Complete Summary

GUIDELINE TITLE

Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology.

BIBLIOGRAPHIC SOURCE(S)

Galie N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, Olschewski H, Peacock A, Pietra G, Rubin LJ, Simonneau G, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie M, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, McGregor K, Morais J, Oto A, Smiseth OA, Barbera JA, Gibbs S, Hoeper M, Humbert M, Naeije R, Pepke-Zaba J. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. Eur Heart J 2004 Dec;25(24):2243-78. [230 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s)/intervention(s) for which important revised regulatory and/or warning information has been released.

- October 18, 2007, PDE5 inhibitors, Viagra (sildenafil citrate), Levitra (vardenafil HCL), Cialis (tadalafil): The PRECAUTION and updated Adverse Reactions Sections of the approved product labeling for Viagra, Levitra, and Cialis were revised in response to reports of sudden decreases or loss of hearing.
- August 16, 2007, Coumadin (Warfarin): Updates to the labeling for Coumadin to include pharmacogenomics information to explain that people's genetic makeup may influence how they respond to the drug.
- June 8, 2007, Troponin-I Immunoassay: Class I Recall of all lots of the Architect Stat Troponin-I Immunoassay. The assay may report falsely elevated or falsely decreased results at and near a low level, which may impact patient treatment.
- October 6, 2006, Coumadin (warfarin sodium): Revisions to the labeling for Coumadin to include a new patient Medication Guide as well as a reorganization and highlighting of the current safety information to better inform providers and patients.

- March 2, 2006, Tracleer (bosentan): Changes to the prescribing information based on cases of hepatotoxity reported.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Pulmonary arterial hypertension (PAH), including idiopathic pulmonary hypertension (IPAH) and pulmonary hypertension associated with various conditions such as connective tissue diseases, congenital systemic-to-pulmonary shunts, portal hypertension and human immunodeficiency virus (HIV) infection

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Cardiology
Critical Care
Internal Medicine
Pulmonary Medicine
Thoracic Surgery

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To provide clear and concise indications for the practical use of the new clinical classification of pulmonary hypertension, and a brief description of new pathological classification and of the recent pathogenetic insights
- To propose a logical sequence of investigations for aetiology identification, disease assessment, and follow-up
- To provide an evidence-based treatment algorithm for patients with pulmonary arterial hypertension (PAH)

TARGET POPULATION

Patients with pulmonary arterial hypertension (PAH)

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation

1. Symptoms and physical evaluation
2. Screening assessments when predisposing abnormalities are present
3. Electrocardiography (ECG)
4. Chest radiograph
5. Transthoracic (TT) echocardiography
6. Pulmonary function tests
7. Arterial blood gases (ABG)
8. Ventilation/perfusion lung scan
9. High resolution computed tomography (HRCT)
10. Spiral computed tomography (CT)
11. Pulmonary angiography
12. Magnetic resonance imaging
13. Blood tests and immunology
    - Thyroid function tests
    - Routine biochemistry
    - Thrombophilia screen including antiphospholipid antibodies
    - Autoimmune screen (antinuclear antibodies including anti-centromere antibody, anti-SCL70, and ribonucleoproteins (RNP)
14. Human immunodeficiency virus (HIV) test
15. Abdominal ultrasound scan
16. Exercise test:
    - 6 minute walk test (6MWT)
    - Cardiopulmonary exercise testing (CPET) with gas exchange measurement
17. Haemodynamics:
    - Right heart catheterisation + vasoreactivity
    - Blood pressure
    - Right atrial pressure (RAP)
    - Systolic, diastolic, and mean pulmonary artery pressure (PAP)
    - Pulmonary capillary wedge pressure (PWP)
    - Cardiac output
    - Heart rate
    - Pulmonary and systemic vascular resistance
    - Arterial and mixed venous oxygen saturation
    - Superior vena cava saturation
18. Acute calcium channel blocker (CCB) vasoreactivity test

19. Open or thoracoscopic lung biopsy (considered, but not recommended)
20. Liver function tests
21. Haematocrit
22. International normalized ratio (INR)
23. Prothrombin time (PT)

General Measures for Management

1. Physical activity (limitations)
2. Supplemental oxygen during travel/high altitude
3. Influenza and pneumococcus pneumonia vaccines
4. Appropriate contraception in women with childbearing potential
5. Monitoring of haemoglobin levels and appropriate treatment for anemia of elevated haematocrit (e.g., phlebotomy)
6. Monitoring of concomitant medications
7. Provision of psychological assistance
8. In the case of elective surgery, epidural anesthesia in preference to general anesthesia

Pharmacological Treatment

1. Oral anticoagulant treatment
2. Diuretics
3. Oxygen therapy
4. Digitalis
5. Dobutamine
6. Calcium channel blockers (CCBs)
    - Nifedipine
    - Diltiazem
7. Synthetic prostacyclin and prostacyclin analogues
    - Intravenous (iv) epoprostenol
    - Subcutaneous treprostinil
    - Oral sodium beraprost
    - Inhaled or iv iloprost
8. Endothelin-1 (ET-1) receptor antagonists
    - Bosentan
    - Sitaxsentan
    - Ambrisentan
9. Type 5 phosphodiesterase (PDE) inhibitors
    - Sildenafil
10. Combination therapy
    - Epoprostenol + bosentan
    - Epoprostenol + sildenafil

Interventional Procedures

1. Balloon atrial septostomy
2. Lung transplantation
3. Heart and lung transplantation

Special considerations in the following specific conditions: Pediatric pulmonary artery hypertension, pulmonary arterial hypertension associated with

Eisenmenger syndrome, porto-pulmonary hypertension, pulmonary arterial hypertension associated with HIV infection, pulmonary arterial hypertension associated with connective tissue diseases, and pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis.

MAJOR OUTCOMES CONSIDERED

- Sensitivity and specificity of diagnostic tests
- Predictive value of diagnostic tests
- Survival
- Morbidity and mortality
- Quality of life
- Exercise capacity
- Haemodynamics
- Symptoms
- New York Heart Association (NYHA) functional class

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

A. Data derived from multiple randomised clinical trials or meta-analyses
B. Data derived from a single randomised clinical trial or multiple trials with heterogeneous results
C. Consensus of opinion of the experts and/or small studies, retrospective studies, registries

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Introduction to Level of Evidence and Grade of Recommendation

The grading system for the Level of Evidence is substantially based on the number of favourable randomised controlled trials (RCTs) performed with a given treatment strategy (see "Rating Scheme for the Strength of the Evidence" above) and has been adapted to the specific requirements of a rare disease. The only difference is that the Task Force did not include in category B "non-randomised studies" because all these studies in pulmonary arterial hypertension (PAH) are rather small; therefore they are included in category C. In category B the Task Force included the wording "multiple randomised controlled trials with heterogeneous results" because this situation may happen (and has happened) and this definition is more comprehensive even if the first result is that "a single randomised controlled trial" resulted positive. The analysis takes into consideration the studies and the RCTs on PAH patients published in peer-reviewed journals or presented in recent major meetings.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Class of Recommendations

Class I: Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful, and effective

Class II: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment

- **Class IIa**: Weight of evidence/opinion is in favour of usefulness/efficacy.
- **Class IIb**: Usefulness/efficacy is less well established by evidence/opinion.

Class III*: Evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful

*Use of Class III is discouraged by the European Society of Cardiology (ESC)

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The class of recommendations (I-III) and level of evidence (A-C) are defined at the end of the "Major Recommendations" field.

Clinical Classification of Pulmonary Hypertension

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (PAP) >25 mmHg at rest or >30 mmHg with exercise. Current classification of PH is presented in the table below titled "Clinical Classification of Pulmonary Hypertension - Venice 2003." It is a result of extensive discussion and represents a consensus accommodating the European Society of Cardiology's present understanding of pathophysiology as well as of clinical-based differences or similarities within PH. Understanding and correct clinical application of the classification should be aided by the discussion found in the original guideline document.

Table: Clinical Classification of Pulmonary Hypertension - Venice 2003
1. Pulmonary arterial hypertension (PAH)
1.1 Idiopathic (IPAH)
1.2 Familial (FPAH)
1.3 Associated with (APAH):
1.3.1 Connective tissue disease (CTD)
1.3.2 Congenital systemic pulmonary shunts
1.3.3 Portal hypertension
1.3.4 Human immunodeficiency virus (HIV) infection
1.3.5 Drugs and toxins
1.3.6 Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies,

Table: Clinical Classification of Pulmonary Hypertension - Venice 2003
myeloproliferative disorders, splenectomy) 1.4 Associated with significant venous or capillary involvement 1.4.1 Pulmonary veno-occlusive disease (PVOD) 1.4.2 Pulmonary capillary haemangiomatosis (PCH) 1.5 Persistent pulmonary hypertension of the newborn (PPHN)
2. Pulmonary hypertension associated with left heart diseases 2.1 Left-sided atrial or ventricular heart disease 2.2 Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung respiratory diseases and/or hypoxia 3.1 Chronic obstructive pulmonary disease 3.2 Interstitial lung disease 3.3 Sleep disordered breathing 3.4 Alveolar hypoventilation disorders 3.5 Chronic exposure to high altitude 3.6 Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease 4.1 Thromboembolic obstruction of proximal pulmonary arteries 4.2 Thromboembolic obstruction of distal pulmonary arteries 4.3 Non-thromboembolic pulmonary embolism (tumour, parasites, foreign material)
5. Miscellaneous Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumour, fibrosing mediastinitis)

PH was previously classified into 2 categories: primary pulmonary hypertension (PPH) or secondary PH depending on the absence or the presence of identifiable causes or risk factors. The diagnosis of PPH was one of exclusion after ruling out all causes of PH.

