Updated definition of exercise pulmonary hypertension

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A mean pulmonary arterial pressure/cardiac output slope >3 Wood units assessed by right heart catheterisation defines exercise pulmonary hypertension https://bit.ly/3P7MfNX

Cite this article as: Zeder K, Olschewski H, Kovacs G. Updated definition of exercise pulmonary hypertension. *Breathe* 2022; 18: 220232 [DOI: 10.1183/20734735.0232-2022].

Received: 5 Oct 2022
Accepted: 2 Dec 2022

Abstract

In the recently published European Society of Cardiology/European Respiratory Society guidelines on the diagnosis and treatment of pulmonary hypertension (PH) the haemodynamic definitions of PH were updated and a new definition for exercise PH was introduced. Accordingly, exercise PH is characterised by a mean pulmonary arterial pressure/cardiac output (CO) slope >3 Wood units (WU) from rest to exercise. This threshold is supported by several studies demonstrating prognostic and diagnostic relevance of exercise haemodynamics in various patient cohorts. From a differential diagnostic point of view, an elevated pulmonary arterial wedge pressure/CO slope >2 WU may be suitable to identify post-capillary causes of exercise PH. Right heart catheterisation remains the gold standard to assess pulmonary haemodynamics both at rest and exercise. In this review, we discuss the evidence that led to the reintroduction of exercise PH in the PH definitions.

History of exercise pulmonary hypertension and its definition

There has been great interest in pulmonary haemodynamics during exercise ever since the introduction of right heart catheterisation (RHC) into clinical practice in the 1940s [1], and it was discussed in detail at the World Health Organization (WHO) meeting on cor pulmonale in 1960 [2] as well as later at the first WHO meeting on primary pulmonary hypertension in 1973 [3]. At this meeting, based on the available data and expert opinion, it was postulated that "mean pulmonary arterial pressure (mPAP) does not normally exceed 30 mmHg during exercise" [3]. This assumption led to the introduction of "exercise pulmonary hypertension" (exercise PH), defined as mPAP >30 mmHg on effort in the European Society of Cardiology (ESC) guidelines on pulmonary hypertension in 2004 [4]. A few years later, however, it was recognised that exercise haemodynamics are strongly dependent on the level of exercise and age and that even healthy subjects frequently exceeded this threshold at high exercise levels [1, 5]. As a consequence, the term exercise PH was abandoned from the following ESC/European Respiratory Society (ERS) PH guidelines [6, 7]. Based on recent evidence, however, the most recent ESC/ERS PH guidelines, published in August 2022, re-introduced exercise PH as part of the haemodynamic definitions of PH [8].

New definition of exercise pulmonary hypertension

According to the current ESC/ERS PH guidelines, exercise PH is defined as an mPAP/cardiac output (CO) slope >3 mmHg·min·L^{-1} during the transition from rest to end-exercise [8]. At the introduction of this haemodynamic threshold, both the upper limit of normal values and the prognostic relevance of pulmonary haemodynamics during exercise were taken into consideration.

Pulmonary haemodynamics during exercise in healthy subjects

The ranges of normal pulmonary haemodynamics during exercise were investigated by two recent comprehensive systematic literature searches and meta-analyses [1, 9]. In the first analysis, the haemodynamic data of 1187 healthy individuals from 47 studies were collected and stratified by sex, age, geographic origin, body position and exercise level [1]. The study confirmed that mPAP during exercise depended on age and the level of exercise. At mild exercise levels, subjects aged ⩾50 years presented with

significantly higher mPAP values as compared with subjects aged <50 years (29±8 *versus* 19±5 mmHg, p<0.001), and subjects aged ⩾50 years very frequently attained mPAP >30 mmHg at maximum exercise levels. Even 20% of the young subjects attained mPAP values >30 mmHg at maximum exercise, although this was associated with very high CO. These findings showed that it is not possible to define an upper limit of exercise mPAP without relating it to CO [1].

