015 ESC/ERS PH Guidelines, in a session entitled "Pulmonary Hypertension in Turkey" in the ESC Congress 2015. In this session, the management of a PH case that was presented by Barış Kaya, MD was also discussed within the frame of the new recommendations. This review article summarizes Dr. Kaymaz's talk: "What Do the New Guidelines Tell Us?"

Changes in hemodynamic and clinical definitions: *PH is defined as an increase in the mean pulmonary arterial pressure (≥25 mm Hg) at rest as assessed by the right heart catheterization (RHC). The new nomenclature and parameters for the hemodynamic definition of pre- and post-capillary PH subgroups have been adopted, and pulmonary vascular resistance (PVR) has been included in the hemodynamic definitions of pulmonary arterial hypertension (PAH) and combined pre- and post-capillary PH subgroups of the post-capillary PH. Importantly, the phrase "out of proportion PH" has been abandoned in PH due to both the left heart disease and lung diseases. As a result of new advances in pathology, pathobiology, genetics, epidemiology, and risk factors, updating the clinical classification of PH has been intended to categorize the multiple clinical conditions in five groups according to similar clinical presentation, pathological findings, hemodynamic characteristics, and treatment strategy. Group 4 definition has been updated to include "PH due to other pulmonary artery obstruction than chronic thromboembolic PH," and new diagnostic and treatment algorithms, including criteria for pulmonary endarterectomy, balloon pulmonary angioplasty, and a new approved drug, riociguat, have been recommended. A short chapter on PH due to unclear and/or multifactorial mechanisms has been added. The risk level of drugs and toxins that are known to induce PAH has also been updated.*

Changes in the recommendations for diagnostic algorithms, referral patterns, and confirmative hemodynamic assessment: The model for echocardiographic estimation of PH probability on the basis of pre-defined cut-off limits of Doppler-calculated tricuspid regurgitant peak velocity has been improved by adding seven echocardiographic criteria that are suggestive of PH. The importance of expert centers in the management of patients with PH has been highlighted in both the diagnostic and treatment algorithms, and the definitive criteria for referral patterns and expert centers have been clarified. The recommendations for indications and standarts of RHC and vasoreactivity test (VRT) and agents used in VRT have been updated, and most importantly, it is clearly mentioned that VRT is not recommended either in patients with PAH other than idiopathic, heritable, and drug-associated PAH nor in PH groups 2, 3, 4 and 5 (Class III). The updated correctability criteria for PAH associated with systemic-to-pulmonary shunts recommend that patients with indexed PVR < 4 (WU.m^2) or absolute PVR < 2.3 WU should be corrected, whereas indexed PVR > 8 (WU.m^2) or PVR > 4.6 WU should be left uncorrected (Class IIaC). It is recommended that patients with measures in between should be individually evaluated in tertiary centers (Class IIaC).

Changes in the risk assessment of PAH and new treatment algorithms: Several prognostic factors derived from clinical studies or registries have been implemented in the risk assessment of PAH (low, intermediate, or high risk) as determinants of prognosis on the basis of the estimated annual mortality, and new treatment goals have been proposed. Undoubtedly, the most important changes have been observed in the new PAH treatment algorithm. The vast majority of the evidence for this "paradigm shift" have been derived from four event-driven randomized clinical trials (RCTs): SERAPHIN, GRIPHON, COMPASS-2, and AMBITION, in which "time to first mortality/morbidity (M/M) event" has been adopted as a novel primary endpoint for long-term treatment benefit (2-5). The first two RCTs have demonstrated significant M/M benefits in both treatment-naive and previously treated PAH patients with two novel drugs, macitentan and selexipag, respectively (2, 3). In the SERAPHIN trial, background PAH treatment with phosphodiesterase-5 inhibitor (PDE5I) and/or oral or inhaled prostanoids were documented in 63.7% of patients, and reduction in M/M with 10 mg macitentan was demonstrated both for patients who had not previously received treatment (55% reduction, p<0.001) and for those receiving therapy for PAH (38% reduction, p=0.009). In the GRIPHON trial, background treatment with endothelin receptor antagonist (ERA) and/or PDE5I were noted in 80% of patients, whereas the remaining patients were treatment naive (3). Selexipag significantly reduced the risk of M/M events by 40%