Diagnostic Strategy

The diagnostic process of PH requires a series of investigations that are intended to make the diagnosis, to clarify the clinical class of PH and the type of PAH, and to evaluate the functional and haemodynamic impairment. For practical purposes it can be useful to adopt a sequential approach that includes four stages (see figure 2 of the original guideline document):

I. Clinical suspicion of PH
II. Detection of PH
III. PH clinical class identification
IV. PAH evaluation (type, functional capacity, haemodynamics)

Clinical Suspicion of PH

The clinical suspicion of PH should arise in any case of breathlessness without overt signs of specific heart of lung disease or in patients with underlying lung or heart disease whenever there is increasing dyspnoea unexplained by the underlying disease itself. The *symptoms of PH* can also include fatigue, weakness, angina, syncope, and abdominal distension. Symptoms at rest are reported only in very advanced cases.

The *physical signs of PH* may require experience to be appreciated. They include left parasternal lift, accentuated pulmonary component of S2, pansystolic murmur of tricuspid regurgitation, diastolic murmur of pulmonary insufficiency, and right ventricular S3. Jugular vein distension, hepatomegaly, peripheral oedema, ascites, and cool extremities characterise patients in a more advanced state with right ventricular failure at rest. Central cyanosis (and sometime peripheral cyanosis and mixed forms) may also be present. Lung sounds are usually normal.

The clinical suspicion is raised when symptoms and signs are present in subjects with conditions that can be associated with PAH such as CTD, portal hypertension, HIV infection, and congenital heart diseases with systemic-to-pulmonary shunts. In the presence of these pre-disposing abnormalities some experts support a rationale for periodic screening assessments to identify asymptomatic patients in the early stage of PH (See Specific Conditions below).

Finally, PH can be suspected when abnormal *electrocardiographic*, *chest radiograph*, or *echocardiographic findings* are detected in the course of procedures performed for other clinical reasons.

Detection of PH

The detection phase requires investigations that are able to confirm the diagnosis of PH. They include the electrocardiogram (ECG), the chest radiograph, and transthoracic Doppler-echocardiography (TTE).

ECG

The ECG may provide suggestive or supportive evidence of PH by demonstrating right ventricular hypertrophy and strain and right atrial dilation. Right ventricular hypertrophy on ECG is present in 87% and right axis deviation in 79% of patients with IPAH. However, the ECG has inadequate sensitivity (55%) and specificity

(70%) to be a screening tool for detecting significant PAH. A normal ECG does not exclude the presence of severe PH.

Chest Radiograph

In 90% of IPAH patients the chest radiograph is abnormal at the time of diagnosis. Findings include central pulmonary arterial dilatation which contrasts with "pruning" (loss) of the peripheral blood vessels. Right atrial and ventricular enlargement may be seen and it progresses in more advanced cases. The chest radiograph allows associated moderate-to-severe lung disease or pulmonary venous hypertension due to left heart abnormalities to be reasonably excluded. However, a normal chest radiograph does not exclude mild post capillary pulmonary hypertension including left-heart disease or PVOD.

TTE

TTE is an excellent non-invasive screening test for the patient with suspected PH. TTE estimates pulmonary artery systolic pressure (PASP) and can provide additional information about the cause and consequences of PH. PASP is equivalent to right ventricular systolic pressure (RVSP) in the absence of pulmonary outflow obstruction. RVSP is estimated by measurement of the systolic regurgitant tricuspid flow velocity (v) and an estimate of right atrial pressure (RAP) applied in the formula: $RVSP=4v^2 + RAP$. RAP is either a standardised value or estimated value from characteristics of the inferior vena cava or from jugular venous distension. Tricuspid regurgitant jets can be assessed in the majority (74%) of patients with PH. Most studies report a high correlation (0.57-0.93) between TTE and right heart catheterisation (RHC) measurements of PASP. However, in order to minimise false positives it is important to identify specific values for the definition of PH as assessed by TTE.

The range of RVSP among healthy controls has been well characterised. Among a broad population of male and female subjects ranging from 1 to 89 years old, RVSP was reported as 28 $\pm$ 5 mmHg (range 15-57 mmHg). RVSP increases with age and body mass index. According to these data mild PH can be defined as a PASP of approximately 36-50 mmHg or a resting tricuspid regurgitant velocity of 2.8-3.4 m/sec (assuming a normal RAP of 5 mmHg). It should be noted that also with this definition a number of false positive diagnoses can be anticipated especially in aged subjects, and confirmation with RHC is required in symptomatic patients (New York Heart Association [NYHA] class II-III). In asymptomatic subjects (NYHA class I) a concomitant CTD should be excluded and echocardiography should be repeated in six months. It should be noted that defining the level for an elevated RVSP does not define the point at which an increased RVSP is clinically important, is predictive of future consequences, and/or requires specific treatments. Also the possibility of false negative Doppler-echocardiographic results should be considered in case of high clinical suspicion.

Additional echocardiographic and Doppler parameters are important for diagnosis confirmation and assessment of severity of PH including right and left ventricular dimensions and function, tricuspid, pulmonary, and mitral valve abnormalities, right ventricular ejection and left ventricular filling characteristics, inferior vena cava dimensions, and pericardial effusion size.

Besides identification of PH, TTE also allows a differential diagnosis of possible causes and virtually starts the phases III and IV of the diagnostic process. TTE can recognise left heart valvular and myocardial diseases responsible for pulmonary venous hypertension (Clinical Class 2) and congenital heart diseases with systemic-to-pulmonary shunts can be easily identified (Clinical Class 1.3.2). The venous injection of agitated saline as contrast medium can help the identification of patent foramen ovale or small sinus venosus type atrial septal defects that can be overlooked on the standard TTE examination. Trans-oesophageal echocardiography (TEE) is rarely required and is usually used to confirm the presence, and assess the exact size, of small atrial septal defects.

Pulmonary Hypertension Clinical Class Identification

The next step after the detection of PH is the identification of the Clinical Class according to the clinical classification of Venice (see table above). This is accomplished by the use of essential tests such as TTE (as specified above), pulmonary function tests (PFT) (including arterial blood gas sample), and ventilation and perfusion (V/Q) lung scan. If required, in particular circumstances additional tests can be performed such as chest high resolution computed tomography (HRCT), spiral computed tomography (CT), and pulmonary angiography.

PFTs and Arterial Blood Gases

PFTs and arterial blood gas sampling can identify the contribution of underlying airway of parenchymal lung disease. Patients with PAH usually have decreased lung diffusion capacity for carbon monoxide (DL_{CO}) (typically in the range of 40-80% predicted) and mild to moderate reduction of lung volumes. The arterial oxygen tension (PaO_2) is normal or slightly lower than normal, and arterial carbon dioxide tension ($PaCO_2$) is decreased as a result of alveolar hyperventilation. Chronic obstructive pulmonary diseases as a cause of hypoxic PH, is diagnosed on the evidence of irreversible airflow obstruction, usually by measuring the forced expired volume in one second (FEV1). These patients often have a normal or increased $PaCO_2$ together with airflow limitation and increased residual volumes and reduced DL_{CO}. Emphysema is now diagnosed using HRCT. A decrease in lung volume together with a decrease in DL_{CO} may indicate a diagnosis of interstitial lung disease (ILD). Again the HRCT is the principle way of assessing the severity of interstitial lung disease. If clinically suspected, screening overnight oximetry and polysomnography will exclude significant obstructive sleep apnoea/hypopnoea and nocturnal desaturation.

Ventilation and Perfusion (V/Q) Lung Scan

In PAH the lung V/Q scans may be entirely normal. However, they may also show small peripheral non-segmental defects in perfusion. These are normally ventilated and thus represent V/Q mismatch. Lung V/Q scan provides a means of diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH, Clinical Class 4). In CTEPH the perfusion defects are usually found in lobar and segmental regions leading to segmental defects in the perfusion image. As these areas are normally ventilated, the perfusion defects are described as being unmatched by ventilation defects. V/Q scanning showed sensitivity of 90-100% with specificity of 94-100% for distinguishing between IPAH and CTEPH. A caveat is that unmatched

perfusion defects are also seen in veno-occlusive disease. Such a patient requires careful further investigation (see the section below titled "HRCT of the Lung"). In patients with parenchymal lung disease the perfusion defects are *matched* by ventilation defects.

