COMMENTS ON THE GUIDELINES ON BEHALF OF THE INDUSTRY

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THE FIRST COMMENT

AN IMPRESSIVE PIECE OF WORK

- In-depth evaluation of PAH
  - From classification to diagnosis to clinical characteristics to therapy
  - Evaluation of specific PAH subsets
- Diagnosis and therapy of PH
- An impressive collection of references

COMMENTS ON THE FOLLOWING POINTS

- Risk assessment
- Evaluation of clinical trials and therapies
- Disease definition
- Endpoint definition

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RISK ASSESSMENT

THE IMPORTANCE: IT DRIVES TREATMENT INTENSITY

- Very clear table with no ambiguity
- Clear categorization of patients based on multiple parameters

Questions

1. Does the table apply in patients newly diagnoses as well as in patients already receiving PAH specific therapy(ies)?
2. Does the mortality rate apply irrespective of background therapy?
3. Life is not green/yellow/red…what about patients “in between”?

Determinants of prognosis* (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

RISK ASSESSMENT

COMMENTS

- Clarify when & how to utilize the table
  - Newly diagnosed patients
  - Patients on therapy to determine if treatment should be intensify
- Clarify how to evaluate patients with parameters in different columns
- **Suggestion**: patient cases in the online material

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%
Clinical signs of right heart failure	Absent	Absent
Progression of symptoms	No	
Syncope	No	
WHO functional class	I, II	
6MWD	>440 m	
Cardiopulmonary exercise testing		Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9
NT-proBNP plasma levels		BNP 50–300 ng/l NT-proBNP 300–1400 ng/l
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- Disease definition
- Endpoint definition

LEVEL OF EVIDENCE

- Bosentan
  - 3 trials[1,2,3] in PAH
  - Duration: 12 – 24 weeks
  - Primary endpoint: 6 MWD
  - Patients enrolled: 430
- Macitentan
  - 1 trial[4] in PAH
  - Median duration: 115 weeks
  - Primary endpoint: Composite of M/M
  - Patients enrolled: 742

1. R. Channick, Effects of the Dual Endothelin-Receptor Antagonist Bosentan in patients with Pulmonary Hypertension; A randomised controlled trial. The Lancet 2001
2. L. Rubin, Bosentan therapy for Pulmonary Arterial Hypertension. NEJM 2002
3. N. Galiè, Treatment of patients wild mildly symptomatic Pulmonary Arterial Hypertension with Bosentan: a double-blind randomized controlled study . Lancet 2008
4. T. Pulido, Macitentan and morbidity and mortality in Pulmonary Arterial Hypertension. NEJM 2013

LEVEL OF EVIDENCE

- Bosentan **A**
- Macitentan **B**

Table 2 Level of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Bosentan has more evidence than macitentan in randomized clinical trials

Bosentan is a better therapy than macitentan

LEVEL OF EVIDENCE

- **Perception is wrong**

If initial monotherapy is chosen, since head-to-head comparisons among different compounds are not available, no evidence-based first-line monotherapy can be proposed. In this case the choice of the drug may depend on a variety of factors, including the approval status, labelling, route of administration, side-effect profile, potential interaction with background therapies, patient preferences, co-morbidities, physician experience and cost.

EVALUATION OF THERAPIES

AN EXAMPLE

- Macitentan
  - Monotherapy: I B
  - Initial combination therapy: IIa C
  - Sequential combination therapy: I B

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

EVALUATION OF THERAPIES

AN EXAMPLE

- Macitentan
  - Monotherapy: I B
  - Initial combination therapy: IIa C
  - Sequential combination therapy: I B

- **Question**: how clear is it for the end users? Which is the overall evaluation?