In a second systematic review and meta-analysis, we and others, analysed the most recently published systematic literature on physiological exercise haemodynamics and searched for variables that may indicate an abnormal haemodynamic response to exercise and a poor prognosis [9]. Due to the flow-dependent increase of pulmonary pressures, special attention was paid to pressure–flow slopes. According to the meta-analysis of 250 subjects from 11 studies, the mPAP/CO slope was positive in every single case and showed a significant increase with age. Mean values were 0.8±0.4 Wood units (WU) (upper limit of normal (ULN) 1.6 WU) in subjects around 30 years of age, 1.6±0.2 WU (ULN 2.1 WU) in subjects around 50 years of age and 2.4±0.5 WU (ULN 3.3 WU) in subjects around 70 years of age. This means that an mPAP/CO slope >3 WU can be considered as pathologic in most healthy subjects, even among the elderly. Similarly, the pulmonary arterial wedge pressure (PAWP)/CO slope ranged from 0.3±0.2 WU (ULN 0.6 WU) in subjects around 30 years of age to 1.4±0.2 WU (ULN 1.8 WU) in 70-year-old subjects (figure 1).

Prognostic relevance of pulmonary haemodynamics during exercise

Based on studies investigating the prognostic relevance of pulmonary haemodynamics during exercise, the mPAP/CO slope and peak cardiac index proved to be the most robust and statistically independent prognostic markers in different medical conditions. In the largest available study, Ho *et al.* [10] included 714 subjects and analysed the association between exercise PH (defined as mPAP at rest ⩽20 mmHg but mPAP/CO slope >3 mmHg·min·L^{-1} at exercise) and a combined end-point defined as all-cause mortality or cardiovascular hospitalisation. The presence of exercise PH was associated with a two-fold increased risk of an event after adjustment for potential clinical confounders including age, sex, hypertension, prior heart failure, COPD, interstitial lung disease, and smoking status. The results remained significant even after further adjustment for the presence of resting PH (defined as resting mPAP >20 mmHg). When comparing their prognosis, patients with resting PH had the poorest overall survival, followed by those with exercise PH and patients without resting or exercise PH who had the best prognosis (figure 2). In this study, in addition to the mPAP/CO slope, both the trans-pulmonary gradient (TPG)/CO and PAWP/CO slopes were independently associated with survival [10].

Another important recent study investigated the prognostic relevance of pulmonary haemodynamic factors during exercise in 110 patients with dyspnoea and suspected heart failure with preserved ejection fraction (HFpEF) but normal PAWP and left ventricular ejection fraction at rest. The authors defined the ULN PAWP/CO slope at 2 WU (1.2±0.4 WU), based on the ULN in a control group. A PAWP/CO slope >2 WU was found in ∼40% of subjects and was associated with poor clinical outcomes, defined as cardiovascular death, hospitalisation due to heart failure, or abnormal resting PAWP in a future RHC [11].

Recently, the prognostic relevance of pulmonary haemodynamics during exercise was also demonstrated in patients with systemic sclerosis. 80 patients with resting mPAP <25 mmHg were investigated with exercise RHC and followed-up for more than 10 years. The authors found that exercise pulmonary resistances (pulmonary vascular resistance (PVR) and total pulmonary resistance (TPR)), as well as the mPAP/CO and TPG/CO slopes, but none of the resting haemodynamic variables, predicted 10-year mortality (figure 3). Of note, the best mPAP/CO slope to classify long-term mortality was 3.5 WU, and none of the participating patients below this cut-off died or developed PH during follow-up [12].

Finally, the added value of pulmonary haemodynamics during exercise was recently investigated by adjusting for resting haemodynamic parameters and the mPAP/CO, PAWP/CO and TPG/CO slopes, as well as peak CO, turned out to be independent predictors of all-cause mortality [13].

Early recognition of cardiopulmonary diseases using pulmonary exercise haemodynamics?