HRCT of the Lung

HRCT provides detailed views of the lung parenchyma and facilitates the diagnosis of interstitial lung disease and emphysema. The presence of interstitial markings similar to those seen with advanced left ventricular failure such as diffuse central ground-glass opacification and thickening of interlobular septa suggest PVOD; additional findings are lymphadenopathy, pleural shadows, and effusions. Diffuse bilateral thickening of the interlobular septae and the presence of small, centrilobular, poorly circumscribed nodular opacities suggest PCH.

Contrast Enhanced Spiral CT of the Lung, Pulmonary Angiography, and Magnetic Resonance Imaging

Contrast-enhanced spiral (or helical) CT is indicated in pulmonary hypertensive patients when the V/Q lung scintigraphy shows segmental or sub-segmental defects of perfusion with normal ventilation (i.e., evidence of a V/Q mismatch and may demonstrate central chronic pulmonary thromboemboli). CT features of chronic thromboembolic disease are complete occlusion of pulmonary arteries, eccentric filling defects consistent with thrombi, recanalisation, and stenoses or webs.

Traditional pulmonary angiography is still required in the work-up of CTEPH to better identify patients that can benefit from the intervention of endarterectomy. Pulmonary angiography is more accurate in the identification of distal obstruction and it is indicated also in cases of inconclusive contrast-enhanced spiral CT in patients with clinical and lung scintigraphy suspicion of CTEPH. This procedure can be safely performed by experienced staff in patients with severe PH. Useful technical details include the utilisation of modern contrast media, right and left main branch selective injections, and multiple views.

Magnetic resonance imaging is increasingly used in patients with PAH for the evaluation of pathological and functional changes of both heart and pulmonary circulation. However, additional experience is needed before introducing this tool in the routine assessment of patients with PAH.

PAH Evaluation (Type, Exercise Capacity, Haemodynamics)

When the Clinical Class of PAH (Clinical Class 1) has been determined, additional investigations may be required for the exact identification of the type of PAH for the assessment of exercise capacity and haemodynamics.

Blood Tests and Immunology

Routine biochemistry, haematology and thyroid function tests are required. Thrombophilia screen should be performed including antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies). CTD are diagnosed primarily on

clinical and laboratory criteria and an autoimmune screen consists of antinuclear antibodies (ANA), including anti-centromere antibody, anti-SCL 70, and ribonucleoproteins (RNP). About one third of patients with IPAH have positive but low antinuclear antibody titre ($\leq$1:80 dilutions). Patients with a substantially elevated antinuclear antibodies and/or suspicious clinical features require further serological assessment and rheumatology consultation. Finally, all patients should be consented for and undertake a HIV serology test.

Abdominal Ultrasound Scan

Liver cirrhosis and/or portal hypertension can be reliably excluded by the use of abdominal ultrasound scan. The colour-Doppler examination also allows the differentiation between passive portal hypertension, due to right heart failure, from portal hypertension caused by an increase in the trans-hepatic venous gradient associated with liver cirrhosis. The use of contrast agents may improve the diagnosis. Portal hypertension can be confirmed by the detection of an increased gradient between free and occluded (wedge) hepatic vein pressure at the time of right heart catheterisation (RHC) (see Porto-pulmonary hypertension).

Exercise Capacity

The objective assessment of exercise capacity in patients with PAH is an important instrument for evaluating disease severity and treatment effect. The most commonly used exercise tests for PH are the six-minute walk test (6MWT) and cardiopulmonary exercise testing (CPET) with gas exchange measurement.

The 6MWT is technically simple and inexpensive. It is predictive of survival in IPAH and also correlates inversely with NYHA functional status severity. 6MWT is usually combined with the Borg score that assesses the subjective level of dyspnoea with the exercise. Reduction of arterial oxygen saturation >10% during 6MWT increases mortality risk 2.9 times over a median follow-up of 26 months. 6MWT is the traditional "primary" end point for the great majority of controlled clinical trials performed in PAH.

CPET allows measurement of ventilation and pulmonary gas exchange during exercise testing providing additional "pathophysiologic" information to that derived from standard exercise testing. PAH patients show reduced peak VO_2, reduced peak work rate, reduced ratio of VO_2 increase to work rate increase, reduced anaerobic threshold; and reduced peak oxygen pulse; they show also increased volume of expired gas (VE) and VCO_2 slope representative of ventilatory insufficiency. Peak VO_2 is correlated with the prognosis of PAH patients.

CPET has been used in recent multicentre trials, but it failed to confirm improvements observed with 6MWT. A possible explanation for these findings is that CPET is technically more difficult than 6MWT and its results may be influenced by the experience of the centres. An alternative explanation may relate to a lack of sensitivity of CPET in measuring response to treatment which has less effect on maximal as opposed to submaximal exercise.

Haemodynamics

RHC is required to confirm the diagnosis of PAH, to assess the severity of the haemodynamic impairment, and to test the vasoreactivity of the pulmonary circulation. The following parameters should always be assessed: heart rate, RAP, PAP (systolic, diastolic, and mean), pulmonary capillary wedge pressure (PWP), cardiac output (by thermodilution or the Fick method in cases of systemic-to-pulmonary shunts), blood pressure, pulmonary and systemic vascular resistance, arterial and mixed venous oxygen saturation (and superior vena cava saturation in cases of systemic-to-pulmonary shunts).

PAH is defined by a mean PAP >25 mmHg at rest or >30 mmHg with exercise, by a PWP $\leq$15 mmHg, and by PVR >3 mmHg/L/min (Wood units). Left heart catheterisation is required in the rare circumstances in which a reliable PWP cannot be measured.

Confirmation of diagnosis by RHC is required in cases of symptomatic patients (NYHA class II and III) with mild PH as assessed by Doppler echocardiography (see above for definition) to identify subjects needing further diagnostic and therapeutic procedures. The assessment of PWP may allow the distinction between arterial and venous PH in patients with concomitant left heart diseases.

RHC is important also in patients with definite moderate-to-severe PAH because the haemodynamic variables have prognostic relevance.

Elevated mean RAP, mean PAP, and reduced cardiac output and central venous O_2 saturation identify IPAH patients with the worst prognosis. Haemodynamic measurements have been used to estimate the natural history of IPAH in an individual patient by the use of a prediction equation that has also been utilised for assessing the long-term effects of new treatments on survival. However, this formula has been derived by patients on conventional therapy followed up almost 15-20 years ago that may not represent an appropriate "control" group for current PAH populations.

Uncontrolled studies have suggested that long-term administration of calcium-channel blockers (CCB) prolongs survival in the rare case of acutely responsive patients compared with unresponsive patients. It is generally accepted that patients who may benefit from long-term CCB can be identified by an acute vasodilator challenge performed during RHC. However, it has been proposed that the definitive recognition of patients who benefit from CCB treatment requires both (1) the demonstration of a positive acute vasoreactive response and (2) the confirmation of a sustained response to long term treatment of CCB.

Acute vasodilator testing should only be done using short-acting pulmonary vasodilators at the time of the initial RHC in experienced centres to minimise the potential risks. Currently the agents used in acute testing are intravenous (iv) prostacyclin or adenosine and inhaled nitric oxide. Half-lives, dose ranges, increments, and duration of administration for these compounds are provided in Table 5 in the original guideline titled "Route of administration, half-lives, dose ranges, increments and duration of administration of the most used substances on pulmonary vasoreactivity tests."

A positive acute vasoreactive response (*positive acute responders*) is defined as a reduction of mean PAP $\geq$10 mmHg to reach an absolute value of mean PAP $\leq$40

mmHg with an increase or unchanged cardiac output. Generally, only about 10-15% of IPAH will meet these criteria. Positive acute responders are most likely to show a sustained response to long-term treatment with high doses of CCB and are the only patients that can safely be treated with this type of therapy. An empiric treatment with CCB without acute vasoreactivity test is strongly discouraged due to possible severe adverse effects.

Positive long-term responders to high dose CCB treatment are defined as patients being in NYHA functional class I or II with near normal haemodynamics after several months of treatment with CCB alone. Only about a half of IPAH positive acute responders are also positive long-term responders to CCB and only in these cases the continuation of CCB as single treatment is warranted.

The usefulness of acute vasoreactivity tests and long-term treatment with CCB in patients with PAH associated with underlying processes, such as CTD or congenital heart disease, is less clear as compared to IPAH. However, experts suggest also in these cases to test patients for acute vasoreactivity and to look for a long-term response to CCB in appropriate subjects.

Lung Biopsy

Open or thoracoscopic lung biopsy entails substantial risks of morbidity and mortality. Because of the low likelihood of altering the diagnosis and treatment, routine biopsy is discouraged.

Assessment of Severity

Several variables have been shown to predict prognosis in IPAH when assessed at baseline or after targeted treatments. Very little information is available in other conditions such as PAH associated with CTD, congenital systemic to pulmonary shunts, HIV infection, or portal hypertension. In these circumstances, additional factors may contribute to the overall outcome. In fact, PAH associated with CTD disorders has a worse prognosis than IPAH patients, whereas patients with PAH associated with congenital systemic-to-pulmonary shunts have a more slowly progressive course than IPAH patients.