FROM THERAPIES TO STRATEGIES

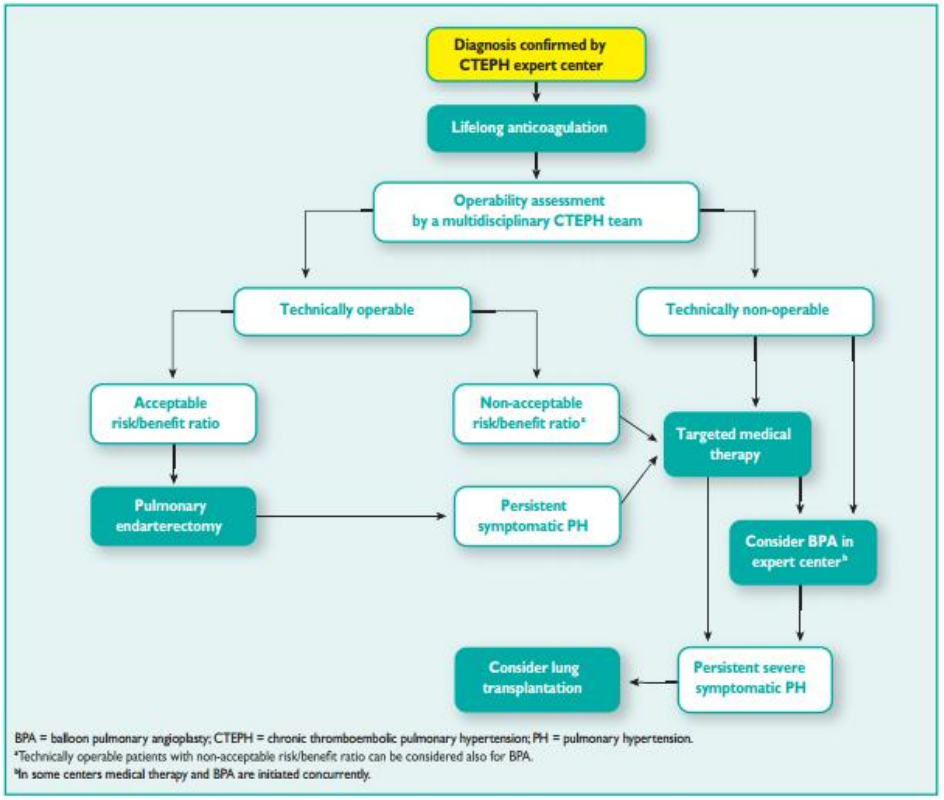
- Initial combination
- Sequential combination
  - Guidelines driven

Can a delay of 3 months make a difference in outcome?

The second therapy is added if the treatment goals are not met and not in case of worsening

TREATMENT ALGORITHM IN GROUP 4

- Which is the definition of *non acceptable risk/benefit*? What about second opinion for PEA?
- Targeted medical therapy and BPA have different level of evidence but look interchangeable
- Do we need the risk assessment table for CTEPH?



COMMENTS ON THE FOLLOWING POINTS

- Risk assessment
- Evaluation of clinical trials and therapies
- **Disease definition**
- Endpoint definition

THE IMPORTANCE OF DISEASE DEFINITION

- Disease definition indicates a clearly defined patient population
  - Important to avoid the treatment of a specific disease with non appropriate treatments
- Disease definition may drive the identification of patient population to be enrolled in randomized clinical trial
- Disease definition should be very solid and based on registries or multicentre experiences

THE IMPORTANCE OF DISEASE DEFINITION

EXAMPLE IN GROUP 2

- PH due to Left Heart Disease
  - With combined pre and post capillary PH (Cpc-PH)
    - Diastolic Pressure Gradient ≥ 7mmHg and/or PVR > 3 WU
- A randomized clinical trial – MELODY[1] – has been performed in this specific patient population
  - The trial results may be informative on the effect of the therapy on that disease but also on the behaviour of this patient population

1. ClinicalTrials.gov Identifier: NCT 02070991

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- **Endpoint definition**

ENDPOINTS

- Recommendations on endpoints for clinical trials are issued by the World Symposium on Pulmonary Hypertension[1]
  - Not addressed in the Guidelines
- 4 outcome event driven trials have been performed…..
  - AMBITION[2], COMPASS-2[3], GRIPHON[4] and SERAPHIN[5]
- ….. all with a different primary endpoint
- The CHMP has *issued Guideline on the clinical investigations of medicinal products for the treatment of PAH*[6] with an additional definition

1. M. Gomberg-Maitland, New trial design and potential therapies for Pulmonary Arterial Hypertension. JACC 2013
2. N. Galiè, Initial use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. NEJM 2015
3. V. Mclaughlin, Bosentan added to Sildenafil therapy in patients with Pulmonary Arterial Hypertension. ERJ 2015
4. O. Sitbon, Selexipag for the treatment of Pulmonary Arterial Hypertension. NEJM 2015
5. T. Pulido, Macitentan and morbidity and mortality in Pulmonary Arterial Hypertension. NEJM 2013
6. EMEA/CHMP/EWP/356954/2008

ENDPOINT DEFINITION

- It would be beneficial to organize a consensus meeting with
  - Experts
  - Regulatory agencies
  - Companies
- Objective
  - To define an endpoint that would be utilized in future studies

CONCLUSIONS

- Guidelines are extremely important because they provide to treating physicians a scientific overview on how to manage PAH from diagnosis to treatment
- Thanks to the classification and disease definition it allows companies to perform clinical trials in an homogeneous population
- The risk assessment provides a guidance on the severity of the disease
  - More clarity could be beneficial
- The assessment of medical therapies is evidence-based, but it does not take into account the nuance of a rare disease

THANK YOU.