It has been postulated that exercise haemodynamics may help to uncover cardiopulmonary diseases at an early stage. However, large longitudinal studies investigating this question are currently missing. Based on the available data, an increased PAWP/CO slope with a best cut-off >2 WU may be the most important indicator of a post-capillary cause for abnormal cardiopulmonary haemodynamics during exercise. Nearly all patients with overt HFpEF and elevated resting PAWP (PAWP >15 mmHg) had a PAWP/CO slope above this threshold [11]; in subjects with normal resting PAWP, a PAWP/CO slope >2.0 WU was associated with adverse cardiovascular outcomes [11]. In addition, patients with normal resting PAWP and elevated PAWP during exercise presented with increased left atrial volumes [14].

https://doi.org/10.1183/20734735.0232-2022

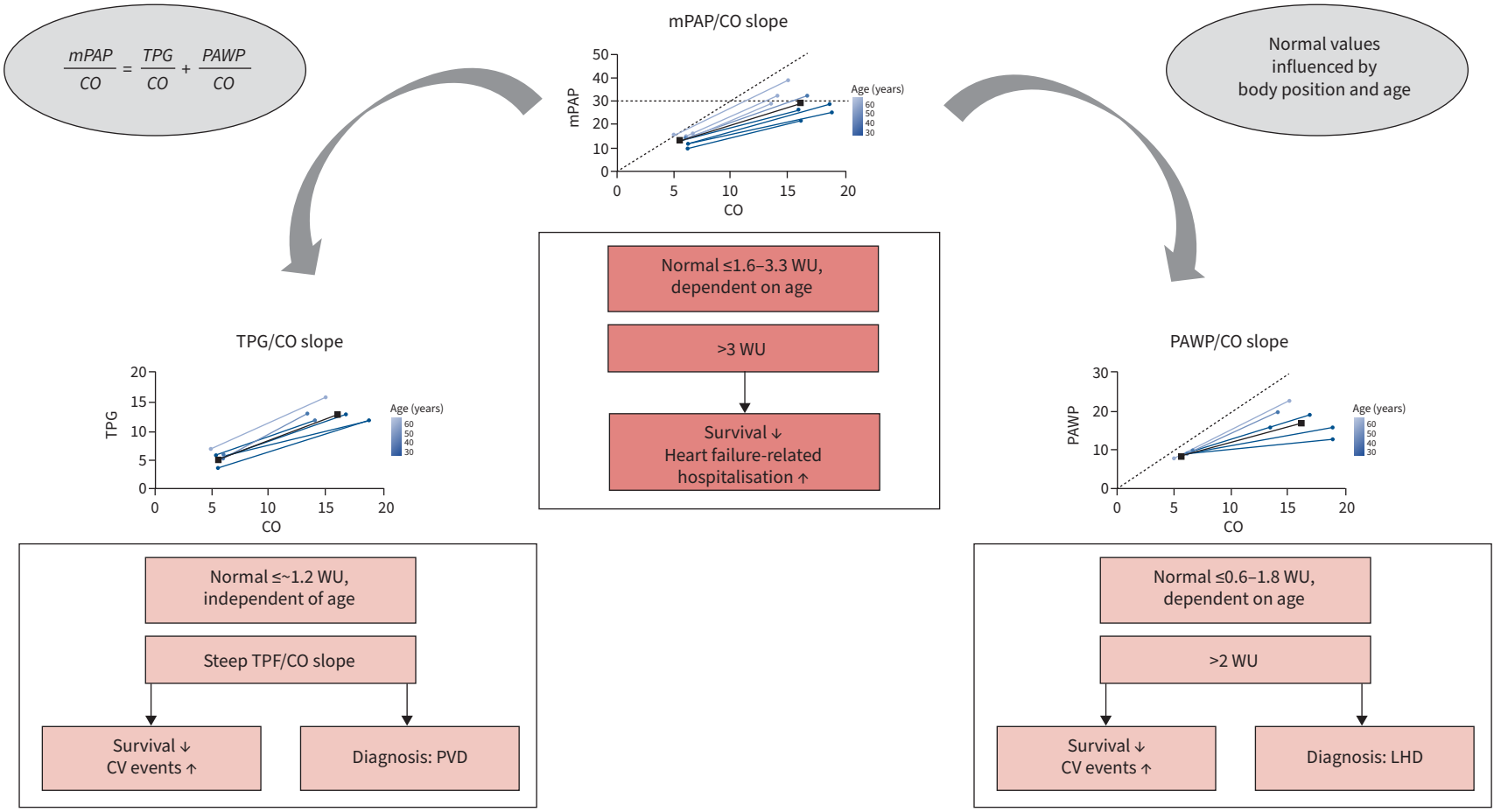

FIGURE 1 Mean pulmonary arterial pressure (mPAP)/cardiac output (CO), pulmonary arterial wedge pressure (PAWP)/CO and trans-pulmonary gradient (TPG)/CO slopes for the characterisation of pulmonary haemodynamic parameters during exercise. Abnormal pulmonary haemodynamic parameters during exercise may be defined by an increased mPAP/CO slope. The mPAP/CO slope is strongly age-dependent and its upper limit of normal (ULN) (mean+2SD) ranges from 1.6 Wood units (WU) (in ~30-year-old healthy subjects) to 3.3 WU (in ~70-year-old healthy subjects) in the supine position (see also table 2 in [9]). The ULN based on the weighted mean and SD of all healthy subjects included in this analysis was 2.7 WU in the supine position. An increased mPAP/CO slope with a cut-off above >3 WU is independently associated with poor survival and heart failure-related hospitalisations. The mPAP/CO slope corresponds to the sum of the TPG/CO slope and the PAWP/CO slope. Like the mPAP/CO slope, the