In practice, the prognostic value of a single variable in the individual patient may be less than the value of multiple concordant variables (see table below).

Table: Prognostic Parameters in Patients with IPAH
Clinical parameters • NYHA functional classification • NYHA functional class on chronic epoprostenol treatment • History of right heart failure
Exercise capacity • 6MWT distance • 6MWT distance on chronic epoprostenol treatment

Table: Prognostic Parameters in Patients with IPAH
• Peak VO_2
Echocardiographic parameters • Pericardial effusion • Right atrial size • Left ventricular eccentricity index • Doppler right ventricular (Tei) index
Haemodynamics • RAP • Mean PAP • Cardiac output • Mixed venous O_2 saturation • Positive acute response to vasoreactivity tests • Fall in PVR <30% after 3 months of epoprostenol
Blood tests • Hyperuricaemia • Baseline Brain natriuretic peptide • Brain natriuretic peptide after 3 months therapy • Troponin - detectable, especially persistent leakage • Plasma norepinephrine • Plasma endothelin-1

Treatment

The treatment of PAH has been traditionally characterised by few and difficult options. Recently, there has been a dramatic change from the slow progress in the past decades to the remarkable number of randomised controlled trials (RCT) accomplished in the last few years. However there are now different treatments that are generally accepted to be efficacious (e.g., oral anticoagulants, oxygen, CCBs), although not supported by RCT and not formally approved by Regulatory Agencies for the specific PAH indication.

The objective of this section is to review each form of therapy according to the Level of Evidence classification (see "Rating Scheme for the Strength of the Evidence" above) as suggested by the Committee for Practice Guidelines of the European Society of Cardiology. In addition, the Grade of Recommendation (see "Rating Scheme for the Strength of the Recommendations") will be provided that will take into account the clinical efficacy of treatments that, for different reasons, have not been tested in RCTs such as oral anticoagulants, oxygen, CCBs, balloon atrial septostomy and/or lung transplantation. Furthermore, information will be provided concerning current country-specific regulatory approval and labelling for each compound. Finally, an evidence-based treatment algorithm will be proposed that is intended to provide a guide to the selective use of each form of therapy.

Introduction to Level of Evidence and Grade of Recommendation

Both components Grade of Recommendation and Level of Evidence are provided in order to give a complete profile for each treatment (see table below). No grade of recommendation is given for drugs that are currently available only for patients enrolled in RCTs. Country-specific regulatory approval status and labelling for each compound is also provided in Table 11 of the original guideline document.

Table: Grading of Recommendations and Level of Evidence for Efficacy in IPAH

Treatment	Grade of Recommendation			Level of Evidence
	Ia	IIa	IIb	
General measures		X		C
Oral anticoagulants[a]		X		C
Diuretics	X			C
Digoxin			X	C
Oxygen[b]		X		C
CCBs[c]	X			C
Epoprostenol	X			A
Treprostinil		X		B
Iloprost (inhalation)		X		B
Iloprost (iv)		X		C
Beraprost			X	B
Bosentan	X[d]			A
Sitaxsentan[e]				B
Ambrisentan[e]				C
Sildenafil	X[d]			A
Combination therapy			X	C
Balloon atrial septostomy		X		C
Lung transplantation	X			C

Notes
[a] IIa for IPAH, IIb for other PAH conditions
[b] If arterial oxygen saturation <90%
[c] Only in patient responders to acute reactivity tests, I for IPAH, IIb for other PAH conditions
[d] IIa B in NYHA class IV
[e] These drugs are currently available only for patients enrolled in RCTs and no grade of recommendation is given.

General Measures

General measures include strategies devoted to limit the deleterious impact of some circumstances and external agents on patients with PAH. As for other clinical conditions, the impact of these measures has not been tested scientifically and the recommendations are based on the experts' opinion.

Grade of Recommendation = IIa; Level of Evidence = C

Physical activity - It is unclear whether physical activity may have a negative impact on the evolution of PAH. However, potentially hazardous symptoms like severe dyspnoea, syncope, and chest pain should be clearly avoided. Exercise should be limited to a symptom-free level in order to maintain adequate skeletal muscles conditioning. Physical activity after meals or in extreme temperatures should be avoided. Appropriate adjustments of daily activities may improve quality of life and reduce the frequency of symptoms.

Travel/altitude - Hypoxia may aggravate vasoconstriction in PAH patients and it is advisable to also avoid mild degrees of hypobaric hypoxia that start at altitudes between 1,500 and 2,000 meters. Commercial airplanes are pressurised to equivalent altitude between 1,600 and 2,500 meters and supplemental oxygen in PAH patients should be considered. Before planning to travel, information on nearest PH clinics should be collected.

Prevention of infections - Patients with PAH are susceptible to develop pneumonia that is the cause of death in 7% of cases. Pulmonary infections are poorly tolerated and need to be promptly recognised and treated. Vaccine strategies are recommended for influenza and pneumococcus pneumonia. Any persistent fever in patients with iv catheter for continuous administration of epoprostenol should raise the suspicion of catheter infection.

Pregnancy, birth control and post-menopausal hormonal therapy - Pregnancy and delivery in PAH patients is associated with an increased rate of deterioration and death. Even if successful pregnancies have been reported in IPAH patients, an appropriate method of birth control is highly recommended in women with childbearing potential. There is consensus among guidelines from the American Heart Association, and the American College of Cardiology which recommend that pregnancy be avoided or terminated in women with cyanotic congenital heart disease, PH, and Eisenmenger syndrome. The Expert consensus document of the European Society of Cardiology (ESC) on the management of cardiovascular diseases during pregnancy outlines that severe pulmonary vascular diseases has long been known to carry a maternal mortality of 30-50%. However, there is no agreement among experts on the most appropriate birth control method in these subjects. The safety of hormonal contraception is questioned for its influence on prothrombotic changes. On the other hand, the current availability of low-oestrogen dose products and concomitant oral anticoagulant treatment may limit the risk of these agents. In addition, recent studies of large numbers of patients failed to reveal any relationship between intake of hormonal contraceptive agents and PAH. Some experts suggest the use of oestrogen-free products or surgical sterilisation or barrier contraceptives. It is not clear if the use of hormonal therapy in post-menopausal women with PAH is advisable or not. Probably it can be suggested only in case of intolerable menopausal symptoms and in conjunction with anticoagulation.

Haemoglobin levels - Patients with PAH are highly sensitive to reductions in haemoglobin levels. Any kind of mild anaemia should be promptly treated. On the other hand, patients with long-standing hypoxia, such as those with right-to-left shunts, tend to develop erythrocytosis with elevated levels of haematocrit. In these circumstances, phlebotomies are indicated (see section on Eisenmenger syndrome) if haematocrit is above 65% in symptomatic patients (headache, poor concentration) to reduce adverse effects of hyperviscosity.

Concomitant medications - Care is needed to avoid drugs that interfere with oral anticoagulants or increase the risk of gastrointestinal bleeding. Even if non-steroid anti-inflammatory drugs seem not to be associated to PAH in a case-control study, their use may further reduce glomerular filtration rate in patients with low cardiac output and pre-renal azotemia. Anorexigens that have been linked to the development of PAH are no longer available on the market. The effects of the new generation serotonin-related anorexigens are unknown but no reports of pulmonary-related side effects are available up to now. The efficacy of current treatments for chronic "biventricular" heart failure like angiotensin-converting enzyme (ACE)-inhibitors and beta-blockers has not been confirmed in patients with PAH. On the other hand, the empiric use of these treatments, even at low doses, may result in severe side effects like hypotension and right heart failure and should be discouraged.

Psychological assistance - Patients with PAH have a median age of about 40 years and exercise limitation may interfere considerably with their previous life-style. In addition, information on the severity of the disease may be obtained from many non-professional sources. Such sources may not be up-to-date or may be confusing or inappropriately explicit. For this reason, many PAH patients are affected by a variable degree of anxiety and/or depression that can have a profound impact on their quality of life. The role of the PAH expert is important in supporting patients with adequate information (breaking bad news) and in referring them to psychologists or psychiatrists when needed. Also support groups for patients and families coordinated or not by psychologists or psychiatrists are useful in improving the understanding and the acceptance of the disease condition.

Elective surgery - Even if appropriate studies are lacking, it is expected that elective surgery has an increased risk in patients with PAH. In addition, the risk should increase with the severity of NYHA functional class and in cases of thoracic and abdominal interventions. It is not clear which type of anaesthesia is advisable but probably epidural is better tolerated than general anaesthesia. The latter should be performed by experienced anaesthetists with the support of PH experts for deciding the most appropriate treatment in case of complications. Patients on iv epoprostenol and subcutaneous treprostinil treatment should have fewer problems than subjects on oral or inhaled treatments. The latter may suffer from temporary obstacles to the drug administration like fasting, general anaesthesia, and assisted ventilation. In case a prolonged period of withdrawal is foreseen (more than 12-24 hours) it is advisable to provisionally shift to iv treatments and revert to the original therapy subsequently. Anticoagulant treatment should be interrupted for the shortest possible time and deep venous thrombosis prophylaxis should be performed.