Address for Correspondence: Dr. Cihangir Kaymaz Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Kartal, İstanbul-*Türkiye* Phone: +90 216 459 44 40 Fax: +90 216 500 15 00 E-mail: cihangirkaymaz2002@yahoo.com
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compared with the placebo irrespective of the background treatment status, and the treatment effect was consistent across age, gender, etiology, and baseline functional class (FC) subgroups (3).

In the COMPASS-2 trial, adding bosentan to sildenafil in PAH patients stable under sildenafil therapy was not superior to sildenafil monotherapy in delaying time to the first M/M event (4). However, there are several critical limitations of the COMPASS-2 trial. "*This study was designed to detect a large treatment effect of >40%, and the number of events was too few to allow the detection of smaller but still potentially meaningful effects."* Secondly, "*the extent of missing information because of patients discontinuing the study prematurely, without experiencing a primary end-point, was sizeable"* (4). Moreover, the worsening of PAH was defined by the patient global self-assessment score as the initial step, with subsequent consideration of 6MWD and the need for additional PAH therapy. The older age and the higher frequency of comorbidities requiring concomitant medications compared with other PAH trials may be considered as confounding factors. The authors said, *"Finally, the trial recruited and followed patients over 7.5 years; the long duration of the trial was mainly because of the slow rate of patient enrolment. During this time, the management and treatment options of patients with PAH considerably changed; such changes may have affected the type of patients enrolled and the retention of patients in the trial"* (4).*"Given the limitations of the study, the overall results of the COMPASS-2 study must be interpreted with caution"* (4).

The recently published AMBITION trial has compared the upfront combination of ambrisentan and tadalafil (AMB and TAD) with monotherapy of either drugs, and upfront combination compared with MT have provided 50% reduction in M/M as a primary endpoint (5). Although upfront combination of AMB and TAD has been superior to MT in this RCT, the upfront combination has not been compared with goal-oriented sequential combination of AMB and TAD. Accordingly, the results of this study should be considered against the initial monotherapies of AMB or TAD but not against goal-oriented sequential combination of AMB and TAD. In the absence of the robust data from head-to-head comparisons among upfront double or triple combinations and goal-oriented sequential combinations of the same targeted PAH drugs, the superiority of upfront treatment to goal-oriented strategy remains to be proven. None of these three RCTs that were positive for M/M primary endpoint has shown a significant reduction in all-cause or PAH-related mortality (2, 3, 5).

Initial monotherapy and upfront combinations: For patients with a negative VRT, a completely new treatment algorithm has been recommended (1). For patients with PAH at low or intermediate risk status, two treatment strategies, either initial monotherapy with approved PAH drugs or oral upfront combination therapy, have been recommended. The vast majority of the approved PAH drugs have been indicated for initial monotherapy. *"Since head-to-head comparisons among different compounds are unavailable, no evidence-based first-line monotherapy can be proposed"* (1). However, the difference between the first generation drugs with treatment benefits limited to 6-min walking distance or some hemodynamic measures and new drugs with proven M/M benefit (macitentan or selexipag) has not been considered in recommended strategies for initial monotherapy (1). The other treatment option in FC II or III status is upfront combination, and upfront combination with AMB and TAD has been recommended as Class IB. However, paradoxically, although AMB or TAD initial monotherapies have been proven to be inferior to upfront combination with AMB and TAD in AMBITION trial, the level of evidence for initial AMB monotherapy was more stronger (Class IA) than those for upfront combination of AMB and TAD (1).