PAWP/CO slope is also strongly age-dependent and its ULN ranges from 0.6 to 1.8 WU. An increased PAWP/CO slope with a cut-off >2 WU is associated with impaired survival and increased cardiovascular (CV) events and may be diagnostic for a post-capillary cause of PAP elevation during exercise. The ULN for the TPG/CO slope is 1.2 WU and is age independent. An increased TPG/CO slope is also associated with impaired survival and may be suggestive of pulmonary vascular disease (PVD). LHD: left heart disease. Reproduced and modified from [9].

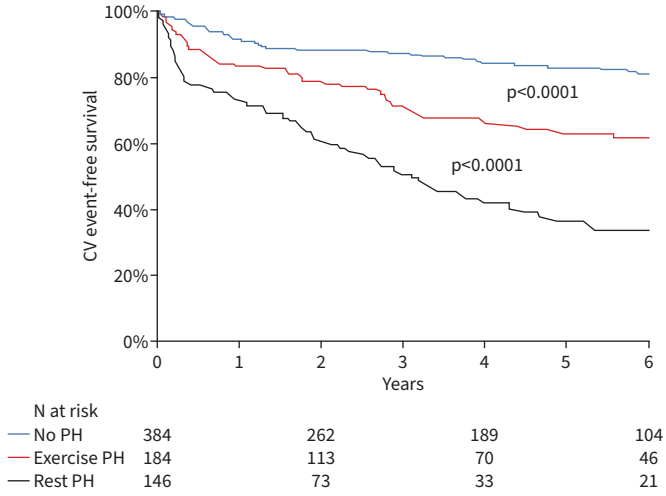

FIGURE 2 Cardiovascular (CV) event-free survival among individuals with dyspnoea by pulmonary hypertension (PH) status. Reproduced from [10] with permission.

Exercise pulmonary haemodynamics may also recognise early pulmonary vascular disease, which is not detected by resting pulmonary haemodynamics. Based on theoretical considerations, elevated PVR, TPG, or the TPG/CO slope during exercise may indicate remodelling with stiffening of the pulmonary vasculature [15, 16], but sufficient evidence for this hypothesis is currently missing.

Methodological details for the correct interpretation of exercise haemodynamics

RHC is currently considered the gold standard for the assessment of pulmonary haemodynamics at rest and during exercise. At least mPAP, CO and PAWP should be measured at each exercise level, and TPR (TPR=mPAP/CO) and PVR (PVR=(mPAP−PAWP)/CO) as well as the mPAP/CO, PAWP/CO and TPG/CO slopes should be calculated [17]. The mPAP/CO slope may be determined either from multipoint mPAP/CO relationships or from two-point measurements, including resting and peak exercise values only [18, 19]. On direct comparison, both methods showed high diagnostic accuracy for exercise PH [20]. However, some methodological details deserve special attention.