Pharmacological Treatment

Oral Anticoagulant Treatment

The rationale for the use of anticoagulant treatment in patients with PAH is based on the presence of traditional risk factors for venous thromboembolism like heart failure and sedentary lifestyle as well as on the demonstration of thrombophilic predisposition and of thrombotic changes in the pulmonary microcirculation and in the elastic pulmonary arteries.

The evidence for favourable effects of oral anticoagulant treatment in patients with IPAH or PAH associated to anorexigens is based on retrospective analysis of single-centre studies. The design of these studies was not randomised and only IPAH and anorexigens-related PAH patients were included in the studies.

The target International Normalized Ratio (INR) in patients with IPAH varies somewhat being 1.5-2.5 in most centres of North America and 2.0-3.0 in European centres.

The evidence supporting anticoagulation in patients with IPAH may be extrapolated to other patients with PAH provided that the risk/benefit ratio is carefully considered.

For example, it is generally thought that the risk of gastrointestinal bleeding may be higher in patients with PAH associated with CTD. Patients with PAH associated with congenital heart disease with intracardiac shunts are at increased risk of hemoptysis but they may be also at increased risk for paradoxical embolism in pulmonary artery and cerebral vein thrombosis. Patients with porto-pulmonary hypertension may be at increased risk for gastrointestinal bleeding due to the presence of varices and low platelet counts. Patients with PAH receiving therapy with chronic iv epoprostenol are anticoagulated in the absence of contraindications, due in part to the additional risk of catheter-associated thrombosis.

In recent RCTs, oral anticoagulants were administered in 51-86% of subjects. Interestingly, the highest prevalence of oral anticoagulant treatment was seen in the trials involving mainly IPAH patients in NYHA class III and IV, while the lowest prevalence was observed in the trial that included only patients with scleroderma. It should be emphasised that there is no evidence of any difference in efficacy of oral anticoagulant therapy according to functional class or other measures of severity.

Grade of Recommendation = IIa; Level of Evidence = C for IPAH
Grade of Recommendation = IIb; Level of Evidence = C for other PAH conditions

Diuretics

Patients with decompensated right heart failure develop fluid retention that leads to increased central venous pressure, abdominal organ congestion, peripheral oedema, and in advanced cases also ascites. Appropriate diuretic treatment in case of right heart failure allows clear symptomatic and clinical benefits in patients with PAH even if specific RCTs have not been performed. In the recent RCTs on new targeted treatments, 49-70% of patients were treated with diuretics. However, the lack of trials with specific classes of diuretics in PAH and the individual variability in responses leave the choice of the type and the dose of the drug to be used in individual cases to the experience of the physician. Serum electrolytes and indices of renal function should be followed closely in patients receiving diuretic therapy.

Grade of Recommendation = I; Level of Evidence = C

Oxygen

Most patients with PAH (except those with associated congenital heart disease) present with only mild degrees of arterial hypoxaemia at rest. The pathophysiological mechanisms in this case include a low mixed venous oxygen saturation caused by low cardiac output and only minimally altered ventilation perfusion matching. In some patients with profound hypoxaemia, a secondary opening of a patent foramen ovale can be found. In patients with PAH associated with congenital cardiac defects, hypoxaemia is related to reversal of left-to-right shunting and is refractory to increased inspired oxygen.

No consistent data are currently available on the effects of long-term oxygen treatment in PAH. Although improvement in PH with low-flow supplemental oxygen has been reported in some PAH patients, this has not been confirmed in controlled studies. However, it is generally considered important to maintain oxygen saturation at greater than 90% at all times. More controversial is the use of oxygen treatment in patients with PAH associated with cardiac shunts. In fact, in a controlled study on Eisenmenger syndrome patients, nocturnal oxygen therapy had no effect on haematological variables, quality of life, or survival. In any case, the effect of continuous oxygen administration in these cases is unknown.

Grade of Recommendation = IIa; Level of Evidence = C

Digitalis and Dobutamine

Since the depression of myocardial contractility seems to be one of the primary events in the progression of right heart failure, inotropic agents have been considered for the treatment of this condition. Short-term iv administration of digoxin in IPAH produces a modest increase in cardiac output and a significant reduction in circulating norepinephrine levels; however, no data are available on the effects of long-term treatment. Accordingly, the use of digitalis in PAH patients with refractory right heart failure is based primarily on the judgment of the physician rather than on scientific evidence of efficacy. Digitalis may be used in the rare PAH patients with atrial fibrillation or atrial flutter to slow ventricular rate. Digoxin was administered in 18-53% of patients enrolled in recent RCTs in PAH. Patients with end stage PAH are treated with iv dobutamine in most expert centres. This treatment often results in clinical improvement that may persist for a variable period of time, like in advanced left heart failure.

Grade of Recommendation = IIb; Level of Evidence = C

CCBs

The evidence for medial hypertrophy in the small pulmonary arteries together with the reduction of PVR obtained by vasodilator drugs led Paul Wood many years ago to elaborate the "vasoconstrictive" hypothesis as the basis for understanding the pathogenesis and the pathophysiology of IPAH. It is now clear that only in a minority of patients with IPAH a clinically significant reduction of pulmonary artery pressure associated with long-term clinical benefits can be achieved by the use of traditional vasodilators such as CCBs.

Favourable clinical and prognostic effects of high doses of CCBs in vasoreactive patients (see in the "Diagnosis and Assessment" section for definition of positive acute vasoreactive response) with IPAH have been shown in single centre, non-randomised, non-controlled studies. In these studies, the control group consisted of non-vasoreactive patients who may have a poorer prognosis "per se" as compared to vasoreactive individuals. However, there is no clear evidence for this hypothesis and it would appear unethical to withhold a therapy with a high-dose CCB from a patient with a consistent reduction of pulmonary artery pressure by acute pharmacological testing and to perform a placebo-controlled clinical trial in these subjects.

The CCBs that have been predominantly used in reported studies are nifedipine and diltiazem, and the choice can be based upon the patient's heart rate at baseline (relative bradycardia favouring nifedipine, and relative tachycardia favouring diltiazem). The doses of these drugs that have shown efficacy in IPAH are relatively high (i.e., up to 120-240 mg/day for nifedipine and 240-720 mg/day for diltiazem). It is advisable, in vasoreactive patients, to start with reduced doses (i.e., 30 mg of slow-release nifedipine twice a day [bid] or 60 mg of diltiazem three times a day [tid]) to be increased cautiously and progressively in the subsequent weeks to the maximal tolerated regimen. Limiting factors for dose increase are usually systemic hypotension and lower limb peripheral oedema. In some cases the addition of digoxin and/or diuretics can decrease the CCB side effects. There are no reports on efficacy, tolerability, and effective doses of new generation CCBs such as amlodipine and felodipine.

As reported above ("Diagnosis and Assessment" section) generally, only about 10-15% of IPAH will meet the criteria for a positive acute vasoreactive response and only about half of them will also be clinical and haemodynamic long-term responders to CCB treatment. It is commonly accepted that only in these cases the continuation of CCBs as single treatment is warranted.

The usefulness of acute vasoreactivity tests and long-term treatment with CCBs in patients with PAH associated with CTD or congenital heart disease is less clear as compared to IPAH. However, experts suggest also in these cases to test patients for acute vasoreactivity and to treat cautiously the vasoreactive ones with oral CCB, monitoring them closely to determine both the efficacy and safety of such therapy.

Favourable results of long-term administration of high doses of calcium-channel antagonists have also been shown in children with IPAH.

Grade of Recommendation = I; Level of Evidence = C for IPAH
Grade of Recommendation = IIb; Level of Evidence = C for other PAH conditions

Synthetic Prostacyclin and Prostacyclin Analogues

The clinical use of prostacyclin in patients with PAH has been extended by the synthesis of stable analogues that possess different pharmacokinetic properties but share qualitatively similar pharmacodynamic effects. Originally, the experience on humans has been collected with epoprostenol that is a synthetic salt of prostacyclin.

Epoprostenol - Epoprostenol is available as a stable, freeze-dried preparation that needs to be dissolved together with an alkaline buffer (glycine), which allows a solution to be infused intravenously. Epoprostenol has a short half-life in the circulation (3-5 min), is rapidly converted to stable breakdown products or metabolites, and is stable at room temperature for only 8 h; this explains why it needs to be administered by continuous iv route by means of infusion pumps (e.g., CADD® pump) and permanent tunnelised catheters (Hickman). The epoprostenol is kept cool by using cold packs, which allows the infusion to be changed daily. The use of subcutaneous catheters with reservoirs and transcutaneous needles (used in intermittent treatments) is discouraged.

The efficacy of continuous iv administration of epoprostenol (synthetic prostacyclin) has been tested in 3 unblinded, controlled clinical trials in IPAH and in PAH associated with the scleroderma spectrum of diseases, and is summarised in Table 12 of the original guideline document. Epoprostenol improves symptoms, exercise capacity, and haemodynamics in both clinical conditions and is the only treatment to be shown in RCTs to improve survival in IPAH.