According to the new PH Guidelines, upfront combination with other ERA and other PDE5I should be considered (Class IIaC). However, no study reference has been provided for this recommendation extrapolated from upfront AMB and TAD combination. Moreover, upfront combination with bosentan and i.v. epoprostenol or triple upfront combination with bosentan, sildenafil, and i.v. epoprostenol have been recommended to be considered in patients at FC III or IV status (Class IIaC). However, among one of the two reference studies, the BREATHE-2 trial revealed no significant benefit with upfront combination of bosentan and epoprostenol as compared with epoprostenol monotherapy in patients with PAH (6). In other study, upfront epoprostenol and bosentan combination was compared by the historical control group of epoprostenol monotherapy. Despite a significantly higher reduction in pulmonary vascular resistance with upfront double combination, overall or transplant-free survival revealed no significant benefit in this retrospective study (7). The recommendation for upfront triple combination therapy has been based on a pilot study comparing the 3-year survival estimates of 19 patients treated by upfront triple combination with expected survival calculated from the French equation (8).

Changes in goal-oriented sequential treatment: The sequential treatment algorithm has also recommended some critical changes resulting in important controversies in the current PAH practice. Macitentan with sildenafil, riociguat with bosentan, selexipag with ERA and/or PDE5I in FC II and III, and sildenafil added to i.v. epoprostenol in FC III have been recommended as Class IB. All these sequential combinations should also be considered in FC IV status (Class IIaB or C). For inhaled iloprost with bosentan recommendation was class IIbB, and two references were given (9, 10). However, the first RCT was terminated after futility analysis, and adding iloprost to bosentan significantly improved pulmonary hemodynamic measures and delayed time to clinical worsening in second RCT (9, 10).

Bosentan with sildenafil or sildenafil with bosentan was less strongly recommended as "may be considered" (Class IIbC). This recommendation is based on the negative results of the COMPASS-2 trial having several limitations (4). However, there has been no negative data concerning the latter combination of sildenafil with bosentan in any trial (4, 11, 12). Furthermore, in

patients at FC II or III status, the class of recommendations and the level of evidence for bosentan and sildenafil combination were paradoxically different for upfront and sequential combinations (1). This combination is recommended as "should be considered" for upfront combination (Class IIaC) but "may be considered" for sequential combination (Class IIbC). The steps of sequential strategy remain to be clarified as well because the class of recommendation for triple sequential combinations other than selexipag with ERA and/or PDE5I has been Class IIbC. The combination of riociguat and any PDE5I is not recommended. Interestingly, the selected wordings defining the M/M end-points for Class I recommendations in initial monotherapy or upfront and sequential combination therapies have shown a lack of uniformity. It is also worthwhile to mention that new guidelines provide no specific recommendation for switching strategies from the first generation drugs to new treatments with M/M evidence.

In conclusion, the 2015 ESC/ERS PH Guidelines have recommended new hemodynamic criteria, an updated clinical classification, new diagnostic and therapeutic algorithms, and referral patterns to expert centers. Drugs with M/M benefit as primary endpoints in RCTs have been highlighted, and this should be considered as an "epistemological break" from previous algorithms leading the apparent "paradigm shift." New guidelines have recommended or allowed monotreatment or oral upfront combinations having evidence for M/M benefit in patients at FC II-III and upfront combinations, including the parenteral prostacyclins, in patients at FC III-IV. Moreover, sequential combination strategies appear to change current practice in PAH treatment. However, some important controversies still exist, and the majority of the critical recommendations have been supported by level C evidence *"based on consensus of the opinions of experts and/or small studies, retrospective studies or registries."* Accordingly, these limitations should be kept in mind while interpreting the recommendations of new Guidelines.

Cihangir Kaymaz, Lale Tokgözoğlu[1]
National Reviewer of 2015 ESC/ERS PH Guidelines, İstanbul-*Turkey*
[1]President of Turkish Society of Cardiology, İstanbul-*Turkey*

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