Zero reference level

The importance of correctly setting the zero reference level has been extensively discussed [21, 22]. Based on international consensus, in the supine position, the zero reference level should be set at the mid-thoracic level that corresponds to the level of the left atrium in most subjects [22]. In the non-supine position, a standardised zero reference point may be considered as the intersection of the frontal plane at the mid-thoracic level, the transverse plane at the level of the fourth anterior intercostal space and the mid-sagittal plane. When RHC is performed in a different position, it is important to adequately set the zero reference level to the level of the left atrium. When the position is changed, the zero level must be adapted [17].

Respiratory swings

Respiratory pressure swings correspond to the changes in the sum of transmural vascular pressure and intrathoracic pressure during the respiratory cycle. Respiratory swings in healthy subjects at rest are small, so there is little difference between pressure values at inspiration and expiration and averaged values over the respiratory cycle. However, during exercise, particularly in patients with obstructive airway diseases, respiratory pressure swings become significantly larger and the only reliable way to assess the value is to average them over 3–4 respiratory cycles [17]. To achieve results that can be compared between rest and exercise, measurements at rest should be performed in a similar manner to those during exercise.

Measurement of PAWP and CO

As PAWP is needed for the calculation of PVR, as well as for the differentiation of pre- and post-capillary causes of pressure elevation, its correct assessment is essential. However, PAWP measurements are sometimes challenging even at rest and become more so during exercise. An incompletely wedged or an “over-wedged” balloon are the most frequent problems, both leading to an overestimation of PAWP [17].