Recently two large series of IPAH patients treated with epoprostenol have been reported. The data showed that survival was about 65% at three years and it was related to the severity at baseline, as well as to the three-month response to therapy. The authors suggested that lung transplantation should be considered in a subset of patients who remain in NYHA functional class III or IV or in those who cannot achieve a significant exercise and haemodynamic improvement after three months of epoprostenol therapy, or both.

Long-term treatment with epoprostenol is imitated at a dose ranging from 2 to 4 ng/kg/min and increased at a rate limited by side effects (flushing, headache, diarrhoea, leg pain). Target doses for the first two to four weeks is usually around 10 to 15 ng/kg/min and periodic dose increases are then required to maximise efficacy and to maintain the results because of possible tolerance to the drug. Optimal dose is variable between individual patients ranging in the majority between 20 and 40 ng/kg/min, but the current strategy for increases is different among centres. In two large recently published series of patients treated with epoprostenol, mean dose was 21 $\pm$ 7 and 27 $\pm$ 8 ng/kg/min, respectively.

Adverse effects with chronic epoprostenol treatment are common and include flushing, jaw pain, diarrhoea, headache, backache, foot and leg pain, abdominal cramping, nausea, and rarely hypotension. The incidence of side effects may relate to how aggressive the dose is initially up titrated. Dose reduction is required only if the intensity is moderate to severe. Recurrence of side effects may be experienced after dose increases but usually they are mild and self-limiting over time without dose changes. In some cases ascites has been reported that may be related to an increased permeability of the peritoneal membrane induced by epoprostenol. Adverse events related to the delivery system are more serious and are essentially linked to pump malfunction, local site infection, catheter obstruction, and sepsis. In two large series, 0.14 and 0.19 episodes of sepsis per patients-year were reported and 8 deaths (2.8%) out of a total of 340 subjects were directly related to catheter infections. Localised infections can also occur, such as small exit site reactions, tunnel infections, and cellulitis. Rare events are pneumothorax and haemothorax that occur during catheter insertion. Abrupt interruption of the epoprostenol infusion should be avoided, as this may, in

some patients, lead to a rebound worsening of their PH with symptomatic deterioration and even death. Management of patients on chronic epoprostenol therapy requires a considerable infrastructure, including experienced nurses and physicians.

Even if RCTs with epoprostenol have been performed only in IPAH and PAH associated with scleroderma, favourable results have also been shown in uncontrolled experiences in other subsets such as paediatric IPAH systemic lupus erythematosus and other CTD, PAH associated with congenital heart defects with systemic to pulmonary shunts either repaired or not, in porto-pulmonary hypertension in PAH associated to Gaucher's disease and to HIV infection. There is no consensus among experienced physicians on the effectiveness of epoprostenol in patients with inoperable CTEPH even if some positive effects have been shown.

Epoprostenol in Europe has not been registered through the centralised procedure of the European Union (European Agency for the Evaluation of Medicinal Products [EMEA]) but is approved in different European countries on a local basis for IPAH in NYHA class III and IV. Epoprostenol is approved by the Food and Drug Administration (FDA) in the USA and Canada for IPAH and PAH associated with CTD in NYHA class III and IV.

Grade of Recommendation = I; Level of Evidence = A for IPAH and PAH associated with CTD
Grade of Recommendation = IIa; Level of Evidence = C for other PAH conditions

Four RCTs have been performed with prostacyclin analogues and are summarised in Table 13 of the original guideline document.

Trepostinil - Trepostinil is a tricyclic benzidine analogue of epoprostenol, with sufficient chemical stability to be administered at ambient temperature in a physiological solution. These characteristics allow the administration of the compound by iv as well as subcutaneous route. The subcutaneous administration of treprostinil can be accomplished by micro-infusion pumps (Mini-Med pump®) and small subcutaneous catheters similar to those utilised for the administration of insulin in diabetic patients. In this case, the problems linked to a permanent central venous line, such as infections, are avoided and the management of the system is much simpler.

The effects of continuous subcutaneous administration of treprostinil in PAH were studied in the largest worldwide RCT performed in this condition and showed improvements in exercise capacity, haemodynamics, and clinical events. The greatest exercise improvement was observed in patients who were more compromised at baseline and in subjects who could tolerate upper quartile dose (dose >13.8 ng/kg/min). One earlier pilot controlled study was performed with treprostinil in 26 PAH patients and showed trends in the improvement of 6MWD and in the reduction of PVR.

Infusion site pain was the most common side effects of treprostinil leading to discontinuation of the treatment in 8% of cases on active drug and limiting dose increase in an additional proportion of patients. Overall mortality was 3% and no difference was detected between treatment groups. Preliminary reports have

shown the possibility to transition patients from iv epoprostenol to subcutaneous treprostinil.

In 2002, the FDA approved the use of treprostinil in NYHA class II, III, and IV patients with PAH.

Grade of Recommendation = IIa; Level of Evidence = B for PAH

Sodium beraprost - Sodium beraprost is the first chemically stable and orally-active prostacyclin analogue. It is absorbed rapidly in fasting conditions, peak concentration is reached after 30 min, and elimination half-life is 35-40 min after single oral administration.

The orally-active prostacyclin analogue beraprost has been evaluated in PAH patients in two RCTs in Europe and in the United States. In the first study the drug was administered orally four times a day at the highest tolerated dose (median dose 80 micrograms four times a day [qid]) and an increase in exercise capacity was seen only in IPAH subjects after 3 months. In the second randomised trial that lasted 12 months, improvement in exercise capacity was observed at 3 and 6 months but not thereafter. No haemodynamic improvements were observed in the long-term study and clinical events were reduced only at the 6 month evaluation.

Beraprost sodium has been approved in Japan and South-Korea for IPAH but its development appears to have been stopped in the USA and in Europe.

Grade of Recommendation = IIb; Level of Evidence = B for IPAH

Inhaled iloprost - Iloprost is a chemically stable prostacyclin analogue available for iv, oral and aerosol administration. Iloprost is a chemically stable prostacyclin analogue available for iv, oral and aerosol administration. Inhaled therapy for PAH is an attractive concept that has the theoretical advantage to be selective for the pulmonary circulation. In fact, since intra-acinar pulmonary arteries are closely surrounded by alveolar units, it is possible to vasodilate these vessels by an alveolar deposition of vasodilators. It is critical that aerosolised particles be small enough (diameter 3-5 micrometers) to ensure alveolar deposition.

After a single inhalation of iloprost a reduction of 10-20% of mean pulmonary artery pressure was observed and lasted for 45-60 min. The short duration of action requires frequent inhalations (from 6 to 12 times daily) to obtain a persistent effect with long-term administration. With Jet nebulisers, the duration of each inhalation takes about 15 min; with alternative devices such as ultrasound nebulisers the inhalation time can be reduced to about 5 min.

Inhaled iloprost has been evaluated in one RCT in which daily repetitive iloprost inhalations (6-9 times 2.5-5 micrograms/inhalation, median 30 micrograms daily) were compared to placebo inhalation in patients with PAH and CTEPH (see table 13 of the original guideline document). The study showed an increase in exercise capacity and improvement in symptoms, PVR, and clinical events in IPAH patients only. Overall, inhaled iloprost was well tolerated: cough occurred more frequently in the iloprost group as well as flushing and headache.

A long-term, uncontrolled study on 25 patients with IPAH treated for at least one year with inhaled iloprost 100-150 micrograms daily has been also reported: the data showed a mean increase of 85 meters of the six minutes walk, a reduction of 7 mmHg in mean pulmonary artery pressure, and an increase in cardiac index of 0.6 L/min/m^2. In a small study on 8 patients with PH and lung fibrosis, the acute administration of inhaled iloprost caused marked pulmonary vasodilation with maintenance of gas exchange and systemic arterial pressure showing a possible usefulness in this particular subset of patients.

Inhaled iloprost treatment has been approved by the EMEA in Europe for NYHA Class III IPAH and in Australia and New Zealand for PAH and non-operable CTEPH class III and IV.

Grade of Recommendation = IIa; Level of Evidence = B for IPAH

Intravenous iloprost - Continuous iv administration of iloprost appears to be as effective as epoprostenol in a small series of patients with PAH and CTEPH. Iloprost presents the advantage of being stable at room temperature and does not need to be reconstituted and refrigerated.

Continuous iv administration has been approved in New Zealand for NYHA class III and IV PAH.

