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 diagnosed 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)](image-url)
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

<table>
<thead>
<tr>
<th>Determinants of prognosis* (estimated 1-year mortality)</th>
<th>Low risk ≤ 5%</th>
<th>Intermediate risk 5–10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of right heart failure</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>WHO functional class</td>
<td>I, II</td>
<td></td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt;440 m</td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP plasma levels</td>
<td>BNP 50–300 ng/l</td>
<td>NT-proBNP 300–1400 ng/l</td>
</tr>
<tr>
<td>Imaging (echocardiography, CMR imaging)</td>
<td>RA area 18–26 cm²</td>
<td>No or minimal pericardial effusion</td>
</tr>
<tr>
<td>Haemodynamics</td>
<td>RAP 8–14 mmHg</td>
<td>CI 2.0–2.4 l/min/m²</td>
</tr>
</tbody>
</table>
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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
4. T. Pulido, Macitentan and morbidity and mortality in Pulmonary Arterial Hypertension. NEJM 2013
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

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

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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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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

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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.