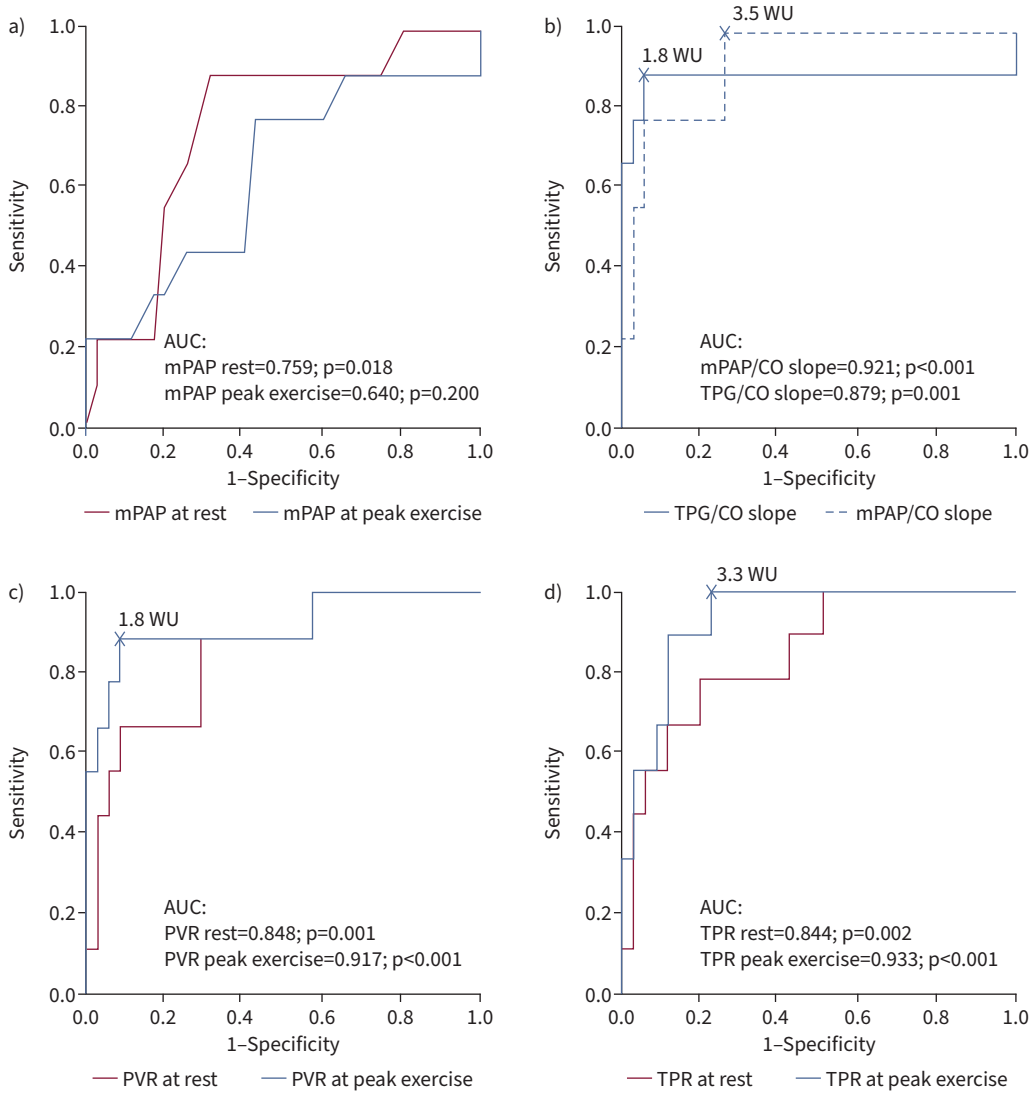

FIGURE 3 Areas under the receiver operating characteristic curve (AUCs) for predicting 10-year mortality (n=44). a) mean pulmonary artery pressure (mPAP); b) mPAP/cardiac output (CO) slope and trans-pulmonary gradient (TPG)/CO slope; c) pulmonary vascular resistance (PVR); and d) total pulmonary resistance (TPR). Resting haemodynamic parameters are presented in blue and exercise haemodynamic parameters are presented in red. WU: Wood unit. Reproduced from [12] with permission.

The gold standard and therefore preferred measurement for measuring CO both at rest and exercise is the direct Fick method, which necessitates the simultaneous measurement of oxygen consumption. Thermodilution represents an acceptable alternative [17]. Other methods like the indirect Fick method, which uses estimated values of oxygen uptake, or the inert gas method, lack reliability (either accuracy or precision) and are not recommended [8].

Body position

Pulmonary haemodynamics are highly influenced by body position. Resting mPAP, PAWP and CO are lower, while heart rate, TPR and PVR are increased in the upright position, as compared to the supine position [17, 23]. In the supine position, TPR and PVR decrease moderately during exercise, while this is more prominent in the upright position [5]. Therefore, for a reliable calculation of the mPAP/CO and PAWP/CO slopes measurements should be performed in the same body position both at rest and exercise. The available data do not suggest significant sex-dependent differences in pulmonary haemodynamics during exercise [17].

Safety

In experienced centres, severe complications during the invasive assessment of pulmonary haemodynamics both at rest and during exercise are rare. However, data from large multicentre trials are missing. Exercise RHC should not be performed without thorough resting work-up and the risk–benefit ratio seems unfavourable in patients with unstable disease or decompensated right heart failure [17].

Conclusion

An mPAP/CO slope >3 WU defines exercise PH according to current guidelines. The evidence for this definition is based on right heart investigations in healthy subjects and the prognostic relevance in patients with chronic diseases. An elevated PAWP/CO slope >2 WU may best identify post-capillary causes of abnormal pulmonary haemodynamics during exercise. RHC remains the gold standard to assess pulmonary haemodynamics both at rest and exercise.

Conflict of interest: K. Zeder reports grants from Fa Janssen and Fa MSD, outside the submitted work. H. Olschewski reports grants from Bayer, Unither Pharmaceuticals, Actelion Pharmaceuticals Ltd., Roche, Boehringer Ingelheim and Pfizer Inc., personal fees from Gilead Sciences Inc., Encysive Pharmaceuticals Ltd. and Nebu-Tec, personal fees and non-financial support from Bayer, Unither Pharmaceuticals, Actelion Pharmaceuticals Ltd., Pfizer Inc., Eli Lilly, Novartis, AstraZeneca, Boehringer Ingelheim, Chiesi, Menarini, MSD and GSK, outside the submitted work. G. Kovacs reports personal fees and non-financial support from Actelion, Janssen, Bayer, GSK, MSD, Boehringer Ingelheim, Novartis, Chiesi, Vitalaire, Ferrer, AOP, outside the submitted work.

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