Grade of Recommendation = IIa; Level of Evidence = C for PAH

Endothelin-1 (ET-)1 Receptor Antagonists

Currently three RCTs with endothelin-1 receptor antagonists have been performed in PAH patients at the time of writing (see Table 14 of the original guideline document):

Bosentan - Bosentan is an oral active dual ET_A and ET_B-receptor antagonist and is the first molecule of this class of drugs to be synthesised. Bosentan has been evaluated in PAH in two RCTs that have shown improvement in exercise capacity, functional class, haemodynamics, echocardiographic, and Doppler variable, and time to clinical worsening. In the larger BREATHE-1 study, patients were randomised 1:1:1 to receive placebo or 62.5 mg of bosentan twice daily for 4 weeks followed by either bosentan 125 mg bid or 250 mg bid for a minimum of 12 weeks. Although both bosentan dosages induced a significant treatment effect, the placebo-corrected improvement tended to be more pronounced for the 250 mg bid than for the 125 mg bid dosage (+54 meters and +35 meters of 6MWT treatment effect, respectively). However, no formal dose response for efficacy could be ascertained. Although a similar treatment effect was achieved in patients with IPAH and in those with PAH associated with scleroderma, bosentan improved the walking distance from baseline in IPAH patients (+46 meters in the bosentan group versus -5 meters in the placebo group) whereas it prevented walk distance deterioration in the scleroderma patients (+3 meters in the bosentan group versus -40 meters in the placebo group). Increases in hepatic aminotransferases occurred in 10% of the subjects and were found to be dose-dependent and reversible after dose reduction or discontinuation. In fact, abnormal hepatic function was more frequent and severe in the 250 mg dose group and a decrease in transaminase concentrations was observed in all cases in which the bosentan

dose was reduced. Based on these results, the recommended target therapeutic dose of bosentan was confirmed as 125 mg twice daily. The most likely mechanism for the liver enzyme changes with bosentan treatment is a dose-dependent competition by bosentan and its metabolites with the biliary excretion of bile salts, resulting in a retention of bile salts that can be cytotoxic to hepatocytes.

Twenty-nine patients received bosentan in an extension study: patients assessed at month 6 maintained the improvement in walk distance, and long-term treatment with bosentan for >1 year was associated with an improvement in haemodynamic parameters and NYHA functional class.

Oral bosentan has also recently been proposed as a transition therapy in patients displaying severe and/or unbearable side effects of prostanoid therapy including sepsis with iv epoprostenol.

An open-label uncontrolled single and multiple-dose study has been performed in children 4-17 years of age with PAH (BREATHE-3) to assess pharmacokinetics, tolerability, and safety of oral bosentan. In this preliminary study a significant improvement in haemodynamics was observed after 12 weeks of treatment in the 18 enrolled children either with bosentan alone or in combination with epoprostenol.

Due to the potential increase in liver enzymes, the FDA requires that liver function tests be performed at least monthly in patients receiving bosentan. In addition, the EMEA recommended to monitor monthly liver function tests, and currently these data are collected in an internet-based program (TRAX). Also, the haemoglobin/haematocrit should be checked regularly because bosentan use may also be associated with the development of anaemia, which seems typically to be mild. Fluid retention and lower limb oedema have been also reported in patients treated with bosentan. Careful attention must be paid to the use of adequate contraception in women of childbearing age due to the potential teratogenic effects of bosentan. In addition bosentan may decrease the efficacy of hormonal contraceptive techniques, and for this reason they should not be used alone. There is concern that the endothelin antagonists as a class may be capable of causing testicular atrophy and male infertility. Younger males who may consider conceiving should be counselled regarding this possibility prior to taking these drugs.

Bosentan has been approved for the treatment of NYHA class III and IV PAH patients in the USA and Canada. In Europe it has been approved by the EMEA for the treatment of NYHA class III patients specifying that efficacy has been demonstrated only in IPAH patients and PAH associated with scleroderma without significant lung fibrosis.

Grade of Recommendation = I; Level of Evidence = A for NYHA class III IPAH and PAH associated with scleroderma without significant lung fibrosis
Grade of Recommendation = IIa; Level of Evidence = B for NYHA class IV IPAH and PAH associated with scleroderma without significant lung fibrosis

Sitaxsentan - Sitaxsentan, a selective orally-active ET_A-receptor antagonist has been assessed in PAH patients in one RCT on 178 patients with NYHA class II, III, and IV PAH. Aetiology included IPAH and PAH associated with CTD or congenital heart diseases. Patients were randomised 1:1:1 to placebo, sitaxsentan 100 mg, or sitaxsentan 300 mg given orally once daily for 12 weeks. The study demonstrated improvements in exercise capacity, haemodynamics, and clinical events. Incidence of abnormal liver function tests, which reversed in all cases, was 0% for 100 mg, and 9.5% for 300 mg. An additional pilot study with this compound in 20 PAH patients has shown similar results.

Sitaxsentan may increase the INR or prothrombin time (PT), due to the inhibition of CYP2C9 P450 enzyme, the principal hepatic enzyme involved in the metabolism of warfarin. This interaction can be managed by reducing the warfarin dose to achieve the desired INR.

A second RCT is currently ongoing with sitaxsentan to further explore both efficacy and side effects profile and to achieve approval from regulatory agencies. No grade of recommendation is given for sitaxsentan because it is currently available only for patients enrolled in RCTs.

Grade of Recommendation = Currently not given; Level of Evidence = B

Ambrisentan - Ambrisentan, a selective orally-active ET_A-receptor antagonist has thus far been evaluated in a pilot blinded dose-comparison study in 64 PAH patients. Preliminary results show improvements in exercise capacity and haemodynamics that appear similar to the results observed with the other ET-1 receptor antagonists. Two RCTs are currently ongoing with ambrisentan to further explore both efficacy and side effects profile to achieve approval from regulatory agencies. No grade of recommendation is given for ambrisentan because it is currently available only for patients enrolled in RCTs.

Grade of Recommendation = Currently not given; Level of Evidence = C

Type 5 Phosphodiesterase (PDE) Inhibitors

Sildenafil - Sildenafil is an orally-active, potent, and selective inhibitor of cyclic guanosine monophosphate (cGMP)-PDE type 5 that exerts its pharmacological effect by increasing the intracellular concentration of cGMP. The increase of this nucleotide induces relaxation and antiproliferative effects on vascular smooth muscle cells. PDE-5 is selectively abundant in the pulmonary circulation, and PDE-5 gene expression and activity are increased in chronic PH. This suggests that sildenafil may have a preferential effect of the lung vasculature.

A number of uncontrolled studies have reported favourable effects of the orally-active type 5 PDE inhibitor sildenafil in PAH, CTEPH and PH associated with lung fibrosis. The drug at a dose ranging from 25 to 75 mg tid appears to improve both cardiopulmonary haemodynamics and exercise capacity. These studies report relatively few minor side effects (e.g., headache, nasal congestion, and visual disturbances). A RCT with a cross-over design has been recently published: sildenafil 25-100 mg tid administered in 22 NYHA II and III PAH patients improved symptoms after 6 weeks, the exercise capacity as assessed by the Naughton protocol on the treadmill (from 475 $\pm$ 168 sec of exercise time at the

end of placebo phase to 686 ± 224 sec at the end of sildenafil phase), and the haemodynamics. The results of a pivotal RCT of 278 NYHA II and III PAH patients were recently presented at the American College of Chest Physicians meeting at the end of October 2004. The data show that mean placebo-corrected treatment effects on 6MWT were around 45 meters for 20, 40, and 80 mg sildenafil 3 times daily. All sildenafil doses reduced mean PAP at week 12 by about 3 to 5 mmHG. At the time of writing sildenafil treatment has not yet been approved by any regulatory agency for treatment of PAH. Currently, treatment with sildenafil should be considered in patients with PAH, who have failed or are not candidates for other approved therapies.

Grade of Recommendation = I; Level of Evidence = A

Combination Therapy

Combination therapy is an attractive option to address the multiple pathophysiological mechanisms that are present in PAH. Combination therapy can be pursued by the simultaneous initiation of two (or more) treatments or by the addition of a second (or third) treatment to a previous therapy that may be considered insufficient. Which of these two strategies is the best choice is currently unknown.

The efficacy and safety of the concurrent initiation of bosentan and epoprostenol were investigated in 33 NYHA class III and IV PAH randomised either to an epoprostenol + placebo group or an epoprostenol + bosentan group (BREATHE-2). Improved haemodynamics, exercise capacity, and functional class were observed in both groups. Data shows that there was a trend for a greater (though non-significant) improvement in all haemodynamic parameters in the epoprostenol + bosentan group. However, an increase of adverse events was observed in the combination group as compared to epoprostenol alone.

Further RCT is ongoing or planned that will explore the effects of the addition of sildenafil to patients already on epoprostenol.

In patients with PAH who were deteriorating despite chronic treatment with non-parenteral prostanoids, addition of bosentan or sildenafil to the ongoing treatment resulted in favourable improvements in pulmonary haemodynamics and exercise capacity in uncontrolled studies.

Grade of Recommendations = IIb; Level of Evidence = C

Interventional Procedures

Balloon Atrial Septostomy

Several experimental and clinical observations have suggested that an inter-atrial defect might be of benefit in the setting of severe PH. In fact the presence of an atrial septal defect would allow right-to-left shunting to increase systemic output that, in spite of the fall in systemic arterial oxygen saturation will produce an increase in systemic oxygen transport. Furthermore, the shunt at the atrial level

would allow decompression of the right atrium and right ventricle, alleviating signs and symptoms of right heart failure.

The role of balloon atrial septostomy in the treatment of PAH patients is uncertain because its efficacy has been reported only in small series and case reports, totalling approximately 120 published cases. In most circumstances, this intervention has been performed in severely ill patients as a palliative bridge to lung transplantation, which may explain a procedure mortality rate ranging from 5 to 15%. In addition to symptomatic and haemodynamic improvement, an increase in survival as compared with historical control groups has also been shown. At present, balloon atrial septostomy is indicated for advanced NYHA class III and class IV patients with recurrent syncope and/or right heart failure despite all available medical treatments; septostomy is used either as a palliative bridge to lung transplantation or as the sole treatment modality when other options are not available. Balloon atrial septostomy should be performed only in experienced centres to reduce the procedural risks.

Grade of Recommendation = IIa; Level of Evidence = C

Lung Transplantation

Lung and heart-lung transplantation in PAH has been assessed only in prospective uncontrolled series, since formal RCTs are considered unethical in the absence of alternative treatment options.

The 3- and 5-year survival after lung and heart-lung transplantation is approximately 55% and 45%, respectively.

Both single and bilateral lung transplantation have been performed for IPAH, and these operations have been combined with repair of cardiac defects for the Eisenmenger syndrome. Recipient survival rates have been similar after single and bilateral transplantation for PAH, and if technically feasible, either of these operations is an acceptable choice for most cases of PAH. However, many transplant centres currently prefer to perform bilateral lung transplantation in part because there are generally fewer postoperative complications. In patients with Eisenmenger syndrome and in those with end-stage heart failure, the option of heart-lung transplantation should be carefully considered for some complex defects, and in cases of ventricular septal defects, a survival advantage of heart lung transplantation has been shown.

Lung and heart-lung transplantation are indicated in PAH patients with advanced NYHA class III and class IV symptoms that are refractory to available medical treatments. The unpredictability of the period of the waiting list and donor organ shortage complicate the decision-making regarding the appropriate timing of listing for transplantation.

Grade of Recommendation = I; Level of Evidence = C

<u>Specific Conditions</u>

See the original guideline document for a discussion of the treatment of "Specific Conditions" including: paediatric PAH, PAH associated with Eisenmenger syndrome, porto-pulmonary hypertension, PAH associated with HIV infection, PAH associated with CTDs, and PVOD and PCH.

Definitions

Class of Recommendations

Class I: Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful and effective

Class II: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment

- **Class IIa**: Weight of evidence/opinion is in favour of usefulness/efficacy.
- **Class IIb**: Usefulness/efficacy is less well established by evidence/opinion.

Class III*: Evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful

*Use of Class III is discouraged by the European Society of Cardiology (ESC)

Levels of Evidence

A. Data derived from multiple randomised clinical trials or meta-analyses
B. Data derived from a single randomised clinical trial or multiple trials with heterogeneous results
C. Consensus of opinion of the experts and/or small studies, retrospective studies, registries

CLINICAL ALGORITHM(S)

An evidence-based algorithm is provided for the treatment of pulmonary arterial hypertension (PAH), New York Heart Association (NYHA) Class III/IV.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriate diagnosis and treatment of pulmonary arterial hypertension

- Appropriate diuretic treatment in case of right heart failure allows clear symptomatic and clinical benefits in patients with pulmonary arterial hypertension (PAH) even if specific randomised controlled trials (RCTs) have not been performed.

POTENTIAL HARMS

- Limiting factors for dose increase of calcium channel blockers (CCBs) are usually systemic hypotension and lower limb peripheral oedema.
- Adverse effects with chronic epoprostenol treatment are common and include flushing, jaw pain, diarrhoea, headache, backache, foot and leg pain, abdominal cramping, nausea, and rarely hypotension. The incidence of side effects may relate to how aggressive the dose is initially up titrated. Dose reduction is required only if the intensity is moderate to severe. Recurrence of side effects may be experienced after dose increases but usually they are mild and self-limiting over time without dose changes. In some cases ascites has been reported that may be related to an increased permeability of the peritoneal membrane induced by epoprostenol. Adverse events related to the delivery system are more serious and are essentially linked to pump malfunction, local site infection, catheter obstruction and sepsis. Localised infections can also occur such as small exit site reactions, tunnel infections and cellulitis. Rare events are pneumothorax and haemothorax that occur during catheter insertion.
- Infusion site pain was the most common side effect reported for treprostinil, leading to the discontinuation of treatment in 8% of cases on active drug and limiting does increase in an additional proportion of patients.
- Studies with sildenafil in patients with pulmonary arterial hypertension reported such minor side effects as headache, nasal congestion, and visual disturbances.
- Due to the potential increase in liver enzymes, the United States Food and Drug Administration (FDA) requires that liver function tests be performed at least monthly in patients receiving bosentan. In addition, the European Agency for the Evaluation of Medicinal Products (EMEA) recommended to monitor monthly liver function tests, and currently these data are collected in an internet-based program (TRAX). Also, the haemoglobin/haematocrit should be checked regularly because bosentan use may also be associated with the development of anaemia, which seems typically to be mild. Fluid retention and lower limb oedema have been also reported in patients treated with bosentan. Careful attention must be paid to the use of adequate contraception in women of childbearing age due to the potential teratogenic effects of bosentan. In addition bosentan may decrease the efficacy of hormonal contraceptive techniques, and for this reason they should not be used alone. There is concern that the endothelin antagonists as a class may be capable of causing testicular atrophy and male infertility.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Significant pulmonary arterial hypertension (PAH) can substantially increase the risk associated with liver transplantation and usually PAH is a

contraindication if mean pulmonary artery pressure (PAP) is ≥35 mmHg and/or pulmonary vascular resistance is ≥250 dynes sec cm.
- In HIV-associated PAH, therapeutic options are less well established as compared to other forms of PAH. Oral anticoagulation is often contraindicated because of frequent reduced platelet counts, difficulty with compliance and potential drug interactions between HIV medications and warfarin.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The grading systems for the Level of Evidence based on the number of randomised controlled trials (RCTs) may present some limitations that need to be taken into account and possibly corrected. In fact, the level of evidence may change over time as a result of additional studies performed. In addition, the grading system does not address the sample sizes of the RCTs, as "small" RCTs are given the same weight as larger ones. Moreover, the Level of Evidence for efficacy should not be confused with the Level of Clinical Efficacy, which depends on the net pharmacodynamic effects of the compound and on possible side effects and shortcomings (e.g., complexity of the route of administration). For example, a treatment strategy with better results but with only one or no RCTs is rated respectively B or C, as compared with a therapy with poorer results and greater side effects assessed in more than one RCT that can be rated as A. Also regulatory agencies may grant approval to a given treatment on the basis of a single RCT with an appropriate sample size and pre-specified adequate statistical requirements.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm
Personal Digital Assistant (PDA) Downloads
Pocket Guide/Reference Cards
Slide Presentation

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Galie N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, Olschewski H, Peacock A, Pietra G, Rubin LJ, Simonneau G, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie M, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, McGregor K, Morais J, Oto A, Smiseth OA, Barbera JA, Gibbs S, Hoeper M, Humbert M, Naeije R, Pepke-Zaba J. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. Eur Heart J 2004 Dec;25(24):2243-78. [230 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004

GUIDELINE DEVELOPER(S)

European Society of Cardiology - Medical Specialty Society

SOURCE(S) OF FUNDING

European Society of Cardiology

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the European Society of Cardiology (ESC) Web site.

Print copies: Available from Elsevier Science Ltd. European Heart Journal, ESC Guidelines - Reprints, 32 Jamestown Road, London, NW1 7BY, United Kingdom. Tel: +44.207.424.4422; Fax: +44 207 424 4515; Web site: http://www.eurheartj.org/

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Diagnosis and treatment of pulmonary arterial hypertension. Pocket guideline. Electronic copies: Available from the European Society of Cardiology (ESC) Web site. Also available for PDA download from the ESC Web site.
- Guidelines on diagnosis and treatment of pulmonary arterial hypertension. Slide set. Electronic copies: Available in Portable Document Format (PDF) from the European Society of Cardiology (ESC) Web site.
- Recommendations for guidelines production. A document for Task Force Members responsible for the production and updating of ESC guidelines. 2006 Jun 28. 21 p. Available from the ESC Web site.

Print copies: Available from Oxford University Press, Great Clarendon Street, Oxford, OX2 6DP, UK, Tel: +44 (0) 1865 353263, Fax: +44 (0) 1865 353774, Web site: http://www.eurheartj.org/.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on March 11, 2005. This summary was updated by ECRI on July 15, 2005 following the FDA advisory on Cialis, Levitra, and Viagra. This summary was updated by ECRI on March 8, 2006 following the FDA advisory on Tracleer (bosentan). This summary was updated by ECRI on March 6, 2007 following the FDA advisory on Coumadin (warfarin sodium). This summary was updated by ECRI Institute on July 12, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Troponin-1 Immunoassay. This summary was updated by ECRI Institute on September 7, 2007 following the revised U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin). This summary was updated by ECRI Institute on November 6, 2007, following the updated U.S. Food and Drug Administration advisory on Viagra, Cialis, Levitra, and Revatio.

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Date Modified: 9/29/2008